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

WARNING: EMBRYO-FETAL TOXICITY

See full Prescribing Information for complete boxed warning.

- ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and 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.

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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Cranbury, NJ 08512

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PLR-00105
CBD penetrates skincare

Patient interest high despite need for more data

WHITNEY J. PALMER | Staff Correspondent

CBD, one of 113 identified cannabinoids, has known anti-inflammatory and pain-relieving properties. In dermatology, a variety of topical products are becoming increasingly available to patients; however, much work remains to create CBD-containing dermatology products that can effectively treat skin disorders, one expert says.

“Currently, there aren’t many high-quality, high-standard CBD products on the market,” says Michael Milane, M.D., MBA, MPH, chief executive officer of Greenway Therapeutics, a company focused on developing novel dermatology therapeutics. “There’s a lot of hype out there, but

TOPICAL HALOBETASOL PROPIONATE 0.01% lotion (Bryhali, Bausch Health) appears to safely and quickly improve lower-extremity psoriatic lesions, according to findings reported recently in the Journal of Drugs in Dermatology.1

A post hoc analysis of data from phase 3 studies investigating the efficacy of halobetasol propionate 0.01% lotion for treating moderate-to-severe plaque psoriasis showed that the topical corticosteroid was associated with rapid improvement, and findings should help dermatologists

ATOPIC DERMATITIS

Re-think rescue Tx

Consider options to target pathophysiology

LISETTE HILTON | Staff Correspondent

DERMATOLOGISTS TREATING moderate-to-severe atopic dermatitis patients should not depend on a rescue approach aimed at responding to atopic dermatitis flares. Rather, clinicians should talk with patients about treatment options that could more optimally control symptoms in the long-term, while avoiding sometimes severe adverse events associated with conventional treatments, according to a paper published February 2019 in the Journal of Clinical and Aesthetic Dermatology.

Specifically, today’s dermatologists should consider using the injectable human IgG4 monoclonal antibody, dupilumab (Dupixent, Sanofi and Regeneron Pharm-

Psoriasis

Topical shows benefit in treating leg psoriasis

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

TOPICAL HALOBETASOL PROPIONATE 0.01% lotion (Bryhali, Bausch Health) appears to safely and quickly improve lower-extremity psoriatic lesions, according to findings reported recently in the Journal of Drugs in Dermatology.1

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1
on the cover

ANTIAGING

CBD penetrates skincare

Patient interest high despite need for more data

ATOPIC DERMATITIS

Re-think rescue Tx
Consider options to target pathophysiology

PSORIASIS

Topical shows benefit in treating leg psoriasis
DermaLight
KTP Laser System

Treatment of Choice for Vascular and Pigmented Lesions

- Color Touch Screen
- Wireless Foot Pedal
- Preset Protocols
- Portable / Affordable

INCLUDES:
- Mobile Cart
- Carry Case
- Two Year Warranty

“We use our DermaLight KTP Laser every day. It is very effective for treating vascular and pigmented lesions. We are very satisfied with the affordability, reliability and ease of use of this system.”

~ Dina N. Anderson, MD
Dermatologist, Clinical Instructor
Mount Sinai, New York City

For questions or to schedule a demo contact:

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Laser-assisted PLLA may optimize injectable results.
A look back to see what lies ahead

by MIKE HENNESSY, SR

Over this past year, we’ve reported on many advances in the understanding of the pathophysiology of some of the most impactful skin conditions. There has been a continued focus on the role of the microbiome in many conditions, as well as hormonal influences. New drug entities are being studied to target new pathways in the understanding of these conditions.

In the coming year, we are looking forward to more advances in therapeutic options for patients who suffer from acne, psoriasis, eczema, as well as rarer, but as impactful conditions such as epidermolysis bullosa.

In this issue, Dr. Leon Kircik shares insight into promising new therapies in the pipeline for acne on page 28. We also take a look at an antibacterial alternative to treatment with data indicating nanopulse technology may be an antibiotic alternative to treatment with data indicating nanopulse technology may be an antibiotic alternative to treatment with data indicating that patients… have significant unmet therapeutic needs,” the authors suggest (page 16). Underscoring patients’ search for therapies that work are results of a survey that notes adults with atopic dermatitis report a high burden of disease despite the number of treatments available. “These results suggest that patients … have significant unmet therapeutic needs,” the authors say (page 18).

We look forward to reporting on how you can improve access to care and the availability of promising new treatments in the New Year.

MIKE HENNESSY, SR., is CHAIRMAN AND FOUNDER OF DERMATOLOGY TIMES® PARENT COMPANY, NICH LIFE SCIENCES.

DermatologyTimes® is guided by a core group of trusted physician experts who review meetings, suggest topics & sources, & conduct interviews.

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

Dr. Ronald G. Wheeland
Dr. Wheeland is a private practitioner in Tucson, Ariz.
Our society has undergone seismic shifts in ... technological capacity, and ... expectations of various industries.”

DTC compounded medications: A treatment option for a system in need?

by USAMA SYED, DERMATOLOGY RESIDENT
RAYMOND MILLER, J.D.
BRANDON KIRSCH, M.D., J.D.

We have all been there: An advertisement on television or a pop-up on Facebook beckons us to try the latest “visit-free,” “delivered to your door” treatment for a medical condition. This new model of targeted, direct-to-home commercialization of drugs is radically altering the pharmaceutical industry. The change is perhaps best illustrated by the tremendous success of Hims, Inc., which is responsible for ForHims.com and ForHers.com.

You want oral contraceptive medications without an appointment? There’s Nurx or Pill Club. Going through menopause? Try Rory. Need medical help to quit smoking? Zero has you covered. Get migraines? Cove can get you anti-emetics and even triptan medications in minutes. More grounded and novel formulations. So why are all of these services emerging now? While compounding has always been a potential threat to repurposed or specialized innovation in the pharmaceutical space, statutory limitations on traditional compounding pharmacies related to batch formulating and interstate commerce rendered them competitive only in theory. However, a number of factors have coalesced over the last decade to allow these traditional compounding pharmacies, often referred to as “503As” because of the federal statute that regulates them, to thrive.

First, there is now substantial demand for these services. Our society has undergone seismic shifts in both our technological capacity, and also our expectations of various industries we interact with. We want our bedding to be customized to our needs to be considered. Thankfully, the oversight of their own prescription formulations? Given the complexities and risks of prescription medications, protections are clearly necessary to ensure the public is not exposed to undue harm. There are commercial and legal implications to be considered. Off-label promotion although arguably protected commercial free speech is considered problematic from a regulatory perspective and patent infringement needs to be considered. Thankfully, the oversight of compounding pharmacies is already rigorous and we expect to see more FDA and FTC engagement as this nascent industry expands.

Clearly, the line between highly regulated, approved drug combinations and unregulated compounded formulations has begun to blur. In this way, compounding pharmacies are already beginning to erode the fabric of regulated pharmaceuticals, particularly for repurposed drugs. While commercial free speech is considered problematic from a regulatory perspective and patent infringement needs to be considered. Thankfully, the oversight of compounding pharmacies is already rigorous and we expect to see more FDA and FTC engagement as this nascent industry expands.
Dr. Derm has a 50-year-old staff person who has worked with him for 20 years. He knows her family and has spent time socially with both she and her family. She is under contract and can be terminated within 90 days for almost any non-discriminatory reason and immediately for “cause.” Reasons of termination for cause include conviction of a crime, which is a common termination clause in almost all employment agreements.

Three months ago, the employee was arrested for brutally beating up her husband after finding out about his adulterous relationship with another woman. She threw a wine glass at him and shards of glass cut his neck in numerous places, resulting in extensive bleeding. She also threw a frying pan at him, resulting in numerous other cuts and bruises and a broken nose. He nearly lost consciousness. The employee was immediately arrested, although she argued that her behavior was justified. The story ran in the local newspapers. The photos online were frightening. And, social media lit up with the employee’s actions. In every mention of the story, Dr. Derm was noted as being the employer. Consequently, he was very concerned about the negative impact on his practice as he received word that patients were frightened and multiple appointments were cancelled.

Did he wrongfully terminate the employee?

In the wake of several years of highly publicized domestic abuse scandals, many employers are asking the same question: Can we fire an employee who has committed domestic violence? There is no clear, correct response. However, there are several factors dermatologists should consider before taking any adverse employment actions against employees involved in domestic violence disputes.

The first is: Has the employee been convicted? There’s a big difference between being arrested/charged/accused and actually being convicted. Without a conviction, a physician could open himself to a wrongful termination suit if he or his employee was simply accused of having domestic violence. The tricky part here, of course, is that most employers don’t undertake background checks on existing employees. Dr. Derm only knew about his current employee because of the local press coverage.

The next question is whether employing the individual carries a current workplace risk — regardless of the publicity. If that were the case, it becomes easier to apply the “workplace risk test.” That is questionable with Dr. Derm’s situation where an unknown employee has been accused of the crime. Did he wrongfully terminate the employee?

Dr. Derm could open himself up to a wrongful termination suit if he can’t tie the domestic violence incident directly to a specific workplace risk. Termination of the employee becomes more difficult if the offender is a good performer, co-workers don’t feel at risk and the employee’s spouse does not work in the office. Patients cancelling appointments is not enough to terminate the employee.

The situation might be different if the abuser is in the public spotlight, for example, as a face of the dermatology practice. If that were the case, it becomes safer to let the employee go, particularly if the person is working under an agreement that includes strict prohibitions on offensive behavior. At that point, since the person’s actions are likely eroding your brand, it becomes easier to apply the “workplace risk test.”

This situation also would be different if a person convicted of domestic violence is in a position as a role model for other employees. Keeping this person at an administrative level, could then erode the reputation of the office. That could be grounds for making the argument that the person poses a threat to your business.

In the end, despite the poor publicity this incident has brought to Dr. Derm’s practice and the potential for some financial loss if she stays employed, he would have been wise not to terminate her until — and if — she is convicted of domestic abuse.
For the treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older

Indication
Hidradenitis Suppurativa: HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.

Safety Considerations
Serious Infections: Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies: Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.
Indication

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1 Malignancies: Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

Safety Considerations (cont’d)

Other Serious Adverse Reactions: Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

Please see additional Important Safety Information, including BOXED WARNING on Serious Infections and Malignancy, on the third page of this advertisement.

Please see Brief Summary of full Prescribing Information on the pages following this advertisement.

Use in Adolescents

• Efficacy from the adult HS studies was extrapolated to adolescents through pharmacokinetic modeling
• Safety of the recommended HUMIRA dose in the adolescent HS population is anticipated to be consistent with the known safety profile of HUMIRA

Safety Considerations (cont’d)

For the treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older

Clinically Meaningful Improvement at Week 12

• Many adult patients in clinical trials achieved at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscesses and draining fistulas relative to baseline

To learn more, please go to HUMIRAPro.com/goforward/hs
SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection.
- Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

Do not start HUMIRA during an active infection, including localized infections.

Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.

If an infection develops, monitor carefully and initiate appropriate therapy.

Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with a TNF blocker or 6-mercaptopurine concurrently with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.

In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.

Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-blocked patients. Examine all patients, particularly those with a history of prolonged immunosuppression or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.

In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressants, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.

HYPERSensitivity

- Anaphylaxis and angioedema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medical significance of cytopenia has been infrequently reported with HUMIRA.

Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening and new onset congestive heart failure (CHF) has been reported with TNF blockers. Cases of worsening CHF have been observed with HUMIRA; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.

- Adalimumab is actively transferred across the placenta during the third trimester of pregnancy, and may affect immune response in the utero exposed infant. The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA in utero is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

The most common adverse reactions in HUMIRA clinical trials (≥10%) were:

- Infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

References:
5. Nash P, Vhancocf J, Hall S, et al. Randomized crossover comparison of injection site pain with 40 mg/0.4 mL or 0.8 mL formulations of adalimumab in patients with rheumatoid arthritis. Rheumatol Ther. 2016;3(2):257-270.

Please see Brief Summary of full Prescribing Information on the following pages.
HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

SERIOUS INFECTIONS
HUMIRA® is not recommended in the treatment of patients with RA

ACTIONABLE ANTIMICROBIAL Guidelines

Use with Antituberculosis

ADVERSE REACTIONS

SEROUS REACTIONS

DEFINITIONS

REDUCING SIGNS AND SYMPTOMS OF MODERATE TO SEVERELY ACTIVE

HUMIRA® is indicated for reducing signs and symptoms, in adults with ankylosing spondylitis. See Boxed Warning for serious infection and tuberculosis

NATURAL OUTCOMES

Toxicity

Infections

Hematological Reactions

Hypersensitivity Reactions

Malignancy

Neurologic Reactions

In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, and Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients

Infections

During the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA who tested positive for latent TB infection had a negative tuberculin skin test (i.e., <5 mm). In particular, patients with previous tuberculosis and patients who have had radiation to the chest are at increased risk for reactivation of latent tuberculosis.

In controlled trials of HUMIRA in adults with AS, fewer AS-related serious infections occurred in the HUMIRA group compared with placebo (17% vs. 23%). No deaths were reported in patients treated with HUMIRA.

Total infections were reported in 28% of 7973 HUMIRA-treated patients and 27% of 10,977 placebo-treated patients. The most common infections were upper respiratory tract infections (8% vs. 8%) and sinusitis (2% vs. 2%). HUMIRA-treated patients and placebo-treated patients had similar rates of serious infections (4% vs. 3%) and serious infections leading to death (0.1% vs. 0.2%).

In the controlled clinical trials of HUMIRA in RA and PsA, the most common serious infections were respiratory tract infections (13% and 14%, respectively). Serious infections leading to death occurred at an average rate of 0.1% in both groups.

Infections

Systemic Lupus Erythematosus

The rate of Serious Infections was similar in all treatment groups across trials

Hemorrhagic Reactions

Infections

In controlled clinical trials of HUMIRA in Crohn’s disease, the rate of serious infections was similar in all treatment groups (3% and 2% in the HUMIRA groups vs. 4% in the placebo group). Serious infection rates were higher in the HUMIRA group than in the placebo group (3% and 2% vs. 0%) in two trials of patients who were taking infliximab concomitantly. The rate of serious infection was 4% in the infliximab group. There were no serious infections leading to death in these trials.

SEROUS REACTIONS

Histoplasmosis, legionellosis, listeriosis, sarcoidosis, tularemia, varicella-zoster virus infections, and viral hemorrhagic fevers including monkeypox and marburg virus hemorrhagic fever, and other mycoses and other opportunistic infections (such as pneumocystis, candidiasis, listeriosis, and toxoplasmosis). Because some infections are more likely to occur in patients with CD, patients with CD were at a higher risk for serious infections than patients with UC. Serious infections occurred in 13.5% of patients with CD (22% of patients with CD in the placebo-treated group vs. 19% in the HUMIRA-treated group) and 6.6% of patients with UC (22% of patients with UC in the placebo-treated group vs. 18% in the HUMIRA-treated group).

Hypersensitivity Reactions

Infections

In controlled clinical trials of HUMIRA in Crohn’s disease, the most common serious infections were respiratory tract infections (25% and 20% in the HUMIRA groups vs. 35% in the placebo group). One patient died (1.1%) in the placebo group due to an opportunistic infection (Listeria monocytogenes). Serious infections leading to death occurred in 0.6% of HUMIRA-treated patients and 0.5% of placebo-treated patients.

Infections

Infections

Serious Infections

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HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated upper respiratory tract infection and nasopharyngitis. A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in adults with polyarticular JIA.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent caries, rotavirus gastroenteritis, and varicella. In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included.

Upon initiation of treatment, the most common adverse reactions occurring in this patient population were:

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<tr>
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Adaptive immunity, Clinical Studies

HUMIRA has been shown to be effective in clinical trials in patients with active rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) treated with adalimumab or placebo.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older with active polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients with polyarticular JIA.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant use of methotrexate.

Table 1. Adverse Reactions Reporting in ≥2% of Patients Treated with HUMIRA in Placebo-Controlled Clinical Trials

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Ultrasound technology for rosacea treatment

by MILDRED LOPEZ, M.D., AND JOELY KAUFMAN, M.D.

Dr. Lopez is an ASDS Cosmetic Dermatologic Surgery Fellow, and in practice at Skin Associates of South Florida, Coral Gables, Fla. Dr. Kaufman has vast experience with lasers to treat aging skin and cosmetic procedures and has been involved with numerous research studies for new devices in the cosmetic industry. She practices at Skin Associates of South Florida, Coral Gables, Fla.

Rosacea is a chronic inflammatory cutaneous disorder that is subdivided as erythematotelangiectatic, papulopustular, phymatous and ocular. The pathophysiology is not completely understood, but, in its early stages, it seems to be a manifestation of innate immune system and neurovascular dysregulation. Usually treatment involves a combination of avoidance of triggers (e.g. ultraviolet light, heat, spicy foods), topical medication (e.g. metronidazole, ivermectin, permethrin, oxymetazoline), oral medication including antibiotics, isotretinoin and ivermectin and laser therapy. Laser treatment of rosacea is predominantly focused on reducing the vascular component that leads to erythema or treating the more chronic phymatous component. There is published evidence for the use of the intense pulsed light, pulsed dye laser, 532 nm KTP, 755 nm alexandrite, long-pulsed Nd:YAG and CO2 devices. More recently, there have been two studies using ultrasound technology with frequencies of 3 to 10 MHz as a new modality for treatment of specifically erythematotelangiectatic and refractory rosacea. Ultrasound technology allows for localized delivery of heat within the dermis without harm to the surrounding tissue. It is thought that this sound wave technology is capable of suppressing matrix metalloproteinases which then leads to downstream anti-inflammatory effects.

Dual frequency ultrasound, capable of operating over dual or multiple frequencies, was studied in a retrospective fashion for treating refractory rosacea by Park et al in 2018. They reviewed 42 charts of patients with rosacea treated for 12 weeks with 3/4.5 MHz and a constant 4.5 MHz ultrasound wave (Hyperform, MI Tech Co) twice per week for the first week, followed by one week intervals. They describe a whole face treatment lasting 10 minutes with approximately 10 second per shot. The measured outcomes were erythema index, transepithelial water loss and patient self-assessment. The mean erythema index values decreased from a baseline of 16.3 to 12.7 at week 12 (<.05), transepithelial water loss decreased from a baseline of 35.8 to 22.8 at week 12 (p<.05) and patients also self-assessed improvement of rosacea from baseline to week 12 (p<.01). The treatments were well tolerated, but there was no long-term follow-up. A second study published by Schlessinger et al earlier this year studied microfocused ultrasound (Ultherapy System) for treatment of erythematotelangiectactic rosacea. They enrolled 91 subjects with the diagnosis and randomized them to receive one or two low density treatments or one or two high density treatments. Per their protocol, low density treatment consisted of a minimum of 15 treatment lines per square vs high density which consisted of a minimum of 30 treatment lines per square. They explain each treatment line required approximately three seconds to perform, and no more than two sessions were performed as they were limited by patient discomfort. Treatments were performed 14+/4 days apart. Outcomes were measured through analysis of clinician erythema assessment, patient self-assessment, dermatology life quality index, digital images and colorimeter assessment of the red-green spectrum. Across groups, 75-91.3% of patients achieved treatment success at 90 days, defined as a one-point change in clinician erythema assessment. Moreover, in this study it was noted that a single high-density treatment was the most effective. Notable adverse events were bruising, tenderness and redness. Sustained results were noted at one-year follow-up. Erythema seems to be the most difficult rosacea symptom to treat. There are many innovative studies examining new topical therapies and new procedural protocols trying to elucidate a reliable and durable way to safely control redness without rebound. Both of these studies remarkably showed objective and subjective improvement of erythema. Interestingly, these two specific papers used ultrasound technology which did not actually target the telangiectasias themselves, which is what the majority of previous studies focus on, but downregulates the inflammatory cascade that underlies rosacea. Larger randomized trials are necessary to further clarify the treatment protocols and settings required to achieve positive patient outcomes and to further elucidate the precise mechanism of action.

References
Innovation in topical medications: Spotlight on Dermira and the QBREXZA story

by HANS HOFLAND PH.D. AND STEVE XU M.D. FAAD

Hans Hofland, Ph.D., has over 25 years of experience in skin biology, drug discovery and medicines development in industry. Prior to joining Dermira as head of research and nonclinical development, Dr. Hofland was leading the Center for Skin Biology at Stiefel, a GSK company, where he was responsible for target identification and validation, and for the early development of novel compounds in the dermatology portfolio for a wide variety of indications. He has held leadership positions at various other companies and was involved with 12 IND- and 10 NDA-filings. He earned his Ph.D. in Pharmaceutical Sciences from the University of Leiden in the Netherlands, where he studied the interactions between topical drug delivery systems and human skin. Dr. Xu is an instructor in dermatology at Northwestern University Feinberg School of Medicine; medical director, Center for Bio-Integrated Electronics, Simpson Querrey Institute for Bionanotechnology, Northwestern University; and, co-founder, Advancing Innovation in Dermatology.

To be innovative in the dermatology space, we must start with a hard look at the characterize of these topical medicines. Many “innovations” are harder to classify as truly innovative. For instance, the World Health Organization lists 18 topical drugs in dermatology as part of their Essential Medicines list. While topical medications account for more than $167 billion U.S. dollars in global spending, breakthrough innovation in topical medicines lags behind the global pharmaceutical industry. Fundamentally, creating efficacious, safe and cosmetically elegant topical medicines is hard.

There are broader market forces such as lower economic return and lack of surrogate endpoints (thus dependency on subjective scales) that dis-incentivize investment in this space. Dermira (NASDAQ: DERM) is a biopharmaceutical company dedicated to developing novel therapeutics in medical dermatology. This month, we’ll examine a novel topical medicine indicated for primary axillary hyperhidrosis in patients 9 years of age and older.

**QBREXZA (Dermira)**

When QBREXZA (glycopyrronium) was approved by the U.S. Food and Drug Administration in June 2018 for patients nine years and older with primary axillary hyperhidrosis or excessive underarm sweating, few people realized the nearly 15-year odyssey it took to come to market.

Primary axillary hyperhidrosis affects 10 million people in the United States; affects men and women equally; and it often presents in adolescents. Prior to its availability, dermatologists frequently used a combination of unapproved drug therapies or device technologies in an effort to minimize or eliminate sweating. In some instances, patients resorted to surgical procedures such as having sweat glands removed or the nerves associated with sweating cut, often with varying results.

In 2005, Connetics acquired the rights to this novel treatment idea. Researchers sought to develop a new product that would provide a person relief from their excessive sweating throughout the day. The company eventually developed a single-use towelette based on a simple, safe, fast-drying and easy-to-apply ethanol-based formulation.

Stiefel Laboratories acquired Connetics in 2006 charting a new path for the treatment. However, convincing the new commercial leadership organization of the value of the investigational compound proved difficult.

“We knew the need existed based on conversations with dermatologists and patients but demonstrating that a market large enough to develop a therapy like this existed was initially challenging,” says Hans Hofland, vice president for research at Dermira and former researcher at Connetics. Glycopyrronium was tested in a small cohort of Australian patients yielding a positive result, in 2008, and a small dose finding phase 2b study was initiated in 2009, which also showed very promising results.

Stiefel was acquired by GlaxoSmithKline in 2009 thrusting the future development and commercialization of the therapy into question. “There was recognition by this time that hyperhidrosis was an underserved medical condition, but lingering, unfounded concerns over the safety of glycopyrronium prevented the program from continuing,” Dr. Hofland says. The compound was effectively shelved for the next several years before Dermira stepped in to acquire the investigational therapy from the company with a plan to continue its development in 2014.

A new and improved form of the molecule was developed and a phase 2b study initiated in 2014. A year later, promising safety and efficacy results allowed the company to rapidly move to phase 3 testing. While the late-stage trials were underway, the company continued to research the prevalence of the condition and sought to further understand its impact on daily lives of patients. A number of prominent names in dermatology signed onto the phase 3 program and helped design trials that would not only confirm the therapy’s benefit, but also measure its impact on a patient’s quality of life before and after treatment. The lessons learned from the trials, which reported favorable results in 2016, would also serve as the foundation for planning efforts around a multi-channel disease state awareness campaign to raise awareness of the condition. The original vision of a single-use towelette offered patients an intuitive, effective and elegant method of delivery.

When the treatment was finally approved in June 2018, it captured what was known around the halls of Dermira as a long-term passion project for innovation.

Today, more than 50,000 patients have received QBREXZA and just over 16,000 healthcare professionals have prescribed the therapy.

**Disclosures**

The authors highlighted QBREXZA in the 2018 Center for Drug Evaluation and Research’s Annual Report on Advances in Health Through Innovation—New Drug Approvals. The novel hyperhidrosis treatment was noted as an important strategy to improve outcomes by decreasing the botheredness and improving percent drug delivery. Within the halls of Dermira, Dermira’s passion and dedicated efforts resulted in using topicals in healthy patients. Thus, while dermatology, we have an opportunity and duty to support innovation in this space.
Guidelines to manage kids

WHITNEY J. PALMER | Staff Correspondent

Effects in the skin layer play a central role in the development of atopic dermatitis in children, and a new analysis indicates that controlling associated dry skin symptoms with moisturizers can be an important — and inexpensive — prevention and treatment tactic.

Atopic dermatitis is common in childhood, affecting between 10% to 20% of children. Among those who are prone, 90% develop the condition by age 5 with the initial phases emerging between three-to-six months of age. Symptoms, including dry skin, scaling, swelling and itching can lead to significant scratching and sleep disturbances, specifically among younger children and toddlers.

A working group of seasoned clinicians with experience managing pediatric populations with atopic dermatitis reviewed existing literature to identify the most effective interventions for controlling atopic dermatitis in infants and young children. They also examined the associated reactions to environmental triggers, climate and diet.

In that analysis, long-term use of moisturizers emerged as an efficient, easy, low-cost tactic for addressing the impact of the condition. The results indicated the use of plant-based moisturizers free of additives, fragrances, perfumes and sensitizing agents led to a number of benefits, including a prolonged time to flares, as well as a reduction in the number of flares and in the amount of topical corticosteroids required to achieve the same level of control over atopic dermatitis.

Consequently, it’s important to teach parents how to most effectively use moisturizers to alleviate and manage the signs of atopic dermatitis in their children, says group member Anneke Andriessen, Ph.D., a dermatologist with Radboud University Medical Center in the Netherlands.

“Prevention and management of atopic dermatitis hinge on parental education, preventive measures, treatment and control to improve the well-being of the child and the family,” she says. “Important aspects of atopic dermatitis treatment include parental education, avoidance of triggering factors and daily application of moisturizers.”

Training parents to effectively avoid triggers and use moisturizers from birth, she adds, could change how they approach dealing with allergies. Rather than avoiding exposures altogether, pairing a controlled exposure with moisturizer use could help prompt allergen tolerance. Doing so could ultimately lead to creating a therapeutic strategy for preventing allergy, focusing on safe skin treatment, oral tolerance induction and environmental controls, such as lifestyle changes.

In addition, successful use of moisturizers could also reduce a family’s out-of-pocket costs for prescription medications, over-the-counter treatments, physician visits and hospitalizations. It could also reduce work or school absenteeism, bolster productivity for both child and parent and augment quality of life.

MOISTURIZERS FOR PREVENTION

According to the team’s analysis, previous studies have revealed daily moisturizer use can prevent the development of atopic dermatitis. Existing controlled-trial research indicates that, among high-risk newborns, consistent moisturizer application prevented this condition in 32% of Japanese babies and in 50% of Anglo-American infants.

A related study also revealed use of a 2% sunflower oil distillate emollient prompted improvement in both skin conditions and atopic dermatitis symptoms in pediatric patients.

EFFECTS OF VARIOUS MOISTURIZERS

Although studies into the efficiency of various vegetable oils as moisturizers are limited, Dr. Andriessen says, published investigations point to the efficacy of virgin coconut oil and sunflower oil distillate in alleviating the symptoms and impacts of atopic dermatitis in children.

For example, one study demonstrated that topically applied virgin coconut oil was effective in reducing the effect of eczema and controlling the amount of water that evaporated from the skin; thereby reducing dry skin. Based on those results, investigators determined this moisturizer’s efficacy results from its anti-inflammatory activity.

Two other studies also examined the moisturizing properties of sunflower oil, particularly sunflower oil distillate. This substance was found to decrease inflammation, restore filaggrin expression, activate ceramides 3 and regulate kallikrein expression. As a result, a 2% sunflower oil distillate emollient prompted improvement in both skin conditions and atopic dermatitis symptoms in pediatric patients.

A related study also revealed use of a 2% sunflower oil distillate emollient led to a corticosteroid-sparing effect among patients who were also simultaneously being treated with topical corticosteroids every other day.

Ultimately, Dr. Andriessen says, these studies demonstrated that pediatric patients with atopic dermatitis achieve comparable improvement in their skin condition and in their quality of life when they use moisturizers as they do when they rely solely on topical corticosteroids.

“A defective epidermal skin barrier in atopic dermatitis may benefit from daily moisturizer use, which should start after birth, especially in those infants at risk for atopic dermatitis,” she says. “Sunflower oil distillate, as a component in a moisturizer, has exhibited clinical efficacy and safety when used in pediatric patients with atopic dermatitis.”

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'Natural' vinegar solution could be harmful

LISETTE HILTON | Staff Correspondent

Bathing in a 0.5% apple cider vinegar solution isn’t a useful treatment for atopic dermatitis, and it can be irritating to the skin, researchers report in a study published in the September/October issue of Pediatric Dermatology.

Skin barrier dysfunction in people with atopic dermatitis, or eczema, often results in high transepidermal water loss, alkaline skin pH and Staphylococcus aureus colonization. Topical apple cider vinegar is a popular, emerging option that patients and parents think is safer or more natural than prescriptions like topical steroids. And while there is some evidence that dilute apple cider vinegar might improve skin barrier integrity in atopic dermatitis, there isn’t strong safety and efficacy data to support its use in atopic dermatitis, according to the paper.

Researchers studied 11 atopic dermatitis patients and 11 healthy controls. Subjects who were 12 years and older and included Caucasians, African Americans and Asians with mild-to-severe disease soaked both forearms ten minutes each day for 14 days. One forearm was soaked in 0.5% acetic acid, or apple cider vinegar, and the other in water. Researchers measured transepidermal water loss and skin pH on day one before, and up to one hour after the first soak and 24 hours after completing the two weeks of daily soaks.

Researchers found transepidermal water loss increased and pH decreased right after apple cider vinegar treatment, but those effects were not evident at 60 minutes post treatment. More than 70% of subjects — 16 of the 22 — reported mostly mild side effects from apple cider vinegar soaks. The side effects, including forearm skin discomfort and, in one patient, severe pruritus, improved after patients discontinued the soaks.

The study suggests several things to dermatologists who recommend or are thinking about recommending apple cider vinegar to their atopic dermatitis patients, as well as to patients who might be considering it as a treatment option, according to study author Richard H. Flowers, M.D., assistant professor of dermatology at the University of Virginia in Charlottesville, Va.

“Although we know why apple cider vinegar should work in eczema treatment, there is little data to demonstrate its effectiveness. In our study, we showed that any changes that occurred in the skin in eczema patients were not long lasting, even after several weeks of daily soaks in dilute apple cider vinegar,” according to Dr. Flowers. “In addition, we often consider natural treatments as harmless, but our study showed that this may not necessarily be true. Skin irritation can result from apple cider vinegar soaks as a treatment option. This highlights the importance of patients discussing new home remedies with their dermatologist before the first attempt. Physicians should also explain the range of potential side effects before recommending a patient undertake new home remedies.

More patients are seeking complementary and alternative medicines, including apple cider vinegar, which was an incentive for performing the study, according to Dr. Flowers.

The study’s findings have not significantly changed practice for Dr. Flowers and colleagues.

“At the University of Virginia, we actually use dilute bleach baths for atopic dermatitis much more than dilute apple cider vinegar baths,” he says. “Bleach is the other major additive medicines, including apple cider vinegar, which was an incentive for performing the study, according to Dr. Flowers.

The study’s findings have not significantly changed practice for Dr. Flowers and colleagues.

“Specifically, we need to examine the true effect — if any — of the apple cider vinegar on patients’ eczema and symptoms. [That’s] really the most important piece of this puzzle: to look at the effect of apple cider vinegar on Staph aureus in atopic patients and to find an optimal concentration of apple cider vinegar that does not irritate the skin,” Dr. Flowers says. “A head-to-head comparison of dilute apple cider vinegar and dilute bleach baths would be very interesting as well.”

References

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Study underscores need to improve disease control

LISETTE HILTON | Staff Correspondent

Quick Takes

Current systemic agents used to treat AD aren’t doing enough to alleviate disease burden.

Participants reported not only severe disease symptoms but recurrent flares, impaired QoL and reduced work productivity.

Regardless of AD severity, 38% of patients who had received systemic agents in the past 6 months reported that they had not experienced remission in the last 12 months.

A dult atopic dermatitis patients with moderate-to-severe disease who were treated with systemic agents, including cyclosporine, azathioprine, mycophenolate mofetil, methotrexate or cyclophosphamide, reported a high level of disease-related burden despite those treatments, according to research published July 17, 2019 in the Annals of Allergy, Asthma and Immunology.1

They not only reported severe disease symptoms, but also recurrent flares, impaired quality of life, reduced work productivity and compromised daily activities.

“The study period was prior to the availability of dupilumab in moderate-to-severe atopic dermatitis. However, it shows that the standard of care with currently available topical, oral systemic and phototherapies is clearly inadequate and that there is a need to improve control of atopic dermatitis in the United States,” says the study’s senior author Jonathan I. Silverberg, M.D., Ph.D., M.P.H., associate professor of dermatology, medical sciences and preventive medicine at the Feinberg School of Medicine, Northwestern University, Chicago.

Researchers conducted a longitudinal, prospective, observational study of atopic dermatitis patients who had been diagnosed in the last five years and had been prescribed systemic immunosuppressants, systemic corticosteroids or phototherapy. Participants completed a baseline paper survey, followed by web-based surveys at 3, 6, 9, and 12 months, as well as shorter monthly web-based surveys in between.

Of the 801 adult participants analyzed, more than 66% said they had been diagnosed at 21 years or older.

“While 66% is a little on the high side, it is important to note that adult-onset atopic dermatitis is more common than many clinicians recognize. A recent meta-analysis found that approximately 1 in 4 adults with atopic dermatitis report adult onset of their disease,” Dr. Silverberg tells Dermatology Times.

More than 26% of adults reported having severe atopic dermatitis.

Most participants, 63.6%, reported using topical corticosteroids in the last month, while 11.4% used systemic corticosteroids and 5.1% had used systemic immunosuppressants in the last month, according to the 12 months prior to the baseline survey.

More than 81% of patients indicated they had experienced at least one flare over the past month, according to the baseline monthly data.

“Regardless of baseline [atopic dermatitis] severity, and despite having received systemic agents in the past 6 months, a significant proportion of patients (38.3%) had not experienced remission in the prior 12 months,” the authors write.

Data from the Patient-Oriented Eczema Measure (POEM), a 7-item measure of symptom frequency in the past week, revealed that 57.6% of participants reported moderate to very severe symptoms in the short term. More than 34% of patients indicated they experienced 1 to 4 days of disrupted sleep in the last week. Severe atopic dermatitis patients fared worse in those two outcomes.

Nearly 44% indicated that atopic dermatitis moderately to extremely impacted their quality of life. The effect was worse when patients were experiencing flares, more frequent flares or severe disease.

Nearly 79% of working participants reported missing work due to atopic dermatitis an average 7.1 hours in the last 7 days.

“Despite using systemic treatments, patients with severe and currently flaring AD were similarly dissatisfied with the medications that they were taking for their [atopic dermatitis] …,” according to the authors. “These results suggest that patients with [atopic dermatitis] have significant unmet therapeutic needs.”

References
Long-term management options should be discussed with each patient  

Dr. Dao recalls one patient with moderate-to-severe atopic dermatitis who needed dupilumab to give it a try. He says, “Most of my patients with ocular side effects such as conjunctivitis have been well managed with my ophthalmology colleagues, including those with pre-existing atopic keratoconjunctivitis and those with de novo conjunctivitis after dupilumab initiation.”

He counsels patients with atopic dermatitis that dupilumab does not obviate dry skin care regimens and contact allergen avoidance. “They will not fully realize benefits of treatment if they continue hot baths or shy away from regular use of their safe emollients, and I aggressively evaluate any suspicion of allergic contact dermatitis with patch testing as well,” Dr. Dao says. “After all, if there is a concomitant allergic contact dermatitis, dupilumab at best may just mask another fully avoidable process and complicate evaluation of improvement attributable to dupilumab therapy.”

Dr. Dao adds that, while dupilumab can be a great option for these patients, it isn’t for everyone. “A big concern I have is if dupilumab becomes first-line treatment for allergic contact dermatitis, or starts being used for mild cases of atopic dermatitis,” Dr. Dao says. “Traditional pursuits of patch testing to identify occult allergic contact allergens and taking time to counsel patients regarding dry skin care should not be forsaken with new biologic treatments for atopic dermatitis.”

**PIPECLE UPDATE**

Monoclonal antibody IL-13 inhibitors lebrikizumab and tralokinumab are in development and early research suggests they’re promising options in the treatment of adults with moderate-to-severe atopic dermatitis. In the case of tralokinumab, research suggests that serum level of dipeptidyl peptidase 4 might be a predictive biomarker for which patients might benefit from tralokinumab therapy, according to Dr. Del Rosso.

“While we are not yet at the level of personalized medicine, targeted therapy is the next step in evolution of our medical treatments. With targeted therapy comes a large responsibility to continually monitor our patients, however, as we never can fully understand the implications of modulating complex signaling pathways,” Dr. Dao says.

**Disclosures**

Dr. Del Rosso is a consultant, speaker, and/or researcher for several companies whose marketed products are in the management of atopic dermatitis or their compounds under development. These include Almirall, Dermira, Galderma, Genentech, Llogic, Baxalta, Leo Pharma, Loxo, Ortho Dermatologics, Pfizer, Pramius, Regeneron, Sanofi-Genzyme, Skinceuticals, Sor NSoma, Sun Pharma, and Taro.

Dr. Dao reports no conflicts of interest on this topic.
Early drug levels may influence treatment response

DAVID OZERI, M.D. | Staff Correspondent

Monitoring drug levels may be a useful tactic for directing the therapeutic strategy in patients with psoriasis, according to a study published in the September issue of *JAMA Dermatology.*

Monoclonal antibodies have shown great efficacy at treating psoriasis and, specifically, this recent study indicates that adequate and early treatment exposure to ustekinumab (Janssen Immunology), which targets IL-12 and IL-23, may positively influence clinical outcome. Researchers found a statistically significant association between early drug levels and six-month Psoriasis Area and Severity Index (PASI) 75 response in patients with psoriasis taking ustekinumab.

Ustekinumab therapy is weight-based with patients >100 kg receiving 90 mg and patients <100 kg receiving 45 mg. It is postulated that treatment failure in patients may be related to sub-therapeutic dosing of this medication. In this study, Teresa Tsakok, M.A., MRCP, and colleagues from the St John’s Institute of Dermatology in London examined the association between drug level and response on the same day the drug level was measured, as well as the association between early drug level and response at six months.

The authors invited all UK adults who fulfilled inclusion criteria for the Biomarkers of Systemic Treatment Outcomes in Psoriasis study, and who were enrolled in the British Association of Dermatologists Biologic and Immunomodulators Register to participate. Clinical response to ustekinumab was assessed longitudinally using PASI scoring. Blood samples were collected between June 2009 and December 2016 to measure levels of ustekinumab and anti-drug antibodies.

The primary endpoint of the study was achieving a PASI 75. The secondary outcomes included a PASI 90% reduction in PASI score from baseline, and a PASI score of 1.5 or less. The association of drug levels and treatment response was calculated using logistic regression models. The cohort analyzed was comprised of 491 subjects, which were mostly male.

In this cohort, 70% of the subjects achieved PASI 75 within a year of starting therapy. There was no clear association between early drug level and response at six months. These patients had higher drug levels on average compared with patients who did not achieve PASI 75.

The key findings of this trial include:

- Early response to ustekinumab was correlated with elevated drug levels. This data may have clinical ramifications as we attempt to better treat patients with refractory disease. Should treatment be introduced with target drug levels to improve response rates?

- There were no antibodies to ustekinumab found in this cohort, which suggests that treatment failure to ustekinumab is not due to immunogenicity.

The take home message is that there may be an association between early drug levels and treatment response. Practically speaking, ustekinumab drug levels are not widely available; therefore, using serum ustekinumab as a treatment target in psoriasis is not possible. However, this study reinforces the importance of using the loading dose when initiating therapy.

While the authors found a statistically significant association between early drug levels and six-month PASI75 response, they noted their “statistical approach did not take into account patient-level pharmacokinetic parameters such as volume of distribution and clearance, nor potential differences in evolution of PASI score over time vs changing drug levels.”

Therefore, they wrote, new research should examine the whole course of response to ustekinumab over time.

References

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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.

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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 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.

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

WARNING: EMBRYO-FETAL TOXICITY
See full Prescribing Information for complete boxed warning.

- ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and 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.

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%), 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.
Utilizing ultrasound (US) may be the best and least invasive method to examine hand joint and tendon inflammation in patients with psoriatic arthritis (PsA), according to a new study.

In the study, conducted by the University of Medicine and Pharmacy of Craiova, Romania, researchers found when musculoskeletal ultrasonography (MUS) is used on PsA patients, physicians are able to thoroughly assess PsA in order to improve the diagnosis, prognosis and possible treatments of the condition.

Between 2016-2018, researchers studied 28 patients with PsA in the Department of Rheumatology of the Emergency Clinical County Hospital of Craiova who exhibited swelling and pain in the small joints of their hands and wrists.

Due, in part, to the lack of evidence using US in patients with PsA, researchers compared their particular study to research examining the use of MUS in rheumatoid arthritis patients.

Across 28 patients, 840 joints were clinically analyzed alongside US. Clinical evaluation results showed 59 joints were tender while 32 joints displayed signs of swelling.

While differentiating between arthritis, enthesopathy and tenosynovitis proved to be difficult at times during clinical assessments, the two-year study proved US was useful in showing the particular pathology that affected joints.

The study also revealed when MUS was utilized, researchers were able to take a deeper look into the affected joints and tendons to identify more problem areas not otherwise known during the clinical examination.

“Apparently normal joints upon clinical examination may present synovial hypertrophy or power Doppler signal using MUS examination, thus proving the utility of MUS in identifying more affected joints,” the authors of the study state.

When MUS was used on PsA patients, researchers found synovial proliferation in 108 of the 840 examined sites, in which four of the 108 identified joints presented grade 1 synovitis, 94 joints with grade 2 and 10 joints with grade 3. The study also identified 280 fingers that exhibited 5.71% dactylitis using MUS.

“Ultrasound has proven its utility in assessing joint and tendon inflammation to a higher extent than clinically expected. It is a safe, inexpensive, non-invasive method, accessible in the majority of hospitals and clinical practice,” according to the authors of the study.

US is not a revolutionary new technology, but according to the results of the study, it offers physicians an easy, non-invasive and inexpensive method to safely examine the extent of a patient’s psoriatic arthritis, and can help them identify problem areas that could otherwise be missed in a typical clinical examination.

References

Comorbidity trends in kids similar to adults

DAVID OZERI, M.D. | Staff Correspondent

Pediatric patients with psoriasis may experience comorbid conditions more frequently than children without the condition, and findings were similar to trends for comorbidities in adults with psoriasis, according to a study published in Pediatric Dermatology.1

Psoriasis impacts the lives of approximately 0.3% of children in the United States,2 and the incidence of psoriasis rises linearly with age reaching 1.3% after puberty.2-4 It is well known that psoriasis carries with it the risk of developing other serious health conditions, but little is known about the prevalence of comorbidities in pediatric psoriasis patients.

Investigators conducted a retrospective cohort study to evaluate the incidence of comorbidities in pediatric patients with psoriasis. They gathered retrospective data from the MarketScan Commercial Claims and Encounters Database between January 1, 2009, and June 30, 2015. The database includes inpatient, outpatient, and outpatient prescription drug information from 190,000,000 unique patients between 1996 and 2017. The information includes detailed cost, use and outcomes data for healthcare services performed in both inpatient and outpatient settings.

Patients aged 4 to 17 years were classified into a psoriasis cohort and a non-psoriasis cohort using administrative claims to confirm diagnosis. Of the 38,430 patients that were included in the study, 7,686 had psoriasis and 30,744 did not. Three relatively healthy patients without psoriasis were paired with every psoriasis patient. Researchers found that, in the psoriasis cohort, the prevalence per 1,000 patients of any comorbidity was 49.05; while the prevalence per 1,000 patients of any comorbidity in the non-psoriasis cohort was 11.94.

Individuals in the psoriasis cohort most commonly experienced Crohn’s disease and psoriatic arthritis; while patients in the non-psoriasis cohort experienced diabetes and serious infections. Individuals in the psoriasis cohort also experienced psychiatric comorbidities at a greater rate than the non-psoriasis cohort (22.64 to 13.4, respectively). Of the psychiatric conditions, individuals with psoriasis were most likely to experience depression (16.91), followed by bipolar disorder (4.94) and anxiety (4.55).

The investigators further examined the psoriasis cohort based on disease severity. Of the patients with psoriasis, 15% were considered moderate-to-severe based on their therapies, which included phototherapy, disease modifying antirheumatic drugs (DMARDs), TNF inhibitors and other biologic therapies. Surprisingly, researchers discovered that patients with moderate-to-severe disease didn’t have a greater incidence of serious infections than patients with mild psoriasis. Further, there was no significant difference between the two subsets regarding the prevalence of other comorbid conditions, such as obesity and psychiatric comorbid conditions, with the exception of anxiety.

The findings of this study reinforce earlier data that indicate an increased prevalence of comorbidities in pediatric patients with psoriasis. But, unlike previous studies, researchers didn’t find an association between hypertension and diabetes in pediatric patients with psoriasis; although, this may be due to the use of claims-based data on ICD-9 coding rather than laboratory data, which was unavailable.

“This descriptive study offers more insight, based on a very large sample size, of the association between psoriasis and comorbidities in pediatric patients,” wrote Amy Paller, M.D., and colleagues in the department of dermatology, Northwestern University Feinberg School of Medicine, Chicago.

Strengths of this study included population size and the method used to compare cohorts. Its retrospective design and dependence on ICD-9 coding rather than laboratory values, however, may have acted as a major limitation. Disease severity was also defined by the treatment modality used to treat patients with the assumption that more treatment means worse disease. This may not have accurately reflected the disease severity of the cohort as patients receiving more therapy could have improved control of their psoriasis, which would reduce their associated comorbid conditions.

The take home message is important: Dermatologists should be vigilant in screening all pediatric psoriasis patients for common comorbidities, including psychiatric disorders, as these patients may be more likely to experience serious, life-altering health conditions without children compared to the cohort of patients who did not have psoriasis.

Investigators found higher incidence rates of certain comorbid conditions in patients with psoriasis compared to the cohort of patients who did not have psoriasis.

Quick Takes

A descriptive, claims-based, retrospective study examined rate of comorbidities in children with psoriasis.

Pediatric patients with psoriasis were matched 1:3 with a cohort of patients who did not have psoriasis.

Investigators found higher incidence rates of certain comorbid conditions in patients with psoriasis compared to the cohort of patients who did not have psoriasis.

References

“Past studies measuring changes in PASI scores have shown more rapid improvement of plaques involving the head and trunk compared to the lower extremities. This subgroup analysis demonstrated a reasonable and sustained response was achieved using halobetasol 0.01% lotion for lesions on the legs.”

Neal Bhatia, M.D., Therapeutics Clinical Research, San Diego

Leg psoriasis improves with topical lotion, study shows

with treatment decisions for patients with disease involving leg lesions, said Neal Bhatia, M.D., director of clinical dermatology at Therapeutics Clinical Research, San Diego, and the lead author of the paper.

At the end of the eight-week treatment period, rates of treatment success and overall treatment success were significantly higher for patients randomized to once-daily treatment with halobetasol 0.01% lotion compared with vehicle-treated controls (P<0.001 for both comparisons).

“Many patients with psoriasis experience stubborn plaques on the legs,” Dr. Bhatia says. “Past studies measuring changes in PASI scores have shown more rapid improvement of plaques involving the head and trunk compared to the lower extremities. This subgroup analysis demonstrated a reasonable and sustained response was achieved using halobetasol 0.01% lotion for lesions on the legs.”

It was encouraging to see that the lotion was effective at improving disease on a larger, hair-bearing area of the skin, he adds.

“Traditionally, a lotion has not been the vehicle of choice for treating psoriasis given perceptions about penetration, but it might be preferred by patients over ointments or foams for use on the lower extremities.”

The analysis of adverse event data from the two phase 3 studies showed there were minimal safety concerns associated with the eight-week treatment course, he says.

“Potent topical corticosteroids are generally approved for use over two to four consecutive weeks because of safety issues,” he explains. “This lower concentration of a potent corticosteroid brings new flexibility and safety for longer treatment duration.”

STUDY DETAILS

The post hoc analysis included data from 234 participants in two multicenter, randomized, double-blind, vehicle-controlled studies. The subjects were randomized 2:1 to once-daily treatment with halobetasol 0.01% lotion or vehicle. Treatment continued for eight weeks and patients were followed for four weeks thereafter.

The efficacy endpoints included treatment success, defined as a ≥2-grade improvement from baseline in individual signs of psoriasis (erythema, plaque elevation, and scaling) and overall treatment success, defined as a ≥2-grade improvement from baseline in the Investigator Global Assessment (IGA) score and a rating of “clear” or “almost clear.” The three psoriasis signs and IGA scores used a 5-point rating scale where 0=none and 4=severe.

To be eligible for enrollment, patients had to have a score ≥2 for all three psoriasis signs, a score of 3 or 4 for at least two of the signs and a total score ≥8. In addition, they were required to have an IGA score of 3 or 4. Eligible patients also had to have an overall body surface area (BSA) ranging from ≥3% to 12%.

“The sample size and methods for assessment used in this study were appropriate for delivering the message about the value of this concentration of halobetasol,” Dr. Bhatia says.

Mean size of the leg target lesion at baseline for the 234 patients was 42.0 cm2; 91% of the randomized patients completed the study. The overall success rates in the halobetasol and control groups were 37.1% and 8.4%, respectively.

Efficacy was also evaluated by calculating an IGA x BSA composite score. Analyses showed that the mean percent change in the composite score was significantly greater in the halobetasol group compared with controls (50.5% vs 13.8%, P<0.001). In addition, a significantly higher proportion of halobetasol-treated patients achieved the composite score cutoff that defines a clinically meaningful effect (≥75% reduction from baseline; 37.7% vs. 7.2%, P<0.001).

Patients also completed the 10-question Dermatology Life Quality Index (DLQI) at baseline and during follow-up. Corresponding with the improvements seen in disease severity, the DLQI results showed that by week 4, the halobetasol-treated patients achieved quality of life improvement that represents a clinically important difference. Mean DLQI score was improved further at week 8 in the halobetasol group, and at both visits, the improvement from baseline was significantly greater than in the control group.

Disclosures

Dr. Bhatia is an advisor and/or investigator for Bausch Health.

References

Nonthermal energy shows promise as Tx for back acne

Early results from the first patients treated for back acne with Nano-Pulse Stimulation (“NPS”, Pulse Biosciences) in a controlled study show that use of this nonthermal energy modality is providing rapid and sustained clearance of inflammatory lesions, reported Mark Nestor, M.D., Ph.D., at the 2019 annual meeting of the American Society for Dermatologic Surgery.

“NPS causes selective reduction of sebaceous gland cells which explains the rationale and the efficacy that is being observed with its use for treatment of acne,” says Dr. Nestor, director for Cosmetic Enhancement and Center for Clinical and Cosmetic Research, Aventura, Fla., and voluntary professor, department of dermatology and cutaneous surgery, University of Miami Miller School of Medicine, Miami. “The study is ongoing. More patients are being enrolled and we are working to optimize the energy level and the technology, as well as exploring the use of new tips that will enable treatment of a larger surface area.”

NPS is performed with a proprietary device (CellFX System, Pulse Biosciences) that uses a sterile treatment tip containing microneedles to deliver a series of timed, ultrashort (nanosecond), high voltage, electrical energy pulses to the target site. The nonthermal energy causes disruption of cellular membranes and internal cell organelles, leading to the activation of pathways that result in regulated cell death. Histological studies have shown that NPS treatment selectively affects cellular structures within the treatment zone, including melanocytes, sebaceous glands and hair follicles, without affecting acellular structures, such as elastic fibers and collagen, or adjacent tissue.

“The melanocytes, however, reappear over time and reach levels comparable to those seen in untreated controls by one month after NPS treatment,” Dr. Nestor says.

In large clinical studies, this technology has demonstrated 90% to 99% efficacy in clearing sebaceous hyperplasia. These incredible results spurred our interest in investigating its use for treating acne,” Dr. Nestor says. “We chose to study acne vulgaris on the back because it is typically challenging to treat and because the back provides a relatively large surface area that allows for an intrapatient control design that compares changes after NPS treatment vs. sham and untreated control sites.”

The study of NPS for back acne is being conducted by Dr. Nestor and Bruce Katz, M.D., clinical professor of dermatology, Icahn School of Medicine at Mount Sinai, and director, Juva Skin & Laser Center, New York. It is comparing the effects of NPS against sham treatment and an untreated control site.

It has a planned enrollment of up to 20 patients and follow-up of 90 days posttreatment.

To be eligible for participation, patients must have a minimum of three areas measuring 7x 7 cm of active acne on the back, each containing at least five inflammatory lesions rated moderate to severe. The lesion count must also be similar across the three areas on the back.

NPS energy titration is performed at the baseline visit. One week later, treatment with NPS or sham is applied to one-half of the designated area, and the remaining section is treated on day 21. Patients return for safety and efficacy evaluations at 30, 60 and 90 days thereafter.

Data are available from six patients who each had at least seven to 10 inflammatory lesions within each of the three target sites on the back. The applied energy dose was already titrated down in this first cohort of patients, but across the dose range studied, benefit was noted by 30 days and has been sustained with follow-up reaching up to eight months.

“Our initial data show an 89% lesion reduction in the treated areas,” Dr. Nestor says. “The durability of the responses is expected based on the theory that NPS would be an effective treatment for acne because it destroys the sebaceous gland.”

Post-inflammatory hyperpigmentation was the only significant side effect observed so far. The hyperpigmentation resolved over time, was greater in patients with a darker skin type (patients with up to Fitzpatrick skin type 4 are eligible for enrollment), and has been minimized as the energy dose was reduced.

Disclosures
Dr. Nestor is a consultant to and receives research grants from Pulse Biosciences.

Data are available from six patients who each had at least seven to 10 inflammatory lesions within each of the three target sites on the back. The applied energy dose was already titrated down in this first cohort of patients, but across the dose range studied, benefit was noted by 30 days and has been sustained with follow-up reaching up to eight months.
Promising new therapies

INGRID TORJESEN | Staff Correspondent

Quick Takes
A first new chemical entity approved for treating acne in many years is likely to be followed by more in coming years, experts say.

Current drug development is focused on targeting inflammation and new vehicles to increase efficacy of existing drugs.

The pipeline includes two topicals: an antiandrogen therapy and a cannabidiol formulation.

Sarecycline is the first new chemical entity approved for treating acne in years and the first antibiotic in four decades. It is likely to be followed by other new drugs, including clascoterone and cannabidiol (CBD) in the coming years, predicts Leon Kiricik, M.D., Icahn School of Medicine at Mount Sinai, New York.

Drug development in acne is currently focused on targeting inflammation and reworking the vehicles of existing active drugs to increase their efficacy and tolerability, he adds in a review of acne treatments published in Cutis.1 Inflammation underlies the pathophysiological characteristics of acne: the proliferation of Cutibacterium acnes (formerly Propionibacterium acnes), increased sebum production with an increase in circulating androgens and faulty keratinization. Research has even indicated that the microcomedone is essentially an inflammatory lesion, the review notes.2

“This realization has clearly influenced the approach to acne treatment, but has not yielded a bevy of new treatments,” says Dr. Kiricik who is also affiliated with Indiana University Medical Center in Indianapolis, Physicians Skin Care in Louisville, Ky., and DermResearch and Skin Sciences, PLLC, Louisville; and Skin Sciences, PLLC, Louisville.

Topical and oral antibiotics are still primarily used to treat acne, along with topical retinoids and benzoyl peroxide, but a better understanding of acne pathophysiology and the role of inflammation has led to insight into the role of existing therapies and to more comprehensive, multi-targeted treatment strategies.

Key takeaways from the review regarding current and future therapies for the management of acne vulgaris:

SARECYCLINE Sarecycline is the first new oral antibiotic approved by the U.S. Food and Drug Administration (FDA) in 40 years. The once-daily formulation is designed to treat inflammatory lesions of nonnodular moderate-to-severe acne vulgaris in patients 9 years and older.

Broad spectrum tetracycline antibiotics have been used to manage acne for several decades but have been associated with an increased risk of antibiotic resistance and gastrointestinal problems, says the review. Sarecycline is a tetracycline, but is considered narrow spectrum, meaning it does not act as strongly against enteric gram-negative bacteria.3

TOPOCAL MINOCYCLINE Systemic minocycline is often prescribed for acne management, but the oral antibiotic comes with potential safety concerns. These concerns include a risk for systemic lupus erythematosus and autoimmune treatment emergent adverse effects, along with gastrointestinal side effects and bluish discoloration, according to the review.4

“Topical application of minocycline for acne would optimize the therapeutic effect while reducing systemic effects,” Dr. Kiricik says. An investigational minocycline foam (FMX101 4%) is being tested and pharmacokinetic studies showed no evidence of minocycline accumulation over the 21 days of application,5 and the foam appeared to be safe and well tolerated in phase 3 trials.6 A similar foam formulation of minocycline (1.5% concentration) has shown benefit for rosacea in phase 3 studies.7

TAZAROTENE Approved in 2012 for patients 12 years and older for the treatment of acne vulgaris, the topical retinol tazarotene was recently relaunched in an aqueous foam formulation to mitigate the potential for skin irritation. The improved tolerability of the foam vehicle is meant to encourage patient compliance and increase satisfaction, according to the review.9

IN THE PIPELINE Two topicals are in the pipeline: an antiandrogen therapy and a cannabidiol formulation.

Researchers are exploring the use of clascoterone cream 1% for the treatment of moderate-to-severe acne in patients 9 years and older. The topical acts locally on androgen receptors in the skin to block the effects of circulating endogenous androgens. It’s well known that androgens influence both sebum production and inflammatory responses within the follicle, which contributes to the development of acne.10

“Antiandrogen therapy would, therefore, inhibit excess sebum production and directly reduce the presence of certain inflammatory mediators in skin. This effect is expected to lead to reduced follicular plugging and a reduction in growth of C. acnes and its inflammatory by-products,” Dr. Kiricik says.

Systemic antiandrogens and hormonal modulation are already used to treat acne successfully in some women, but there are concerns about systemic exposure.11 As clascoterone is applied topically and acts locally on androgen receptors in the skin, no systemic exposure has been seen and preliminary data from phase 2 trials suggest it has the potential to be an effective and well-tolerated formulation.12

Researchers have found that CBD, one of the 113 cannabinoids identified from Cannabis sativa, has anti-inflammatory properties which can prevent the proliferation of sebocytes,13 inhibit human keratinocyte proliferation14 and to possess potent antimicrobial activity against Gram-positive bacteria such as C. acnes.15 A synthetic cannabidiol topical formulation, BTX 1503, is being tested in acne, Dr. Kiricik says.

“Early clinical data confirm both the anti-inflammatory effects of topical BTX 1503 as well as its effects on noninflammatory lesions, with four-week reductions in inflammatory lesion counts similar to what are reported in clinical trials for leading FDA-approved topical therapies in the same time frame,” he says.16

References online bit.ly/promisingnewacnetherapies
Adult, teen acne differ

Hormonal component more likely at play in older females

LISETTE HILTON | Staff Correspondent

Adult acne in women is not related to a specific Cutibacterium acnes (C. acnes) subtype, according to a small study, published recently. Results support the notion that adult female acne should be treated very differently than classic teenage male acne, one expert says. Researchers collected skin samples of inflammatory lesions of female acne patients from 2014 to 2017. They compared C. acnes very differently than classic teenage male acne, one expert says.

The study now we can say for sure that it’s not because it’s a different bacterium,” she says.

This is the first paper to report no link between adult female acne and a specific C. acnes subtype, according to the authors.

“This study reiterates that there is a hormonal component at play rather than a bacterial pathogenesis that dermatologists should consider when treating female adult acne patients,” according to Emmy M. Graber, M.D., founder and director of the Dermatology Institute of Boston and clinical affiliate instructor of dermatology at Northeastern University in Boston. Dr. Graber, who directs the Spironolactone Forum at the American Academy of Dermatology (AAD) each year, is not an author on the JAAD study.

“Adult women oftentimes have a hormonal type of acne that looks so different on the skin than the classic teenage acne. It often has a different pattern on the face. Patients have a different history as to how it flares. Yet it’s seen as caused by bacteria,” Dr. Graber says.

“In clinical practice we see that adult acne in women does not respond to antibiotics as well as the traditional teenage acne, so there are two questions: Is it because it’s a different type of bacteria, or is it because of other factors? I think from the study now we can say for sure that it’s not because it’s a different bacterium,” she says.

Dermatologists should start by asking adult female acne patients key questions during the history taking.

“The history is very important, especially for adult hormonal acne in women because it can flare cyclically and around menstruation,” she says.

Dr. Graber asks female acne patients: Is what I’m seeing today how it typically looks? Is this a good day for your skin? Is this a bad day?

“A lot of time the adult hormonal acne patients will say, it looks different depending on the time of the month,” she says.

Dr. Graber adds, she generally does not target bacteria when she treats adult hormonal acne. Rather she targets hormonal acne triggers and often uses spironolactone in her adult female patients. Spironolactone isn’t an antibiotic and it doesn’t directly impact bacteria. She recommends dermatologists consider spironolactone or birth control pills as first-line treatments, rather than an oral antibacterial agent, for adult hormonal acne.

There is research suggesting spironolactone is efficacious for female acne. Researchers using the comprehensive acne severity scale to analyze spironolactone treatment in 110 women, mean age 27 years, with acne found the majority of women experienced dramatic improvement in acne on their face, chest and back with spironolactone treatment, according to a study published in 2017 in the International Journal of Women’s Dermatology.

When managing these patients, Dr. Graber says it’s important to set realistic expectations about the potential need for long-term treatment.

“I tell patients with adult hormonal acne that we don’t really know when it’s going to end. We don’t have a cure for it, but at some point it seems that it does burn out in adult women,” she says. “We just don’t know when that will be.”

There is a topical spironolactone agent in the pipeline that appears to behave similarly to oral spironolactone. In August, Cassiopea SpA announced that it submitted a New Drug Application to the FDA for marketing approval of clascoterone cream 1%, a topical androgen receptor inhibitor, for acne treatment. Clascoterone 1% cream is in late stage development for acne treatment.

Dermatologists should start by asking adult female acne patients key questions during the history taking.

“There is a hormonal component at play rather than a bacterial pathogenesis that should be considered.”

Quick TAKES

Adult female acne should be treated differently than teenage acne.

There is a hormonal component at play rather than a bacterial pathogenesis that should be considered.

References


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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

• The use of SEYSARA 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).

• Clostridium difficile associated diarrhea (CDAD) 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.

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).
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TOUGH ON ACNE.

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- 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 needed 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 moderate to severe acne vulgaris in patients 9 years of age and older.

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 6 years) may cause permanent discoloration of the teeth (yellow-brown-gray). 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 fibula 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 surgical evaluation should be considered only as indicated [see Warnings and Precautions].

Central Nervous System Effects
Central nervous system side effects including lightheadedness, 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 may disappear after discontinuation of treatment, the possibility for sequelae such as visual loss that may be permanent or severe exists. Women 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 isoretinoin and SEYSARA should be avoided because isoretinoin may cause a systemic retinoid effect which 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 UVAB treatment) while using SEYSARA. If patients need to be outdoors while using SEYSARA, they should wear loose-fitting, long-sleeve clothes 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 that was reported in at least 1% of subjects was nausea, SEYSARA (3.1%) versus placebo (2.0%).

The following 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 isoretinoin 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 from antacids 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 of SEYSARA 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 and 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 skeletal malformations 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 defect, 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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The health-related quality-of-life (HRQoL) impact of centrofacial erythema associated with rosacea correlates positively with erythema severity, according to a recent survey. These results should prompt clinicians to discuss this impact with patients, study authors add.

Previous studies have examined the impact of rosacea on quality of life in a general way, says lead author Hilary Baldwin, M.D. But few, if any, have looked specifically at the impact of erythema in this regard. She is director of the Acne Treatment and Research Center in Morristown, New Jersey.

“There are so many people with rosacea,” says Dr. Baldwin, “and so few of them seeking treatment.” Patients invariably say that rosacea and its erythema impact their lives severely. “Yet they don’t end up doing much about it. We’re having a hard time trying to figure out the disconnect between rosacea being a life-changing event and people not seeking care.”

Perhaps people are unaware that care is available.

Erythema severity mirrors quality-of-life impact

JOHN JESITUS | Staff Correspondent

A web-based survey indicates erythema severity correlates with rosacea’s quality-of-life impact. Patients estimated severity of their erythema using a photographic guide. Authors hope outcome will encourage doctors to proactively discuss impact of rosacea.

Quick TAKES

A web-based survey indicates erythema severity correlates with rosacea’s quality-of-life impact. Patients estimated severity of their erythema using a photographic guide. Authors hope outcome will encourage doctors to proactively discuss impact of rosacea.

Erythema severity continues on page 36

Image: © PalookPook/Stock.Adobe.com

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Researchers are considering a new use for oxymetazoline after results from a recent preclinical trial showed its promise when used in conjunction with a pulsed dye laser (PDL). Until recently, α-1A agonist was typically used as a nasal decongestant that works by reducing the size of dilated blood vessels in the nasal passage. The U.S. Food and Drug Administration, however, approved a topical formulation of oxymetazoline as a treatment for rosacea and other facial erythema diseases in January 2017.

In a preclinical trial, conducted by researchers from the University of California located in Irvine, Calif., investigators found that oxymetazoline, when used with PDL, caused a higher rate of vascular shutdown than a combination of saline and PDL. Researchers began their trial by surgically installing a dorsal window on 20 mice to examine vasoconstriction. The mice were split into four groups. Each group received 10 microliters of saline or oxymetazoline, while only two of the four groups received a combination of PDL and either saline or oxymetazoline. Over the course of seven days, researchers applied saline or oxymetazoline to the epidermal side of the dorsal windows once a day, along with PDL if it was applicable. Brightfield and laser speckle imaging was also utilized to monitor any changes.

The results of the trial showed there was still persistent blood flow in the oxymetazoline-only and saline-only groups. However, researchers found there was a higher rate of vascular shutdown with PDL and oxymetazoline (66.7%) than with PDL and saline (16.7%) — a 50% difference.

In addition, five minutes after oxymetazoline was applied, the venule diameter increased, while the arteriole and venule diameters decreased after 60 minutes of the application. According to the researchers, “an increase in vessel diameter would increase the local volume of hemoglobin, which, in turn, would increase the volumetric heat generation resulting from PDL irradiation. The decrease in arteriole and venule diameter at 60 min may facilitate the ensuing photo-induced coagulation effect.”

While the results of the preclinical trial show promise, clinicians need to determine efficacy, safety of combined protocol in humans.
Rosacea classification system can improve

BOB KRONEMYER | Staff Correspondent

There is still room for improvement to the National Rosacea Society (NRS) Expert Committee’s updated classification schema for rosacea, according to William James, M.D., a professor of dermatology at the University of Pennsylvania in Philadelphia.

The new guidelines, published in 2018, have abandoned the four main subtypes (erythematoleangiectatic [ETR], papulopustular, phymatous and ocular), replacing them with a phenotype system based upon mostly observable findings.

“Shifting from a subtype focus to individual clinical findings or a phenotype classification allows both for better selection of treatment modalities and improved ability to conduct research,” says Dr. James, co-author of a recent clinical review that evaluates the new rosacea classification and its controversies.

“By subtyping, there was unnecessary division of interrelated disease into individual disorders; an individual’s clinical presentation might fall along a spectrum rather than within a discrete box,” the authors write.

“Each manifestation is now approached individually, which allows for more flexibility and better care,” Dr. James tells Dermatology Times. However, he believes refinements should be made in some of the definitions of the clinical characteristics of rosacea, “not only specifying more precisely the features which comprise the diagnostic findings, but also expanding the list of diseases that need to be excluded when making the diagnosis of rosacea. For instance, providing timelines to fixed erythema and flushing, including periorcular sparing in the list of characteristic features, and aiding in assessing how chronic solar damage may be differentiated would be helpful.”

The list of exclusions to the diagnosis has been altered in the new NRS classification system. It lists lupus erythematosus and steroid- and drug-induced rosacea; however, listing seborrheic eczema is confusing, he says.

Dr. James believes the intent is to exclude seborrheic dermatitis, but not atopie or other forms of eczema. Mastocytosis, carcioid, polycythemia vera and dermatomyositis are also not listed.

“The potential for error, due to a lack of specific detail in defining the individual manifestations and inclusion of non-rosacea disease, still persists,” he says.

Dr. James believes the new phenotype classification system fails to improve on the separation of the polar ends of the rosacea spectrum. More emphasis about the characteristics of those patients at the phymatous pole needs to be emphasized, he says. Recognizing these differences in the basic skin types will allow for better patient education about their prognosis.

“For example, I believe a smooth-skinned, bright red-faced woman will not eventuate into a patient with a large phymatous nose and large pustules and nodules,” he says. “I have not seen evidence that the inflammatory cascades now being recognized as abnormal in such a patient, referred to in the NRS paper as subclinical neuroinflammation, leads to phymatous change. Because most patients with this manifestation are men, I wonder if it is not more influenced by androgens than inflammation.”

Despite Dr. James’ reservations about the NRS Expert Committee’s update, “there are some excellent changes,” he says. “I applaud that the committee has worked to improve the prior classification system, which I also criticized. While I still would like to see more specificity, the old system was much too general.”

Dr. James believes most dermatologists will embrace the update. “An update was long overdue. I am hopeful that with the pace of progress of new knowledge and new therapeutics that the updates will be more frequent.”

Quick TAKES

Newer rosacea guidelines replaced four main subtypes with phenotype system.

Shift allows for better treatment selection and improved research.

Refinements in clinical characteristic definitions may still be necessary.

Dr. James reports no relevant financial disclosures.

References

In a preclinical trial...investigators found that oxymetazoline, when used with PDL, caused a higher rate of vascular shutdown than a combination of saline and PDL.”

Kristen M. Kelly, M.D., et al., University of California, Irvine, Calif.

Oxymetazoline plus PDL from page 34

Erythema severity mirrors quality-of-life impact from page 33

Dr. Baldwin

Limitations of the study include the small sample size of the trial, and the fact that mice have different skin and vasculature dorsals than humans, according to the investigators.

References


Disclosures

Dr. Baldwin is an investigator for Allergan.
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Nearly half of all advanced melanoma patients carry the BRAF mutation, and testing for it is a key precision medicine tool to evaluate optimal treatment options, according to Novartis.

The company began a collaboration mid-2019 with Quest Diagnostics to offer free genetic mutation testing for patients with stage III or stage IV melanoma. The Know Now BRAF program provides kits that perform BRAF V600E/K mutation testing. All costs for the testing are covered for eligible patients regardless of whether they test positive or negative for the mutation.

WHY DO DERMS NEED TO KNOW?
Dermatologists usually follow stage I and II melanoma patients monitoring for possible recurrence. But they often become part of a multidisciplinary team, co-managing melanoma patients with medical or surgical oncologists once patients progress to stage III or IV, according to Sancy Leachman, M.D., Ph.D., professor and chair of dermatology and director of the Melanoma and Skin Cancer Program at Oregon Health and Science University.

State-of-the-art dermatologic care for melanoma includes management through often toxic treatments and survivorship; following people who need regular skincare and screening even if they have stage III or stage IV disease. And dermatologists should remain actively engaged in and knowledgeable about care for these patients, including treatment, drug reactions and long-term follow-up needs, according to Dr. Leachman.

"Dermatologists need to be actively and intellectually-engaged in the multi-disciplinary team. We aren’t responsible for administering systemic melanoma therapies, but knowing the BRAF status of a patient’s tumor allows us to understand which treatment options are available for these patients. It also helps dermatologists to be better prepared for drug reactions or side effects," Dr. Leachman says.
A new systemic medication option offers promising results for patients with high-risk squamous cell carcinoma for whom surgery has not worked, according to Chrysalyne Schmults, M.D., associate professor of dermatology at Harvard Medical School and vice chair of surgical oncology at Brigham and Women’s Hospital dermatology department, Boston. An intravenous, programmed death receptor-1 inhibitor drug called cemiplimab (Libtayo, Sanofi and Regeneron Pharmaceuticals) could offer a long-term halt of disease for a significant number of patients with this disease.

“We’ve gone for so many years, in fact, the entire history of squamous cell carcinoma without an FDA-approved treatment for people who fail surgery and radiation,” she says. “We’ve been in dire need of a good treatment option for when patients become unresectable. Now, we have a drug with a 50% response rate, and that’s a big improvement for these patients.”

This therapeutic advancement is significant, she says, because squamous cell carcinoma kills approximately the same number of patients annually as melanoma. But, until now, patients have only received an EGFR antagonist or platinum-based chemotherapy after an unsuccessful surgery or radiation. Efficacy for these options is short term and only occurs in roughly 20% of patients.

For appropriate patients, the cemiplimab dose is 350mg every three weeks. Each infusion session lasts 30 minutes. Although the dermatologist is likely the first provider to identify and diagnose squamous cell carcinoma, a medical oncologist will typically administer the medication in the United States, Dr. Schmults says. Still, it is important for dermatologists to be aware of the drug and to become familiar with its impact and side effects, especially since these drugs will likely be combined in the future with drugs that will be injected directly into tumors by dermatologists.

Few dermatology centers nationwide are equipped to deliver cemiplimab, but providers who wish to assume a more active role with the medication could pursue treatment privileges at an infusion center with appropriate safeguards and nursing support for intravenous systemic therapy, she says. Additional education is currently available via the European Academy of Dermatologic Oncology.

“I suggest that dermatologists who are interested in learning more about cemiplimab and participating in this aspect of patient care should talk to people in their community who have experience with immunotherapy,” she says.

Alongside its 50% efficacy rate, cemiplimab does produce a 50% response rate is a big improvement for patients with cutaneous SCC. Familiarity with this and other drugs is important for dermatologists because understanding the impact, side effects, and how to combine existing and future treatments with intravenous systemic therapies will be vital to patient management.
We’ve been in dire need of a good treatment option for when patients become unresectable. Now, we have a drug with a 50% response rate, and that’s a big improvement for these patients.”

Chrysalyn Schmults, M.D., Brigham and Women’s Hospital, Boston

Some side effects. The most common are rash, fatigue and diarrhea. Less common, but still possible, are pneumonitis, colitis, and hepatitis, occurring in approximately 2.4%, 0.9%, and 2.1% of patients, respectively. For most of these cases, Dr. Schmults says, oral prednisone is the main treatment. When these problems occur, cemiplimab is sometimes discontinued temporarily. In more severe cases, though, it may be discontinued permanently and hospitalization may be needed. The American Society of Clinical Oncology has published guidelines for how to handle immune-related toxicities of immunotherapy drugs like cemiplimab.

Most of cemiplimab’s side-effects are due to overstimulation of the immune system, which can impact any organ in the body. And, in some cases, the effect can be permanent. For example, Dr. Schmults says, the medication frequently affects the thyroid, producing either hypothyroidism, treated with levothyroxine, or hyperthyroidism. A patient could also develop permanent diabetes if autoimmune pancreatitis is present.

Dr. Schmults cautions that cemiplimab is not safe for all patients with squamous cell carcinoma. If a patient has received an organ transplant or has an immune-mediated disease, such as severe lupus, this medication may not be an option. In those cases, a dermatologist should consult with other members of the patient’s healthcare team to determine the best path forward for treatment.

Ultimately, Dr. Schmults says, it’s important for dermatologists to be aware of this treatment option when surgery fails. Knowing how to combine existing and future treatments with intravenous systemic therapies, particularly cemiplimab, will be vital to patient management.

“As providers, dermatologists should know this drug approach is available for patients who have exhausted the other curative methods of surgery and radiotherapy,” she says. “There really isn’t another option right now."

Know Now program aids physicians with selecting optimal therapies

Common cutaneous side effects of BRAF inhibitors in the treatment of metastatic melanoma with BRAF V600E mutation include rash, photosensitivity, hand-foot skin reaction, alopecia, pruritis and more, according to a review published in 2016 in *Dermatology Research and Practice*.

Dermatologists are most likely to recommend free BRAF mutation testing through the Know Now program, according to Dr. Leachman, if a dermatology exam demonstrates that a stage I or II melanoma patient has developed progressive disease, or when a survivor, released from surgical or medical oncologic care, exhibits recurrence.

**WHAT THE TESTING DOES AND DOESN’T DO**

BRAF inhibitors target the common and specific metastatic melanoma mutation V-600E. This test allows you to know if patients’ tumors have this mutation and will be more likely to respond to a BRAF inhibitor. If they don’t have that mutation, a different class of drug or immunotherapy would be more appropriate,” Dr. Leachman says. “It’s vital that we have that genetic information, but the problem is that not every insurance company wants to pay, and not every patient has insurance.”

The Know Now Testing Program takes care of cost concerns for testing. And the downstream benefit for patients and research quality is that this particular test might help standardize testing. Standardization can lead to quality assurance and more comparable results for research studies, according to Dr. Leachman.

But it is important to recognize that the test in the Know Now Testing Program is not a germline test that predicts risk of developing a melanoma or familial risk for melanoma, according to Dr. Leachman. This is a somatic genetic test that determines whether a melanoma has developed a BRAF mutation as part of the progression to malignancy.

“This test is testing the tumor — the melanoma, itself. And it only tests for BRAF,” she says. “It’s a very targeted genetic test for a very specific gene that has an important purpose, which is to direct the therapy that the patient is going to get. It is a precision medicine tool.”

**Disclosures**

Dr. Leachman reports ties with Myriad Genetic Laboratories and CastleBioSciences (early Access Programs); PolioTherapeutics (advisory board); DermDetect (Business Associate Agreement); Merck (advisory board); and Vertex has asked Dr. Leachman to be a member of its clinical advisory board but she has not yet attended a board meeting.

**References**

A preparatory webinar which approximates the image segment of the current Core Practical/Certifying Examination of the American Board of Dermatology. Open to all 1st, 2nd and 3rd year residents, as well as, those dermatologists preparing for the Maintenance of Certification (MOC).

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Chicago-based dermatologist Jeffrey Hsu, M.D., is injecting fat into the face for volumization. He can harvest and reinject in two steps in the exam room using a technology that eliminates multiple steps, an operating room and time, as well as the need for patients to undergo general anesthesia.

There is a need for facial volumization options, says Dr. Hsu, clinical assistant professor of dermatology, University of Illinois, Champaign, Ill. "Physicians know the importance of using fillers to volumize the face for rejuvenating and enhancing appearance," he says.

The downsides of synthetic dermal fillers are that they’re temporary and can quickly become cost prohibitive. Patients are demanding alternatives that are more organic and natural.

Fat as a filler makes sense to patients because it’s natural, long-lasting and can be more economical than synthetic fillers in the long term, according to Dr. Hsu. But traditional fat harvesting methods, from mechanical liposuction to ultrasound and laser-based methods, typically are intended to destroy fat rather than keep it viable. And keeping fat cells intact and alive is key to the longevity and success of fat transfer, according to Dr. Hsu.

Dr. Hsu uses BeautiFill (Alma Lasers), an FDA-cleared technology that combines tumescent infiltration, laser energy to loosen harvested fat, aspiration and a process for successfully separating viable fat cells for re-injection.

“The harvesting process, once you become comfortable with it, can be a matter of 10 or 15 minutes. That’s the biggest hurdle for some dermatologists,” he says.

BeautiFill includes a 1470 nm laser that is embedded in the device’s suction canula. The low and gentle laser energy loosens fat cells for removal with much less effort and trauma, according to Dr. Hsu. The machine then processes the fat, separating the pure fat from the liquid. A study on BeautiFill found 95% of fat cells were intact and unharmed after processing.

“That was verified by a study that had 10 patients that had split body work. Half the body was treated with traditional mechanical liposuction and half the body with BeautiFill. The researchers found that the fat cells on the BeautiFill side had approximately 95% survival,” Dr. Hsu says.

Fat cell survival on the mechanical lipo side was an average 80%, according to Dr. Hsu. But average survival doesn’t tell the whole story, he says. “… it’s the difference in variation, as well,” Dr. Hsu says. “In the mechanical side, the survival was as low as 50% in two cases. In the BeautiFill side, the lowest survival was 90%. So not only did BeautiFill give better average survival but [a] much more consistent result, as well.”

At the end of the BeautiFill procedure the dermatologist injects pure fat that is contained in one cannister.

“I typically harvest the fat from the abdomen or the flanks or thighs and then place it into the face. In many other practices, they’re using the same technique to enhance the buttocks or enhance the breasts,” he says.

Among Dr. Hsu’s tips for best outcomes: Dermatologists and other providers should educate themselves. “As much as this device can simplify the procedure for you, it still takes a basic understanding of the anatomy and of pharmacology, given that we do have to anesthetize the harvest sites,” he says.

Facial fat grafting also does not entirely replace antiaging.

Fat grafting offers a facial volumizing option to differentiate practice. All-in-one technology may simplify the process and deliver reliable results. Studies are underway to look at the longevity with BeautiFill fat grafting.

**Quick Takes**

**Fat transfer complements filler armamentarium**

**New option for facial volume**

Exam room fat transfer complements filler armamentarium.

LISETTE HILTON | Staff Correspondent
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CBD products may be beneficial, but more research required

From Page 1

it’s still the Wild West. For the most part, they don’t reach the standards we’re accustomed to in dermatology.”

To date, most CBD products haven’t provided much therapeutic effect, Dr. Milane says. In most instances, they don’t contain enough CBD to be significantly impactful. And, there’s no existing data identifying the best CBD concentration.

Additionally, CBD is most often included in oil solutions or emulsions, and the molecules respond exactly like oil when it touches water — it clumps up, making it impossible for CBD to penetrate the skin. Greenway Therapeutix is actively trying to solve this problem, he says.

“Barrier penetration is an issue,” he says. “We’ve put a lot of nanotechnology science into making CBD component penetration in these products a lot more feasible.”

So far, they’ve been successful in reducing the symptoms of atopic dermatitis and acne. Clinical testing is still underway, he says.

How it works

The human body is naturally equipped to respond to CBD through its endocannabinoid system, Dr. Milane explains. With two major receptor sites — CB1 and CB2 — cannabinoids bind to it much like a lock-and-key. When the system activates, it plays a key role in regulating inflammation, pain perception, immunity, neuropathy and metabolism. Specifically, the CB2 receptor reduces the concentration of pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-alpha.

Of all cannabinoids, he says, CBD has been the most thoroughly investigated for its therapeutic potential. Current data points to high anti-inflammatory properties on multiple skin targets, including keratinocytes, dermal immune cells, sensory neurons, sebocytes and hair follicles. Additionally, clinical observations have revealed CBD reduces redness and itching within 10 minutes of application. It’s these impacts that are critical in treating skin disorders, Dr. Milane says.

“Inflammation and inflammatory disorders are a significant part of dermatological disease,” he says. “If we can find potential in a different pathway other than steroids, which are heavily used for anti-inflammatory properties, then it would be a huge advantage for us.”

Unlike steroids, existing research shows CBD is safe for all populations — children, adolescents, adults, and the elderly. It can be used on almost any body area, and it doesn’t cause any side effects that limit how long it can be used to treat skin conditions.

OBSERVED EFFICACY

While current products on the market don’t provide a satisfactory therapeutic effect, initial clinical trials show CBD may be a safe, effective treatment for skin disorders, says Daniel Siegel, M.D., M.S., clinical dermatology professor at State University of New York Downstate Medical Center. According to Greenway Therapeutix testing, the most substantial improvements appeared in reducing atopic dermatitis symptoms.

“With atopic dermatitis, the associated itch goes away within minutes of application, and the lesions disappear within a day or two of once or twice-daily use,” says Dr. Siegel, who has worked with Dr. Milane on Greenway Therapeutix endeavors. “It does seem to have a beneficial effect. Think of it as a drug to replace steroids in places you don’t want to use steroids.”

Alongside the company’s nanotechnology option, atopic dermatitis is also treated with a 2% topical adelmidrol emulsion. A 3% cannabis seed topical cream has been used to reduce inflammation and sebocyte production in patients with acne. And, a 3% CBD topical has been applied to reduce inflammation and suppress keratinocyte proliferation in patients with psoriasis.

BOTTOM LINE

In a market with few high-standard CBD options, Dr. Siegel says, providers should educate themselves even if they don’t intend to recommend the products.

“My advice to providers who strive to maintain the highest standard of ethics is to be aware there aren’t any products out there right now that really deliver the expected effect,” Dr. Siegel says. “If you use topical CBD products now, you’ll likely be unimpressed.”

The market could change within a year, he says. Meanwhile, he cautions providers to examine patients who use these products for contact dermatitis.

Despite the lack of high-quality products, Dr. Milane says, providers should expect an increasing number of patients to inquire about them.

“Patients are going to the doctor and asking for CBD, and most doctors don’t know anything about it because they haven’t had any medical training or they don’t know the pathways these products impact,” he says. “We’re hoping with a higher standard for products and with increasing science behind them, we can shift the paradigm and bring something natural into this world that can be a powerful alternative for some of these diseases we don’t have solutions for.”

Disclosures

Dr. Milane is the president and CEO of Greenway Therapeutix, which is dedicated to the research and development of medical-grade cannabidiol therapeutic products using nanotechnology. Dr. Siegel is CSO and chair, Scientific Advisory Board for Greenway Therapeutix.

My advice to providers who strive to maintain the highest standard of ethics is to be aware there aren’t any products out there right now that really deliver

Daniel Siegel, M.D., M.S.,
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**Vertical lip line treatment**

**LISETTE HILTON | Staff Correspondent**

Traditional treatment options using neurotoxins or filler injections to treat vertical lip lines are far from optimal, says dermatologist Jeffrey S. Dover, M.D., who frequently confronts this challenge at his Chestnut Hill, Mass., practice.

“Upper lip lines — vertical lip lines — are very difficult to treat, and when you survey most women, it’s near the top of their hit parade of things they dislike the most,” Dr. Dover says.

There is an approach, which he and his practice colleagues refined, that uses laser-assisted delivery of topical poly-L-lactic acid (PLLA) to treat upper lip rhytides, which appears safe and effective according to a paper published in *Dermatologic Surgery*.

Dr. Dover, who was senior author, tells *DermatologyTimes* his practice has since performed nearly 100 cases using the approach, and he is a believer.

Clinicians most commonly use either neuromodulators or fillers to treat upper lip lines. Dr. Dover says. Using neuromodulators tends to be the simplest and least expensive of today’s options.

This approach aims to gently weaken the patient’s pucker and is used because it addresses one of the root causes of the lip lines. But good outcomes can be tricky, he says.

“If you use too high a dose, the patient won’t be able to speak or drink from a straw or even out of a glass,” Dr. Dover says. “A very low dose works, but it takes months to see improvement. We believe that if it’s done on a somewhat regular basis, every three or four months, you can stop the natural progression. We believe that it takes months to see improvement. We believe that if it’s done on a somewhat regular basis, every three or four months, you can stop the natural progression, and slowly but surely the lines start to soften.”

Another option is to gently fill the upper lip lines with a soft hyaluronic acid (HA) filler. Dr. Dover will typically use Volbella (Juvéderm, Allergan), Restylane Silk (Galderma) or Belotero (Merz).

Fillers work, but it’s painful. It often causes swelling and bruising and it doesn’t last that long,” he says. “It works well in conjunction with neuromodulators and when lip lines are fine, but it’s doing nothing to actually reverse the cause. That’s why we started to look at other potential ways to improve these lines and to improve photaging around the mouth.”

In a study published June 2014 in *Dermatologic Surgery*, researchers showed they could treat atrophic scars by using fractional ablative laser resurfacing by making thousands of small holes in the skin and applying PLLA, to where the liquid filler entered the holes.

“This was one of the earliest studies in the field now called laser-assisted drug delivery,” Dr. Dover says.

Dr. Dover, along with Omer Ibrahim, M.D., the practice fellow, and Kenneth A. Arndt, M.D., a partner at SkinCare Physicians where Dr. Dover practices, secured funding from the American Society for Dermatologic Surgery for a study using laser-assisted drug delivery on vertical lip lines through the Fredric S. Brandt MD Innovations in Aesthetics grant. The researchers studied 10 women who received fractional ablative laser-assisted topical PLLA (Sculptra, Galderma) delivery to treat their vertical lip lines. Patients had three bi-monthly treatments of low-density fractional carbon dioxide laser followed by topical application of PLLA suspension.

“We treated just the upper lip. We only used topical anesthesia. The procedure was very well tolerated and there was no pain at the procedure. Healing time was, on average, five to six days. There was redness, a bit of swelling and light crust. Simple wound care started the day after with topical anesthesia. The procedure was very well tolerated and there was no pain at the procedure. Healing time was, on average, five to six days. There was redness, a bit of swelling and light crust. Simple wound care started the day after.”

Another benefit to his offering BeautiFill, according to Dr. Hsu, is that it separates his practice from the overabundance of physicians and non-physicians who offer only dermal fillers.

“We’re all busy providing fillers. I feel the injectables have been sort of commoditized by not just doctors in other specialties but by many non-physicians and aestheticians, such that these days it’s very difficult to stand out as a provider of injectable services,” he says. “This is a great procedure for dermatologists to learn and provide because then we establish ourselves as the premier provider of facial volumization. Many other specialties and especially non-physicians will not provide this service given their lack of education and lack of expertise.”

Dr. Hsu, who is not a researcher for BeautiFill but is a speaker and advisor for Alma Lasers, says studies are underway to look at the longevity of results from BeautiFill fat grafting.

**References**


**Disclosures**

Dr. Dover receives research support from and has consulting agreements with Lumenis and Solta (BeautiFill).

**Discussion**

Fat transfer complements filler armamentarium FROM PAGE 42

The need for synthetic dermal fillers. Facial fat grafting is ideal for patients who have more advanced facial atrophy and would require so much filler every year that it becomes cost prohibitive.

“By using fat, we can establish a foundation for the entire face upon which you can finesse the result with fillers. I think it works better hand in hand, in a complementary manner. I don’t think it replaces fillers,” he says.

There’s another benefit to his offering BeautiFill, according to Dr. Hsu. It separates his practice from the overabundance of physicians and non-physicians who offer only dermal fillers.

“We’re all busy providing fillers. I feel the injectables have been sort of commoditized by not just doctors in other specialties but by many non-physicians and aestheticians, such that these days it’s very difficult to stand out as a provider of injectable services,” he says. “This is a great procedure for dermatologists to learn and provide because then we establish ourselves as the premier provider of facial volumization. Many other specialties and especially non-physicians will not provide this service given their lack of education and lack of expertise.”

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there is a possibility that patients may receive ineffective or minimally active forms of medication from suboptimal compounded medicines, if they are willing to take the chance, it may be considered unnecessarily paternalistic to resist allowing them the option to seek treatment.

Moreover, it should be acknowledged that there are certain common medical conditions for which a formalic online telemedicine consultation is especially well-suited and for which custom-compounded medications can provide better safety and efficacy compared to labeled and commercially available products. This is particularly applicable to the field of dermatology, an area of medicine with considerable historic experience with compounding.

In fact, with respect to dermatology, beyond providing an alternative to certain outrageously priced legacy prescription medications, this model simultaneously addresses the additional pressing issue of access to care. A 2019 report by the “Greater Access for Patients Partnership” (GAPP) highlighted the dire state of dermatology appointment wait times in the U.S. With the average wait time having increased from 22 days in 2009 to over 32 days in 2017. The report emphasized that delays in treatment for common skin conditions can result in interference in daily life for 61% of patients, and anxiety regarding their skin condition worsening for 58% of patients.

In the technological and societal climate in which we live, every industry is feeling the pressure of commercial competitors who are seeking to leverage newly developed technologies to disrupt stagnant practice models with agile, convenient and personalized alternatives. These pressures are becoming especially acute in the field of medicine where increasing numbers of high-deductible insurance plans with restrictive drug formularies are causing patients to pay more out of pocket for ever more expensive medicines.

While one of the last to fall, medicine is no longer somehow “off limits.” We believe the ripple effect of the growth in compounding is in its infancy. Rules, laws and regulations have and will likely continue to emerge to address egregious safety concerns. But make no mistake, compounding is necessary and benefits millions of patients. It is also generally considered safe (especially for topical). Given the overwhelming utility to patients, the trend may prove difficult to stop. Both figuratively and literally, for an increasingly unhealthy patient care and pharmaceutical model, it seems to be exactly what the doctor has ordered.

Usama Syed is a dermatology resident at the Icahn School of Medicine at Mount Sinai. He received his medical degree from Imperial College London, United Kingdom and a first class honors bachelor of sciences from the Imperial College London Business School. Prior to dermatology residency, he completed a year-long postdoctoral research fellowship at Mount Sinai Hospital where he focused on the use of mobile applications in healthcare.

Raymond Miller is a partner and vice chair of the Health Sciences Department of Pepper Hamilton LLP, resident in the Pittsburgh office. A registered patent attorney, Mr. Miller focuses his practice on identifying, protecting, securing and maximizing the value of clients’ intellectual property. Mr. Miller is a member of the American Association for the Advancement of Science, the Association of University Technology Managers, Inc. and the American Intellectual Property Law Association.

Brandon Kirsch is a dermatologist and lawyer. In addition to a busy clinical practice, Dr. Kirsch is the President and Chief Executive Officer of ClearRx.com, a dermatology-focused online platform providing personalized prescriptions to treat skin conditions. Dr. Kirsch was previously an Assistant Clinical Professor of Dermatology at the University of Colorado and Medical Director and Vice President of Clinical Development at Bridjell Biotech, Inc.

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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 on the front cover and Brief Summary of Prescribing Information, including Boxed WARNING, inside the front cover.