ACNE

3D imaging measures acne scars

Ilya Petrou, M.D. | Staff Correspondent

A novel 3D imaging technique may help dermatologists accurately measure and grade the severity of acne scars as well as the aesthetic improvements achieved following scar therapy in atrophic acne scar patients, according to a recent study presented at the American Society for Dermatologic Surgery (ASDS) Virtual Annual Meeting.

There is a dire need for improvement in the clinical tools we have to more accurately assess acne scar severity and better visualize the depth of lesions as well as the improvements achieved during scar treatment in order to help optimize therapeutic options and treatment outcomes for our acne patients,” says Hyemin Pomerantz, M.D., dermatologist in the Greater Boston area, who presented on this topic during ASDS’s virtual annual event in October.

It can also be challenging for providers to accurately count the many lesions that are present and follow their individual progression of improvement following therapy.

3D imaging measures acne scars CONTINUES ON PAGE 20 ▶

ATOPIC DERMATITIS

Tralokinumab demonstrates long-term success in phase 3

John Jesitus | Staff Correspondent

In the ECZTRA 1 and 2 trials, most patients treated with tralokinumab (Leo Pharma) maintained 75% reductions in Eczema Area and Severity Index (EASI) scores for one year. Moreover, these trials answer key real-world questions regarding tralokinumab’s mechanism of action and dosing frequency.

The positive results herald a new potential treatment for atopic dermatitis (AD), a condition which previously has limited options available, says principal investigator Eric L. Simpson, M.D., professor of dermatology at Oregon Health & Science University, Portland.

The studies also demonstrate that targeting interleukin (IL)-13 alone suffices to make clinically relevant improvement in AD.

“We weren’t able to make that conclusion with previous therapies,” he says.

TRALOKINUMAB CONTINUES ON PAGE 32 ▶

Telederm learning curve

John Jesitus | Staff Correspondent

Before COVID-19, dermatologists ranked among the least likely physicians to use telemedicine. An international survey of 1,392 physicians showed that, pre-pandemic, dermatologists saw only 5% of their patients via telemedicine, the lowest percentage among the eight specialties surveyed.

However, pandemic-related decreases in patient volume averaging 50% by April and the clear need to find ways to provide non-emergency healthcare services when state governments mandated office closures made the shift from in-office to online practice a priority, if not a necessity.

TELEDERM CONTINUES ON PAGE 58 ▶
For the treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older

HUMIRA is the only FDA-approved treatment for your HS patients

Results Your HS Patients Can See

MODERATE/STAGE II
Actual HUMIRA-treated patient achieving HiSCR

Before

After

HiSCR is at least a 50% reduction in total abscess and inflammatory nodule count, with no increase in abscesses and draining fistulas relative to baseline

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.

DATA LIMITATIONS
• Since PIONEER I did not reach statistical significance at the first key secondary endpoint, all endpoints in this integrated analysis cannot be regarded as statistically significant

Integrated analysis of PIONEER I and PIONEER II through 12 weeks

Flare: ≥25% increase in AN count and an absolute increase of ≥2 relative to baseline

HiSCR is at least a 50% reduction in total abscess and inflammatory nodule count, with no increase in abscesses and draining fistulas relative to baseline

PIONEER I (N=307) and II (N=326) were 36-week, randomized, double-blind, placebo-controlled clinical trials in adult patients with moderate to severe HS on HUMIRA 40-mg weekly (after initial doses).

22% (of 100) patients who were withdrawn from HUMIRA after 12 weeks experienced flare.

PIONEER I control=placebo.

PIONEER II control=placebo +/- antibiotic.

• In the PIONEER clinical trials, (PIONEER I) and (PIONEER II) of HUMIRA-treated adult patients achieved HiSCR at Week 12 (primary endpoint), vs 26% and 28% on placebo, respectively

( PIONEER I) and ( PIONEER II) 42% 59%

Photos courtesy of Dr. Marc Bourcier

Results for HS.com
Clinically Meaningful Improvement (HiSCR) at Week 12

- In the PIONEER clinical trials, 42% (PIONEER I) and 59% (PIONEER II) of HUMIRA-treated adult patients achieved HiSCR at Week 12 (primary endpoint), vs 26% and 28% on placebo, respectively4

HUMIRA also has flare data available for HS

OCCURRENCE OF FLARE THROUGH 3 MONTHS5

Pre-specified Other Secondary Endpoint in Period A

- 88% of patients on HUMIRA experienced no flares
- 65% control

HUMIRA-treated patients n=316 for HUMIRA EW
Control patients n=317 for control

Integrated analysis of PIONEER I and PIONEER II through 12 weeks

Flare: ≥25% increase in AN count and an absolute increase of ≥2 relative to baseline1,5

DATA LIMITATIONS

- Since PIONEER I did not reach statistical significance at the first key secondary endpoint, all endpoints in this integrated analysis cannot be regarded as statistically significant4,5

Safety Considerations1 (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.

To learn more, please go to ResultsforHS.com
In HUMIRA clinical trials, there was an approximate 3-fold higher rate of non-melanoma skin cancer (NMSC) compared to placebo. In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to those treated with other immunosuppressants. These malignancies, including lymphoma and other malignancies, some fatal, have been reported in patients treated with TNF blockers. The risk of malignancies, including lymphoma and other malignancies, may be higher in children and adolescent patients treated with TNF blockers, including HUMIRA. Lymphoma and other malignancies, some fatal, have been reported in patients treated with TNF blockers. In patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

 tnf-blocker therapy. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.

- 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.

- 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.

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

- 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.

- Consider stopping HUMIRA if significant hematologic abnormalities occur.

- 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.

- Patients on HUMIRA should not receive live vaccines. Vitamin supplements, 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 newborn 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.

- If an infant is exposed in utero to adalimumab, consider prior to vaccinating (live or live-attenuated) exposed infants.

- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

- 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.

- Obtain a baseline hepatitis B surface antigen (HBsAg) test before starting adalimumab therapy. If HBsAg is positive, discontinue adalimumab and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

- 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.

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In HUMIRA clinical trials, there was an approximate 3-fold higher rate of MALIGNANCY compared to control patients (2% of placebo-treated patients and 0.5% of HUMIRA-treated patients). Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare and fatal complication in patients with inflammatory diseases, have been reported. HSTCL has mainly occurred in patients with psoriasis or psoriatic arthritis, who have lost response to or were intolerant to TNF blockers. The rate of HSTCL was higher in patients who have lost response to biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers compared to control patients. In controlled trials, the rate of HSTCL in patients treated with HUMIRA was similar to that of placebo. The overall incidence of HSTCL in the trials was lower than other potential malignancies reported in postmarketing studies. It is unknown whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with another immunosuppressant. In a post-marketing study, approximately half of the postmarketing cases of malignancies in patients treated with TNF blockers (or TNF blockers in combination with other immunosuppressants) occurred in patients who were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies

In the controlled parts of clinical trials of all TNF blockers, including HUMIRA, cases of malignancies have been observed among TNF blocker-treated adult patients compared to control adult patients. During the controlled clinical trials, the most commonly reported malignancies observed in patients treated with HUMIRA and placebo were basal and squamous cell skin cancers. Squamous cell skin cancer was observed in 0.1% (1/774) of placebo-treated patients and 0.7% (5/747) of HUMIRA-treated patients. In the postmarketing experience, the rate of squamous cell skin cancer in patients treated with HUMIRA was 0.2% (3/1419) of patients treated with HUMIRA. In patients treated with HUMIRA, the rate of non-melanoma skin cancer was 0.1% (1/774) of placebo-treated patients and 0.5% (4/747) of HUMIRA-treated patients in controlled trials. There was a higher incidence of squamous cell skin cancers in patients who have had prolonged immunosuppressant therapy. These patients also have higher rates of vascular disease and prior malignancies.

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NMSC: Squamous and basal cell skin cancers were reported in patients treated with HUMIRA who had a history of skin cancer. Approximately 2% of patients who were treated with HUMIRA for psoriasis developed skin cancer during the controlled trials, including 2731 HUMIRA -treated patients versus 1594 controls; 12,111 HUMIRA -treated patients versus 6100 controls; and 18,782 HUMIRA -treated patients versus 10,631 controls. HUMIRA-induced skin cancer was usually squamous cell skin cancer. All cases of skin cancer were treated with surgery. No deaths were reported. In the postmarketing experience, the rate of squamous cell skin cancer in patients treated with HUMIRA was 0.2% (3/1419) of patients treated with HUMIRA. In patients treated with HUMIRA, the rate of non-melanoma skin cancer was 0.1% (1/774) of placebo-treated patients and 0.5% (4/747) of HUMIRA-treated patients in controlled trials. There was a higher incidence of squamous cell skin cancers in patients who have had prolonged immunosuppressant therapy. These patients also have higher rates of vascular disease and prior malignancies.

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Juvenile Idiopathic Arthritis Clinical Studies

In the pediatric studies, the most commonly reported adverse reactions in patients treated with HUMIRA were injection site pain and injection site reaction (6% and 4% respectively). Approximately 6% of patients developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity.

Other Adverse Reactions

In clinical studies with patients with JIA, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were similar to those reported in placebo-treated patients.

In an open-label study of 152 pediatric patients with JIA treated with HUMIRA, 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of meningitis, viral gastroenteritis, and varicella. No apparent association between antibody development and safety was observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD in adults. No apparent relationship between adalimumab exposure and maternal or fetal toxicity was observed. In an embryo-fetal perinatal development study in cynomolgus monkeys, adalimumab was administered to pregnant monkeys during the third trimester of pregnancy. Adalimumab was actively transferred across the placentae during the third trimester of pregnancy and may affect the developing fetus. The effects of adalimumab on the developing human fetus are unknown. The estimated background risk of major birth defects and miscarriage for the generalized population is 2 to 4% based on multiple studies and surveillance data. In one study, the overall rate of major birth defects was 1.1% in 1,930 infants of mothers treated with HUMIRA during pregnancy. No overall difference in the rate of major birth defects was observed in infants of women treated with HUMIRA compared to those of women treated with placebo.

Adverse Reactions

In clinical trials with patients with RA, the safety profile with adalimumab was generally similar to that observed in placebo-treated patients. Most patients received 40 mg HUMIRA every other week. No overall differences in effectiveness were observed between these classes of patients and placebo.

The data described below reflect exposure to HUMIRA in 2,147 patients, including 1,036 patients treated for 6 months or longer, 500 patients treated for 1 year or longer, and 96 patients treated for 2 years or longer. Among the patients treated for 6 months or longer, the mean duration of treatment was 21 months. Among those treated for 1 year or longer, the mean duration of treatment was 14 months. Among those treated for 2 years or longer, the mean duration of treatment was 36 months.

Lactation

Limited data from case reports in the published literature describe the presence of adalimumab in human milk. There is no evidence that adalimumab is secreted in quantities that would produce adverse effects in the breastfed infant.

In utero

Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect the developing fetus. The effects of adalimumab on the developing human fetus are unknown. The estimated background risk of major birth defects and miscarriage for the generalized population is 2 to 4% based on multiple studies and surveillance data. In one study, the overall rate of major birth defects was 1.1% in 1,930 infants of mothers treated with HUMIRA during pregnancy. No overall difference in the rate of major birth defects was observed in infants of women treated with HUMIRA compared to those of women treated with placebo.

Postmarketing Experience

In patients treated with HUMIRA, the type and frequency of adverse events are similar to those observed in placebo-treated patients, with the exception of infection. In clinical trials with patients with JIA, approximately 6% of patients developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity.

Warnings and Precautions, Adverse Reactions

The safety profile of adalimumab in pediatric patients was generally consistent with the safety profile observed in adult patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA).

Pediatric Use

Pediatric studies of adalimumab have been conducted in pediatric patients 6 years of age or older. Adalimumab is not approved for the treatment of any pediatric indication.

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In a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years) with moderate to severe plaque psoriasis, the safety profile for subjects with PsA treated with HUMIRA was similar to that of subjects with PsA treated with placebo. The most commonly reported adverse reactions in patients treated with HUMIRA were upper respiratory tract infection and nasopharyngitis.

The effect of adalimumab on the development of new schizophrenia in patients treated with adalimumab for rheumatoid arthritis (RA) and psoriasis has not been evaluated in clinical trials.

In the JIA studies, the most commonly reported adverse events were upper respiratory tract infection and nasopharyngitis. Injection site pain and injection site reaction were also commonly reported by pediatric patients treated with adalimumab. No new onset of serious adverse events attributable to adalimumab occurred with adalimumab in RA, PsA, or AS was observed. Among the patients treated for 6 months or longer, injection site reaction was reported in 2.2% of patients who received placebo and in 2.1% of patients who received adalimumab.

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Adapting to meet the challenges of COVID-19

by MIKE HENNESSY, SR

THE CORONAVIRUS disease 2019 (COVID-19) pandemic continues to present challenges and as influenza season arrives, the practice of dermatology is pushing forward. As I write this, the 2020 Fall Clinical (FC2020) Dermatology Conference was getting set to kick off, joining the ranks of the American Society for Dermatologic Surgery (ASDS) and many professional organizations that have met the unique circumstances of 2020 head-on with adaptation and innovation. Although the FC2020 and ASDS organizers were unable to hold this year’s meetings in person, the meeting planners gathered their visitors in a unique digital space instead. Online this month, we present a comprehensive recap of the ASDS meeting, which was held Oct. 9-11, 2020. We discuss a range of topics, from nuances that influence the neuromodulator decision, to melenoma in situ, to abobotulinumtoxinA for oily foreheads. The COVID-19 pandemic has also brought increased attention to telehealth services and their importance in serving patients unable to have in-person visits with their health care providers. In a recent episode of our recently-launched podcast, the Cutaneous Connection, Michael Sherling, M.D., who is a practicing dermatologist and chief medical and strategy officer at Modernizing Medicine, discusses the recent rise in telemedicine use in dermatology, the benefits and detriments, as well as the future for the industry.

You can stay on top of the latest developments in dermatology on our daily news website at dermatologytimes.com. Follow us on social media channels, and through our e-newsletters to assure your practice is prepared to prosper in these challenging times.

MIKE HENNESSY, SR, is CHAIRMAN AND FOUNDER OF DERMATOLOGY TIMES’ PARENT COMPANY, MJH LIFE SCIENCES.
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3D imaging measures acne scars

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"HITECH violations can lead to civil or criminal liabilities."

**HIPAA, Covid-19 and jail**

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

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

Dr. Derm had been an associate in a large multi-physician dermatology practice for over a decade. Ultimately, he and his other physician associates decided that it is in the best interest of the practice if he leaves the practice. There are no contractile issues of concern. Dr. Derm was to leave as of January 1. He is upset about his termination but simply finishes his days seeing patients and fulfilling his duties.

The dermatology group has a sophisticated electronic medical record (EMR) system. There is full access to all relevant office materials from any computer anywhere in the world. Dr. Derm’s access should have been terminated on January 1 but was not terminated until February 1.

During the month after that, he should not have had access to any medical records. Out of curiosity, Dr. Derm signs into the system and downloads medical records of some of his former associates. He finds out that one of his former associates tested positive for COVID-19 (albeit he was asymptomatic) and continued to work without notifying anybody in the office.

Dr. Derm is perplexed as to whether to report his associate to both the state medical board and/or a variety of legal entities. He is not aware that anybody contracted COVID-19 from the associate.

Three months later, his former associates become aware of what Dr. Derm did and wish to sue Dr. Derm for a Health Insurance Portability and Accountability Act (HIPAA) violation. He contends that he did nothing improper. Now he decides to report the former office for potentially exposing patients to COVID-19.

Where does Dr. Derm legally stand? The former associates contend that the medical records are part of a HIPAA-protected environment and information is only available on a need-to-know basis. If Dr. Derm had no official business pertaining to a file (he was no longer a practice associate), then he did not “need to know”. Healthcare professionals must consider HIPAA to be such a protected environment.

The Health Information Technology for Economic and Clinical Health (HITECH) Act, originally passed in 2009, was a regulatory measure introduced in anticipation of the sudden rise in the volume of healthcare practices adopting electronic health records (EHR). Violations of the HITECH regulations can lead to civil or criminal liabilities. The simple explanation for these rules is to understand that the HIPAA Privacy Rules lay down the standards that should be followed to become HIPAA-compliant. But it is the HITECH Act Rules that elaborate on the criticality of following these norms and lay down enforcement, accountability, penalty and persecution-related guidelines for those involved in sharing or accessing personal health information.

The purpose of HITECH is to:

1. Define penalties imposed on healthcare professionals found guilty of HIPAA Privacy Rule violations.

2. Ensure that access to medical data in the form of EHRs becomes a national standard for storing/accessing patient information.

3. Lay down accountability clauses and define penalties incurred on HIPAA-violating business associates.

4. Introduce strict standards related to the notifications of patients whose personal health information has been violated.

HITECH stipulates that unauthorized access to patient records can lead to jail-time. This has already happened. File snooping out of curiosity is not considered authorized access. There was no “need to know” for Dr. Derm. Accessing records of a neighbor, child’s teacher or friends without authorization can lead to legal difficulties for a physician or any provider within that practice. The COVID-19 information, although certainly a major issue for the practice, is a distraction in this HIPAA-associated case. Dr. Derm is guilty of a HIPAA violation.

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The former associates became aware of what Dr. Derm did and wish to sue Dr. Derm for a Health Insurance Portability and Accountability Act (HIPAA) violation. He contends that he did nothing improper. Now he decides to report the former office for potentially exposing patients to COVID-19.

Where does Dr. Derm legally stand? The former associates contend that the medical records are part of a HIPAA-protected environment and information is only available on a need-to-know basis. If Dr. Derm had no official business pertaining to a file (he was no longer a practice associate), then he did not “need to know”. Healthcare professionals must consider HIPAA to be such a protected environment.

The Health Information Technology for Economic and Clinical Health (HITECH) Act, originally passed in 2009, was a regulatory measure introduced in anticipation of the sudden rise in the volume of healthcare practices adopting electronic health records (EHR). Violations of the HITECH regulations can lead to civil or criminal liabilities. The simple explanation for these rules is to understand that the HIPAA Privacy Rules lay down the standards that should be followed to become HIPAA-compliant. But it is the HITECH Act Rules that elaborate on the criticality of following these norms and lay down enforcement, accountability, penalty and persecution-related guidelines for those involved in sharing or accessing personal health information.

The purpose of HITECH is to:

1. Define penalties imposed on healthcare professionals found guilty of HIPAA Privacy Rule violations.

2. Ensure that access to medical data in the form of EHRs becomes a national standard for storing/accessing patient information.

3. Lay down accountability clauses and define penalties incurred on HIPAA-violating business associates.

4. Introduce strict standards related to the notifications of patients whose personal health information has been violated.

HITECH stipulates that unauthorized access to patient records can lead to jail-time. This has already happened. File snooping out of curiosity is not considered authorized access. There was no “need to know” for Dr. Derm. Accessing records of a neighbor, child’s teacher or friends without authorization can lead to legal difficulties for a physician or any provider within that practice. The COVID-19 information, although certainly a major issue for the practice, is a distraction in this HIPAA-associated case. Dr. Derm is guilty of a HIPAA violation.
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“The skin should never be clean of all organisms, but it is important that it is clean of all pathogenic organisms.”

Cleansing Challenges

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

Q. How clean is clean?
This is an important question because the skin is never perfectly devoid of microorganisms and thus is always dirty. Microorganisms are the constituents of the microbiome, which represents the interface between the body and the external world. The skin contains over 100 species of bacteria with a population of 1 million microorganisms per square centimeter. The organisms present in the normal human microbiome include: Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteriodetes (6.3%). While there might be concern the presence of these organisms represents unclean skin, these organisms actually keep the skin clear of infection.

The skin surface is actually a daily war zone for microorganism survival. The organisms that touch the skin surface consuming sebum will live with survival based on access to nutrition. If the skin is colonized with nonpathogenic organisms, there is no nutrition for pathogenic organisms. If the skin is devoid of bacteria, it is unhealthy. Cleansing can remove beneficial organisms. But the natural microbiome returns fairly rapidly after cleansing, controlled by the immune status of the individual.

The purpose of hand washing is not to remove the entire microbiome, but rather to remove transient pathogenic organisms. For example, you may shake hands with a Methicillin-resistant Staphylococcus aureus (MRSA) carrier who has just rubbed their nose with the palm of their hand and then transferred the organism to your hand during the hand shake. MRSA is not part of your microbiome, but could become part of your microbiome under appropriate conditions. Washing your hands removes this transient pathogenic organism before you, too, become infected or a MRSA carrier. Thus, hand washing is important to maintain a healthy microbiome, but not intended to remove all bacteria from the hands.

Q. What are some of the new microbiome concepts in cleansing?
A new claim appearing on a number of cleanser products is “microbiome friendly.” What exactly does this mean? Not much. This is a clever marketing claim that has no required substantiation. In theory, it means the cleanser does not modify the healthy natural microbiome. This is good, but most cleansers sold OTC for hand washing will allow re-establishment of the natural microbiome rapidly. So this claim does not add much to the current market.

Another interesting marketing concept in marketing is the addition of substances to cleansers that promote the growth of bacteria. These substances are known as prebiotics. Oral prebiotics are nondigestible food materials, such as wheat bran, that can be broken down by gut bacteria into sugars, providing a food source for gut bacteria. On the skin, the addition of nondigestible materials, such as inulin, to cleansers to provide a food source for skin surface bacteria. This use of prebiotics is a little challenging as cleansers have short contact with the skin and the inulin would need to deposit on the skin surface to have an effect.
The health care industry in the United States added 75,000 jobs in August but is still down from February before the beginning of the COVID-19 coronavirus pandemic.

According to an employment summary produced by the US Bureau of Labor Statistics, there was more than 27,000 new jobs added in physicians’ offices, more than 22,000 in dentists’ offices, more than 14,000 in hospitals, and more than 12,000 in home health care services.

Meanwhile, nursing homes and residential care facilities saw a loss in jobs of about 14,000, the summary says.

Between education and health care, which are lumped together in the analysis, there was an increase of 147,000 jobs, but both industries are still down 1.5 million jobs from February before the COVID-19 coronavirus pandemic.

These numbers are a boon to the industry, which saw massive issues caused by the pandemic such as personal protective equipment shortages, mandates limiting nonessential medical procedures, stay-at-home and shelter-in-place orders, and a general fear of infection among patients.

In weekly surveys performed by the Larry A. Greene Center and the Primary Care Collaborative, physicians expressed great fear for the future of their practices. In April, 47% of respondents said they were unsure if they would have enough cash to stay open and 85% said they had seen a dramatic decrease in patient volume during the pandemic.

In late-August, 89% of respondents said they were confident in the ability of their practice to stay open for the next 4 weeks, while 44% said they were receiving financial support through federal programs.

While the monetary situation seems to be improving, physicians are still feeling the stress of the pandemic with 56% of respondents in the late-August survey saying their level of strain are at a 4 or a 5 on a 5-point scale.

The most recent jobs report shows an increase in health care jobs, but the numbers are still down.

BY KEITH A. REYNOLDS

BY THE NUMBERS

PERCENT OF RESPONDENTS SAID THEY WERE CONFIDENT IN THE ABILITY OF THEIR PRACTICE TO STAY OPEN FOR THE NEXT 4 WEEKS.

89%
Beauty & the Bacteria
An Exploration into the World of the Skin Microbiome

In this new educational docuseries, hosted by geneticist Thomas M. Hitchcock, PhD, we will take you on a journey inside the world of the skin microbiome.

Through this journey you will appreciate the entangled relationship between our skin and the microbes living on and in it—and how that affects our lives. Featuring special appearances by a number of leading U.S. dermatologists, the series will guide the audience through the basics of what the skin microbiome actually is and why it is critical to the health of our skin.

Watch new episodes here:
crownlaboratories.com/microbiome
INDICATIONS AND USAGE
AMZEEQ® (minocycline) topical foam, 4% is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older.

Limitations of Use: This formulation of minocycline 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, AMZEEQ should be used only as indicated.

IMPORTANT SAFETY INFORMATION
Contraindications: Persons who have shown hypersensitivity to any of the tetracyclines or any other ingredient in AMZEEQ.

Warnings and Precautions
Flammability: The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

AMZEEQ is a topical foam. While systemic absorption of AMZEEQ is low, and serious adverse reactions were not seen in clinical studies, the following adverse reactions associated with oral minocycline should be considered:

- Teratogenic effects, inhibition of bone growth & permanent tooth discoloration: Use during the 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) and reversible inhibition of bone growth.
- Clostridium difficile associated diarrhea (CDAD): If CDAD occurs, discontinue AMZEEQ.
- Hepatotoxicity & metabolic effects: If renal impairment exists or if liver injury suspected, discontinue AMZEEQ.
- Central nervous system effects: Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.
- Intracranial hypertension: Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue AMZEEQ immediately if symptoms occur.
- Autoimmune syndromes: Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue AMZEEQ immediately if symptoms occur.

IMPORTANT SAFETY INFORMATION (cont.)

Adverse Reactions:
- Hypersensitivity reactions:
  - Discontinue AMZEEQ immediately if symptoms occur.

- Superinfection:
  - Overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ.

- Discoloration of organs, tissue hyperpigmentation:
  - Permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth.
  - Tissue hyperpigmentation:
    - including nails, bone, skin, eyes, thyroid, visceral and childhood up to the age of 8 years may cause permanent tooth discoloration:

- Intracranial hypertension:
  - Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue AMZEEQ immediately if symptoms occur.

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On August 27, 2020, the U.S. FDA approved clascoterone 1% cream (Winlevi; Cassiopea) for the treatment of acne in patients 12 years and older.¹

Clascoterone cream 1% is a first-in-class topical acne treatment that targets the androgen receptors in the skin. The last FDA approval of an acne drug with a new mechanism of action occurred nearly 40 years ago.¹

Clascoterone cream is applied as a thin layer to the affected areas twice daily; avoiding contact with eyes, mouth, and mucous membranes.

The approval is based on data from two clinical trials (CB-03-01/25 and CB-03-01/26), in which clascoterone cream 1% demonstrated a reduction in acne lesions after 12 weeks of treatment. The two trials were identically designed, double-blind, placebo-controlled studies enrolling a total of 1,440 patients nine years or older. Treatment success was defined as an Investigator’s Global Assessment (IGA) score of 0 or 1, and a 2-grade or greater improvement from baseline and absolute change from baseline in noninflammatory and inflammatory lesion counts at week 12.²

At week 12, treatment success rates in CB-03-01/25 and CB-03-01/26 with clascoterone cream 1% were 18.4% (point estimate, 2.3; 95% CI, 1.4-3.8; \( P < .001 \)) versus 9.0% and 6.5% with placebo, respectively. At week 12, in both CB-03-01/25 and CB-03-01/26, treatment with clascoterone cream 1% resulted in a significant reduction in absolute noninflammatory lesions from baseline to \(-19.4\% \) versus \(-9.9\% \) and \(-6.5\% \) with placebo, respectively.²

Overall, clascoterone cream 1% was well tolerated and demonstrated similar safety profile to placebo. The most common adverse events in studies were nasopharyngitis, headache, and oropharyngeal pain.²

“The approval of Winlevi is an exciting breakthrough in acne treatment. This game-changing topical drug offers a non-antibiotic approach to people with acne, by targeting the androgen receptors directly in the skin. It fills a longstanding gap in acne therapy,” says Michael Gold, M.D., investigator and medical director, Gold Skin Care Center and Tennessee Clinical Research Center. “After 40 years, it provides a much-anticipated, complementary new approach to treat acne.”¹

According to Cassiopea, clascoterone cream 1% is expected to be available early in 2021.¹

References:
THE FIRST AND ONLY TOPICAL MINOCYCLINE FOR ACNE
FOR YOUR PATIENTS WITH INFLAMMATORY LESIONS OF MODERATE TO SEVERE ACNE VULGARIS.

The minocycline you know and trust.¹
- In large, 12-week trials, Amzeeq demonstrated an improvement vs. vehicle foam in both inflammatory lesions and IGA scores.¹*¹
- The most commonly reported adverse reaction was headache (3%).¹²

The tolerability of a gentle foam.¹
- Proprietary oil-based foam vehicle contains natural moisturizing ingredients without drying agents like ethyl alcohol.¹²⁺

The innovation you’ve been waiting for.
- Molecule Stabilizing Technology (MST)™ enables minocycline to be placed into a lipophilic vehicle for stable topical delivery.⁴,⁵

IMPORTANT SAFETY INFORMATION (cont.)

- Photosensitivity: Patients should minimize or avoid exposure to natural or artificial sunlight while using AMZEEQ. Advise patients to discontinue treatment with AMZEEQ at the first evidence of sunburn.
- Hypersensitivity reactions: Discontinue AMZEEQ immediately if symptoms of anaphylaxis, serious skin reactions, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome occur.
- Tissue hyperpigmentation: Discoloration of organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves.
- Superinfection: Overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

Adverse Reactions: The most common adverse reaction reported during clinical trials of AMZEEQ was headache.

* Coprimary endpoints at Week 12 were: Absolute change from baseline in inflammatory lesion count and IGA endpoint success. IGA success was defined as an IGA score of 0 or 1 (clear or almost clear), and at least a 2-grade improvement (decrease). IGA = Investigator’s Global Assessment. 2481 patients were included if they had 20-50 inflammatory lesions (papules, pustules, nodules) and 25-100 noninflammatory lesions (open, closed comedones) and an IGA score on a 6-point scale of moderate or severe (grade 3 or 4).
† Amzeeq 4% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol, and propellants (butane + isobutane + propane).


See Brief Summary of Prescribing Information for AMZEEQ on following pages.
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AMZEEQ® (minocycline) topical foam, 4%
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION. PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATION
AMZEEQ is indicated for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older.

Limitations of Use: This formulation of minocycline 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, AMZEEQ should be used only as indicated.

CONTRAINDICATIONS
This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any other ingredients within AMZEEQ.

WARNINGS AND PRECAUTIONS
- **Flammability:** The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).
- **Teratogenic Effects:** Minocycline, like other tetracycline-class drugs, may induce bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.
- **Tooth Discoloration:** The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, childhood up to age 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline drugs. Use of tetracycline drugs is not recommended during tooth development. The safety and effectiveness of AMZEEQ have not been established in pediatric patients less than 9 years of age.
- **Inhibition of Bone Growth:** 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. The safety and effectiveness of AMZEEQ have not been established in patients less than 9 years of age. Results of animal studies indicate that oral 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 orally early in pregnancy.
- **Clostridium difficile Associated Diarrhea:** Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require surgical treatment. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
- **Hepatotoxicity:** Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use in the treatment of acne.
- **Metabolic Effects:** The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, high serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidos. Renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.
- **Central Nervous System Effects:** Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
- **Intracranial Hypertension:** Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of III are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concurrent use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, postmarket pharmacologic evaluation is warranted. Use of intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.
- **Autoimmune Syndromes:** Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have been reported shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including AMZEEQ.
- **Photosensitivity:** Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although AMZEEQ did not induce photosensitivity or phototoxicity in humans, caution should be exercised in patients with a history of photosensitivity. Photosensitivity reactions in human dermatologic studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UV A/B treatment) while using minocycline. If patients need to be outdoors while using AMZEEQ, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with AMZEEQ at the first evidence of sunburn.
- **Serious Skin/Hypersensitivity Reaction:** Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing. The diagnosis of drug reactions with eosinophilia and systemic symptoms (DRESS) syndrome requires a high index of suspicion and may be difficult to establish in some cases. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue AMZEEQ immediately.
- **Tissue Hyperpigmentation:** Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclera and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.
- **Development of Drug-Resistant Bacteria:** AMZEEQ has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using AMZEEQ; therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of AMZEEQ, it should be used only as indicated.
- **Superinfection/Potential for Microbial Overgrowth:** Use of AMZEEQ may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

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. In a randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied AMZEEQ or vehicle once daily for 12 weeks. A total of 1,156 subjects were treated with AMZEEQ and 1,058 with vehicle. The majority of subjects were White (74%) and female (60%). Approximately 34% were Hispanic/Latino and 49% were younger than 18 years of age.
- **The most common adverse reaction reported by >21% of subjects treated with AMZEEQ and more frequently than in subjects treated with vehicle was
Findings from a recent case series study show that on average patients being treated with isotretinoin (Absorica, Sun Pharmaceutical Industries; Amnesteem, Mylan Pharmaceuticals; Claravis, Teva Generics; Myorisan, Akron, Inc.; Zenatane, Reddy’s Laboratories) for moderate-to-severe acne achieve 50% improvement in their quality of life compared to baseline within two months and can expect four-to-five-fold improvement over the full course of treatment.

“Isotretinoin is widely accepted as the most effective treatment for acne. What patients really want to know is how quickly and to what degree are they going to see improvement after starting isotretinoin? We used a validated quality of life measure to better understand this question,” says Aaron M. Secrest, M.D., PhD., vice chair of Business Strategy for Dermatology and an assistant professor in the Departments of Dermatology and Population Health Sciences at the University of Utah.

Secrest and his fellow investigators designed a longitudinal, retrospective case series study to assess mean Skindex-16 scores over time among patients with moderate-to-severe acne receiving isotretinoin treatment. Skindex-16 data for 57 consecutive patients being treated with isotretinoin were collected at monthly visits and evaluated between November 23, 2016 and January 22, 2019. Investigations compared continuous variables using quantile regression. Multivariable linear mixed models evaluated mean (95% confidence interval) score trajectory over time. Skindex-16 scores were normalized to a 0-100 scale (0 meaning no effect and 100 meaning maximal effect) for the emotional, symptomatic and functional aspects of having skin disease as well as an overall score, according to the investigators.

Fifty-seven patients (31 [54.4 %] males), with median [interquartile range] age of 17.2 [15.9-18.1] years) in this case series study completed the Skindex-16 at baseline and at least once during follow-up. “Skindex-16 scores were similar by sex but worse with increasing age,” says Secrest. “Emotional impact was more bothersome to patients with acne requiring isotretinoin treatment than either symptoms or functioning.”

According to the data, improvements in overall and emotional domain scores exceeded 50% by month two of receiving isotretinoin treatment (e.g., overall scores decreased from 39.4 to 17.5 by month two, a decrease of 22.0; \( P < .001 \)). Qualitatively, Skindex-16 scores reached their lowest point between months three and five; at month 4, overall Skindex-16 scores showed a 4.4-fold improvement (from 39.4 at baseline to 8.9; \( P < .001 \)) and emotional domain scores demonstrated a 4.8-fold improvement (from 57.7 at baseline to 11.9; \( P < .001 \)).

“In our findings, patients perceived rapid and significant improvements in how acne affects their quality of life, especially emotional improvements,” says Secrest.

“Acne is a common dermatologic condition and significantly affects psychosocial health and quality of life. An international task force recommended routine use of quality-of-life measures for clinic visits associated with acne management, but this has yet to translate into clinical practice,” adds Secrest. “This study shows the potential of routine administration of quality of life measures to assess patient care in dermatology.”

**Disclosure:**

There are no relevant disclosures.

**Reference:**


**Quick Takes**

| Results were similar by gender, worse with increasing age |
| Quality of life could play role in assessing acne patient care |
| Skindex-16 provides normalized scores for the emotional, symptomatic, and functional aspects of having skin disease |

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**Results suggest four-to-five-fold improvement versus baseline over full treatment course.**

MARY SCOVIAK | Managing Editor

“Emotional impact was more bothersome to patients with acne requiring isotretinoin treatment than either symptoms or functioning.”

Aaron M. Secrest, M.D., PhD., vice chair of Business Strategy for Dermatology and an assistant professor in the Departments of Dermatology and Population Health Sciences at the University of Utah.

**Treatment improves QOL for patients with acne**
headache, which was reported in 3% of subjects treated with AMZEEQ and 2% of subjects treated with vehicle. Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, dryness, hyperpigmentation, skin peeling and itching. The active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with AMZEEQ as follows (mild, moderate, severe): erythema (14.2%, 1.5%, 0%), dryness (6.8%, 0.6%, 0%), hyperpigmentation (12.4%, 2.8%, 0.1%), skin peeling (3.2%, 0.2%, 0%), and itching (3.1%, 0.8%, 0.1%). Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with acne. Local tolerability signs and symptoms occurred in similar frequency and severity as subjects treated with the vehicle component of AMZEEQ. In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment), frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

**DRUG INTERACTIONS**

- **Anticoagulants:** Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
- **Penicillin:** Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.
- **Drug/Laboratory Test Interactions:** False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** Risk Summary: Available data with AMZEEQ use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of AMZEEQ in humans is low following once daily topical administration of AMZEEQ for 21 days. Because of low systemic exposure, it is not expected that maternal use of AMZEEQ will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with AMZEEQ. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during the period of organogenesis induced skeletal malformations in fetuses at systemic exposures of 750 and 500 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of AMZEEQ (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
- **Data/Animal Data:** Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetuses. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (750 and 500 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (250 times the systemic exposure at the MRHD based on AUC comparison).
- **Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (650 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).
- **Lactation:** Risk Summary: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with AMZEEQ.

**Pediatric Use:** The safety and effectiveness of AMZEEQ have been established in pediatric patients 9 years of age and older for the treatment of inflammatory lesions of non-nodulopustular acne vulgaris. Use of AMZEEQ for this indication is supported by three adequate and well-controlled 12-week trials in patients 9 years of age and older; two of the trials included a 40-week open-label extension. Additional data was obtained from a 7-day open-label safety and pharmacokinetics study conducted in 20 patients 10 years to less than 17 years of age with acne vulgaris. A total of 686 subjects 9 years of age and older received AMZEEQ in these clinical trials. Safety and effectiveness for this indication have not been established in pediatric patients less than 9 years of age. The use of oral tetracycline drugs during tooth development below the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and inhibition of bone growth.

**Geriatric Use:** Clinical studies of AMZEEQ did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

**NONCLINICAL TOXICOLOGY**

- **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dose levels up to 200 mg/kg/day, minocycline hydrochloride was associated in both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dose levels up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females. Minocycline was not mutagenic in vitro in a bacterial reverse mutation (Ames test) or CHN/GPT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.

- **Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (10,000 times the systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (3,800 or 10,000 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis. Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshaped heads, and abnormal flagella.

**HANDLING:** Allow the can to warm to room temperature before first use. Shake can well before use.

**WARNING:** Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).

For more information, including the FDA-approved Prescribing Information, go to www.amzqee.com or call 1-844-375-3673.

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Atrophic acne scars are notoriously challenging to treat and, as such, aesthetic improvements following scar therapy are typically scrutinized for visible, measurable improvements before patients are willing to undergo the necessary repeated treatments.

“Acne scar therapy is usually not a one-off treatment and the vast majority of patients will typically undergo multiple procedures to achieve cosmetic improvement of their acne scars,” Dr. Pomerantz adds.

Dr. Pomerantz and Roy G. Geronemus, MD, Director of the Laser & Skin Surgery Center of New York investigated the reliability of a novel 3D high-resolution, stereoscopic optical imaging system (Cherry Imaging, Cherry Imaging, Ltd), as an alternative to traditional grading systems for evaluating acne scars.

Similar to a GPS system, the innovative device uses a stereoscopic technology to lock-on and measure precise 3D coordinates of the targeted area. Akin to facial mapping, the system creates an image of the face upon which the exact placement and measurement parameters of the acne scars are superimposed. According to Dr. Pomerantz, it takes approximately two minutes to scan the entire face and another six minutes to develop the facial mapping image, sparing much valuable time for the operator and patients alike.

Three operators scanned the subjects’ faces at two different times. Image software calculated the volume of atrophic acne scars and index volume (volume normalized by surface area of acne scars) on the forehead and left and right cheeks. ECCA grading was recorded by a dermatologist. A two-way Analysis of Variance (ANOVA) test was used to determine intraclass correlation coefficient (ICC) among the three operators to examine inter-rater reliability and ICC at two different times for each operator to examine intra-rater reliability. The volume from the 3D imaging and ECCA scores were also correlated.

Results showed that the volume and index volume of atrophic acne scars on the forehead, left cheek and right cheek, respectively, were consistent independent of operators (ICC range 0.72 to 0.92). The ICC of volume and index volume of the scars on the areas of the forehead, left and right cheeks combined was 0.88 and 0.89, respectively. Intra-rater reliability was consistent with average ICCs of the three operators showing 0.95 for atrophic acne scar volume and 0.90 for index volume. Data also showed that Pearson correlation with ECCA scores were 0.22 and 0.48 for volume and index volume, respectively.

One of the main advantages of this grading system is that it does not rely on the clinical experience of the evaluator, Dr. Pomerantz notes.

“The procedure could also be easily relegated to office staff as it is non-invasive and standardized to eliminate any subjectivity in evaluation,” says Dr. Pomerantz. “Moreover, it also precisely gives you the total volume of acne scars in the face, which is something more tangible that patients can better understand effects of their treatment course.”

Atrophic acne scars are notoriously challenging to treat and, as such, aesthetic improvements following scar therapy are typically scrutinized for visible, measurable improvements before patients are willing to undergo the necessary repeated treatments.

“Acne scar therapy is usually not a one-off treatment and the vast majority of patients will typically undergo multiple procedures to achieve cosmetic improvement of their acne scars,” Dr. Pomerantz adds.

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There is a gap in measuring the progress of a number of dermatologic conditions during a patient’s therapeutic course, and lesions in 3D configuration like scars and skin laxity are challenging to measure and quantify, notes Dr. Pomerantz.

“This system offers clinicians and their patients an opportunity to accurately and objectively discuss standardized images and results from treatment, instead of viewing before and after treatment images that can be interpreted differently because of subjectivity,” she says. “Having an easy-to-use 3D modality at our disposal to quickly quantify the therapeutic outcomes in our patients is the future of state-of-the-art acne scar therapy.”

Hyemin Pomerantz, M.D., Boston.

Objective 3D measurements enable dermatologists and patients to track progress over the course of treatment, not just before and after.

Quick TAKES

Stereo 3D technology locks on and measures precise 3D coordinates to create standardized images that eliminate subjectivity in evaluation, reports consistent results, independent of operator, making it possible for office staff to perform the noninvasive procedure.

Objective 3D measurements enable dermatologists and patients to track progress over the course of treatment, not just before and after.

"There is a dire need for improvement in the clinical tools we have to more accurately assess acne scar severity..."
New vehicles improve tolerability, acceptability

JOHN JESITUS | Staff Correspondent

A long with new prescription ingredients, patients with acne and rosacea are benefiting from new vehicles designed to improve tolerability and cosmetic acceptability.

“We’ve had many new vehicle innovations leading to improved delivery and cosmetic acceptability of existing active agents — mostly for retinoids and antimicrobials,” says Diane S. Berson, M.D. She is an associate professor of dermatology at Weill Medical College of Cornell University and an assistant attending dermatologist at New York-Presbyterian Hospital.

Tretinoin 0.05% lotion and tazarotene 0.045% lotion both use a polymeric micronized emulsion that localizes delivery to penetrate follicles. Both lotions also use the same sorbitol-based humectant vehicle, she says.

Minocycline foam 4% incorporates a molecule-stabilizing technology in a soluble, triglyceride-based vehicle without surfactants or oily film. “Because it’s hydrophobic, not hydrophilic, it penetrates the sebaceous follicle for targeted delivery.”

An encapsulated benzoyl peroxide-tretinoin combination utilizes a silicone shell to separate the active ingredients while also slowing penetration and increasing tolerability. Additionally, a fourth-generation retinoid product, trifarotene cream 0.005%, is approved for facial and truncal acne in patients age nine years and older.

Clascoterone 1% cream, a topical androgen receptor inhibitor, was approved by the U.S. Food and Drug Administration (FDA) in August 2020. “We’ve never had a topical androgen receptor inhibitor to reduce sebum production. We currently use spironolactone off-label, but this is a topical with a new mechanism of action. It also seems to have anti-inflammatory effects via decreasing cytokines,” she says.

**PIH AND ERYTHEMA**

For acne-related postinflammatory hyperpigmentation (PIH), Dr. Berson typically prescribes tretinoin and azelaic acid because both help fade pigmentation while also preventing new breakouts. Other ingredients that can be used for PIH include hydroquinone, glycolic acid, salicylic acid and kojic acid.

“Cosmeceutical ingredients that can help further fade pigmentation include soy and niacinamide, both of which interfere with the transfer of melanosomes from melanocytes to keratinocytes.” Vitamin C, licorice extract, tranexamic acid (topical and oral) and cysteamine hydrochloride also help fade pigmentation, she says.

Home-use ultrasonic cleansing and light-based devices can also be helpful for acne-prone skin, as can peels, Dr. Berson says. Many patients like the feel of masks, she adds, and some masks are designed to help absorb excess oils. Ingredients she suggests looking for in such masks include clay, charcoal or sulfur.

For the redness of rosacea, topical brimodine tartrate gel and oxymetazoline cream act as adrenergic agonists and vasoconstrictors. Cosmeceutical ingredients that can help reduce erythema include antioxidants, such as vitamin C, vitamin E and niacinamide, and anti-inflammatory ingredients such as soy, green tea and some botanicals.

**THE MICROBIOME**

The microbiome is a hot topic for skin conditions including acne and rosacea, adds Dr. Berson. Composed of bacteria, fungi and yeast, the microbiome should be diverse, populated mostly with commensal organisms. “Our bacteria secrete antimicrobial peptides (AMPs) which help regulate the immune system, promote immune tolerance, fight infection and help maintain low skin pH.” These AMPs are believed to be overactive in rosacea.

“There may be dysbiosis or microbiome alteration in acne. So we are looking for microbiome-friendly skincare for patients — products that won’t disturb the microbiome and will improve barrier repair and decrease inflammation. Prebiotics and probiotics are also becoming more popular in the treatment of acne,” says Dr. Berson, who also recommends probiotics for patients on oral antibiotics.

In the future, she says, treatments that may be evaluated for acne include topical cannabidiol and Active Phage Serum (Ellis Day Skin Care) to balance the skin microbiome. Additionally, topical or injectable neuromodulators could prove helpful in reducing sebum and the appearance of pore size. Such products also might help with erythema and flushing, says Dr. Berson.

**Disclosures:**

Dr. Berson has been an investigator, advisor or consultant for AcneRx, Allergan, Allergan, Allergan, Apple, Bausch, Cambridge, Clarins, Cutislide, Dermaquest, Dr. J, EltaMD, Evolus, Ferndale, Filorga, Galderma, Grand, Hyperderm, L’Oreal, Ortho Dermatologics, Padox Care & Beauty, Poreless, RegimenPro, RosaceaPharmaceuticals, Sirona, Sonoma, ZO.

**Reference:**

INDICATIONS AND USAGE
ZILXI (minocycline) topical foam, 1.5% is a tetracycline-class drug indicated for the treatment of inflammatory lesions of rosacea in adults.

Limitations of Use: This formulation of minocycline 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, ZILXI should be used only as indicated.

IMPORTANT SAFETY INFORMATION

Contraindications
Persons who have shown hypersensitivity to any of the tetracyclines or any other ingredient in ZILXI.

Warnings and Precautions
Flammability: The propellant in ZILXI is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

ZILXI is a topical foam. While systemic absorption of ZILXI is low, and serious adverse reactions were not seen in clinical studies, the following adverse reactions associated with oral minocycline should be considered:

- **Teratogenic effects, inhibition of bone growth & permanent tooth discoloration:** Use during the 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) and reversible inhibition of bone growth.

- **Clostridioides difficile associated diarrhea (CDAD):** If CDAD occurs, discontinue ZILXI.

- **Hepatotoxicity & metabolic effects:** If renal impairment exists or if liver injury suspected, discontinue ZILXI.

- **Central nervous system effects:** Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.

- **Intracranial hypertension:** Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue ZILXI immediately if symptoms occur.

- **Autoimmune syndromes:** Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue ZILXI immediately if symptoms occur.

**IMPORTANT SAFETY INFORMATION, CONTINUED**

Take on inflammatory lesions of rosacea from the top down. Visit ZilxiHCP.com to learn more.
FDA accepts NDA filing for topical rosacea

MORGAN PETRONELLI | Assistant Editor

The U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) filing for a topical 5% encapsulated benzoyl peroxide cream (Epsolay, Sol-Gel Technologies). If approved, Epsolay could become the first single-agent benzoyl peroxide topical prescription drug to gain FDA approval for treating the inflammatory lesions of rosacea.

Benzoyl peroxide is not currently approved by the FDA to treat rosacea and is known to potentially cause skin irritation, including stinging, burning and erythema in individuals with papulopustular rosacea (PPR).

Sol-Gel’s patented microencapsulation technology aims to reduce this risk by encapsulating the benzoyl peroxide inside porous silica microcapsules, according to the company. This generates a barrier between the skin and the drug. The microcapsules dispense doses of the drug while the barrier reduces benzoyl peroxide’s oxidative effect, which can cause skin irritation.

The filing’s acceptance is backed by positive data from two identical phase 3, randomized, double-blind, multicenter, 12-week, clinical trials investigating the safety and efficacy of Epsolay versus vehicle in patients with PPR (n = 733). Sol-Gel reports each study (SGT 54-01 and SGT 54-02) met all primary and secondary endpoints. Primary endpoints for SGT 54-01 and SGT 54-02 included the proportion of patients achieving “clear” or “almost clear” on the Investigator’s Global Assessment (IGA) scale at week 12 (43.5% versus 16.1% vehicle, 50.1% versus 25.9% vehicle respectively) and absolute mean reduction from baseline in inflammatory lesion count (-17.4 versus -9.5 vehicle, -20.3 versus -13.3 vehicle respectively).

“It’s very difficult for patients of any dermatological disease, let alone rosacea, to wait months for a positive clinical result. That a quarter of Epsolay patients in both trials reached their treatment goals within a month, when the efficacy of existing topical products can be quite slow, is clinically meaningful and illustrates a clear unmet need within a rapidly growing marketplace,” says Alon Seri-Levy, M.D., CEO of Sol-Gel.

The company reports a low rate of cutaneous side effects, noting the drug appears to be well-tolerated and safe. Adverse events during the trials included application site pain and erythema in 3.4% of patients. Additionally, while there were no treatment-related serious adverse events; researchers report that a combined 11 participants discontinued treatment (9 benzoyl peroxide, 1 vehicle) due to adverse events.

Epsolay showed a favorable safety and tolerability profile compared to vehicle. The most common adverse reactions occurring in >1% of subjects treated with Epsolay and more frequently than in subjects treated with vehicle was application site erythema (2.3% versus 0.9%), application site pain (2.3% versus 0.9%), and application site pruritus (1.2% versus 0.4%). Most subjects experienced adverse reactions that were mild or moderate in severity.

“Papulopustular rosacea is a chronic and recurrent inflammatory skin disorder that affects nearly 5 million Americans. Regrettably, rosacea patients are dissatisfied with the efficacy of current therapies,” says Dr. Seri-Levy. “The results from our phase 3 studies showed statistically significant higher success in IGA compared with the vehicle, at every visit, and as early as at week two, as well as statistically significant higher reduction in absolute inflammatory lesion counts compared with the vehicle, at every visit, and as early as week two. In addition, a quarter of Epsolay patients in both trials reached their treatment goals within a month, which is very encouraging.”

The Prescription Drug User Fee Act (PDUFA) date for the FDA to make a decision on Epsolay is set for April 26, 2021.1

References:

“…a quarter of Epsolay patients in both trials reached their treatment goals within a month, when the efficacy of existing topical products can be quite slow, is clinically meaningful and illustrates a clear unmet need within a rapidly growing marketplace.”

Alon Seri-Levy, M.D., CEO of Sol-Gel
The first time minocycline has been approved for rosacea

Zilxi is the first and only topical minocycline proven effective in adult patients with inflammatory lesions of rosacea

- Evaluated in 2 large, 12-week phase 3 trials (N=1522)
- Significantly reduced inflammatory lesion count by Week 12
- Demonstrated improvement in IGA treatment success by Week 12

Proven safe and well-tolerated on already-sensitive skin
- The most commonly reported adverse reaction was diarrhea (1%)
- Zilxi was well-tolerated throughout the treatment period

Delivered in a gentle, proprietary foam vehicle
- Leverages Molecule Stabilizing Technology (MST™) for stable topical delivery
- Contains naturally moisturizing ingredients, is surfactant-free, and does not contain drying agents, such as ethyl alcohol

IMPORTANT SAFETY INFORMATION, CONTINUED

- Photosensitivity: Patients should minimize or avoid exposure to natural or artificial sunlight while using ZILXI. Advise patients to discontinue treatment with ZILXI at the first evidence of sunburn.
- Hypersensitivity reactions: Discontinue ZILXI immediately if symptoms of anaphylaxis, serious skin reactions, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome occur.
- Tissue hypopigmentation: Discoloration of organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves.
- Superinfection: Overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue ZILXI and institute appropriate therapy.

Adverse Reactions
The most common adverse reaction reported during clinical trials of ZILXI was diarrhea.

IGA=Investigator’s Global Assessment.
*Co-primary endpoints at Week 12 were: absolute change from baseline in inflammatory lesion count and IGA treatment success. IGA treatment success was defined as an IGA score of 0 or 1 (clear or almost clear) and at least a 2-grade improvement (decrease) from baseline. Patients were included if they had 15–75 facial lesions (papules and pustules), no more than 2 facial nodules, and an IGA score of moderate or severe (grade 3 or 4) (N=1522).
†Zilxi 1.5% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol, and propellants (butane + isobutane + propane).


Please see Brief Summary of Prescribing Information for ZILXI on the following pages.

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ZILXI™ (minocycline) topical foam, 1.5%  
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION.  
PLEASE SEE FULL PRESCRIBING INFORMATION.  

INDICATION  
ZILXI is indicated for the treatment of inflammatory lesions of rosacea in adults.  

Limitations of Use: This formulation of minocycline 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, ZILXI should be used only as indicated.  

CONTRAINDICATIONS  
This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any other ingredients within ZILXI.  

WARNINGS AND PRECAUTIONS  
• Flammability: The propellant in ZILXI is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).  
• Teratogenic Effects: Minocycline, like other tetracycline-class drugs, may inhibit bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.  
• Tooth Discoloration: The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline drugs. Use of tetracycline drugs is not recommended during tooth development.  
• Inhibition of Bone Growth: 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 tetracyclines 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 oral 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 orally early in pregnancy.  
• Clostridioides difficile Associated Diarrhea: Clostridioides difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.  
• Hepatotoxicity: Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use.  
• Metabolic Effects: The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.  
• Central Nervous System Effects: Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.  
• Intracranial Hypertension: Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at 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 tetracycline should be avoided because isoretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Because intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.  
• Autoimmune Syndromes: Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitits. Sporadic cases of serum sickness have presented shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including ZILXI.  
• Photosensitivity: Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although ZILXI did not induce phototoxicity or photoallergic responses in human dermal safety studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVAB treatment) while using minocycline. If patients need to be outdoors while using ZILXI, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with ZILXI at the first evidence of sunburn.  
• Serious Skin/Hypersensitivity Reaction: Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with oral minocycline use. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue ZILXI immediately.  
• Tissue Hyperpigmentation: Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.  
• Development of Drug-Resistant Bacteria: ZILXI has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using ZILXI, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of ZILXI, it should be used only as indicated.  
• Superinfection/Potential for Microbial Overgrowth: Use of ZILXI may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue ZILXI and institute appropriate therapy.  

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. In three (two Phase 3 and one Phase 2) multicenter, randomized, double-blind, vehicle-controlled trials, adult subjects applied ZILXI or vehicle once daily for 12 weeks. A total of 1,087 subjects were treated with ZILXI and 591 with vehicle. The majority of subjects were White (97%) and female (70%). Approximately 67% were non-Hispanic/Latino. The mean age was 50.0 years and ages ranged from 18 to 86 years.  
• The most common adverse reaction reported by ≥1% of subjects treated with ZILXI and more frequently than in subjects treated with vehicle was diarrhea (1% vs. 0%), respectively.  

© 2020 VYNE Therapeutics Inc. All rights reserved. The information in this supplement may be subject to updating and change. For the latest information, including the FDA-approved Prescribing Information, go to www.ZILXI.com. The properties of their respective owners. Allow the can to warm to room temperature before first use. Shake
Adjunctive examined for facial erythema

BY MARY SCOVIAK | Managing Editor

Treatment with oxymetazoline (RHOFADE, EPI Health) as adjunctive therapy with energy-based therapy may offer a safe and well-tolerated option for reducing facial erythema in patients with moderate-to-severe persistent facial erythema associated with rosacea.

A recent phase 4, open-label, intervention study evaluated the safety and tolerability of oxymetazoline hydrochloride cream 1% (oxymetazoline) when used alongside energy-based therapies such as lasers and intense pulsed light (IPL). Efficacy assessments were exploratory.

“These therapies can effectively manage vascular signs of the disease, such as telangiectasia and persistent erythema, by selectively targeting and thermally damaging dysregulated blood vessels. However, not all patients respond to energy-based therapies,” says Emil Tanghetti, M.D., Center for Dermatology and Laser Surgery, Sackville, Canada, and lead author on the study.

He adds that some patients may require more than one treatment, which could add “substantial” costs. Energy-based therapies may result in adverse side effects including unwanted purpura or erythema. They also have limited efficacy in reducing diffuse erythema associated with acne rosacea due to the small caliber of vessels, which are more difficult to target, according to the study.

“A combination approach to treatment including both pharmacological and physical approaches may allow more effective management of the vascular manifestations of rosacea than utilization of any one treatment modality as monotherapy,” says Tanghetti.

Oxymetazoline hydrochloride cream, an alpha-1-adrenoceptor agonist, already has U.S. Food and Drug Administration (FDA) approval for the topical treatment of persistent facial erythema associated with rosacea in adults. Phase 3 clinical trials (Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL), which evaluated data at 29 days and one year, showed a single daily application of oxymetazoline to be well tolerated, safe and effective in the treatment of moderate to severe persistent facial erythema of rosacea.

For the current study, eligible patients with moderate-to-severe facial erythema associated with rosacea received one of four energy-based therapies on day one and day 29: Excel® V (Cutera, Brisbane, CA) potassium titanyl phosphate (KTP) laser; Palomar Icon™ (Cynosure, Westford, MA) IPL therapy; the pulsed-dye laser Vbeam Perfecta® (Syneron-Candela, Mississauga, Ontario, Canada; PDL-Vbeam); or the pulsed-dye laser Cynergy™ (Cynosure; PDL-Cynergy). A total of 46 patients (mean age, 51.1 years; 78.3% female) enrolled in this study. Similar numbers of patients received each of the energy-based therapies in addition to oxymetazoline, according to Tanghetti.

Each study center was assigned a specific device to utilize during the study based on the current expertise and other devices already in place. The investigator’s current standard of practice determined the protocol followed for each laser treatment. Rather than using randomization or stratification, patients were assigned to an energy-based therapy based on their study site.

Patients in the study received a once-daily application of oxymetazoline beginning on day three and continuing through day 27. Following instructions from study staff and an instructional video, participants applied a pea-sized amount of oxymetazoline topically to the face at approximately the same time day. However, on study visit days, they applied the cream after completing predose study assessments and procedures. They underwent a washout of oxymetazoline on day 28 before receiving energy-based therapy the following day.

Daily application of oxymetazoline was re-initiated on day 31 and continued until study end on day 56. Investigators asked patients who discontinued the study to return on the last study visit day for end-of-study data assessment.

Tanghetti and his fellow investigators evaluated improvement from baseline in Clinician Erythema Assessment (CEA) score, patient satisfaction measures, incidence of treatment-emergent adverse events (TEAEs), and worsening from baseline on dermal tolerability assessments and the Clinician Telangiectasia Assessment (CTA).

All patients demonstrated an improvement from baseline in CEA during the study. Among all 44 evaluable patients on day one, 6 (13.0%) showed at least one-grade improvement in CEA one hour after energy-based therapy. On day three, investigators observed one-grade or greater improvement in 20 (45.5%) patients before application of oxymetazoline, and by 35 (79.5%) patients at six hours post-treatment. On day 31, 26 (60.5%) of 43 evaluable patients, demonstrated one-grade or greater improvement before application of oxymetazoline, and by 38 (88.4%) patients at six hours post-treatment.

Data shows 39 of 43 evaluable patients (90.7%) demonstrated an improvement six hours post-treatment on day 56. Most patients were satisfied or very satisfied with treatment at the end of the study, say the investigators.

In terms of adverse effects, some patients experienced worsening in dermal tolerability assessment symptoms (range: 4–21 patients; 8.7–45.7%). Worsening in CEA and CTA were each reported by three patients (6.5%) at any time during the study.

No serious, severe, or fatal TEAEs were reported.

References and additional copy available at Dermatologytimes.com.
CONTRAINDICATIONS

Indicated in the following population: Patients with known hypersensitivity to minocycline or any of the ingredients of ZILXI.

Information from the literature indicates that oral tetracyclines are excreted in human milk. The potential for milk substitution and adverse reactions in nursing infants is unknown. Because of the potential for serious adverse reactions, advise that breastfeeding is not recommended during treatment with ZILXI.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ZILXI™ (minocycline) topical foam, 1.5% is intended for the topical treatment of inflammatory lesions of rosacea (N=216) in a 12-week trial (NCT03276936), frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

DRUG INTERACTIONS

• Anticoagulants: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
• Penicillin: Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.
• Drug/Laboratory Test Interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

USE IN SPECIFIC POPULATIONS

• Pregnancy: Risk Summary: Available data with ZILXI use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of ZILXI in humans is low following once daily topical administration of ZILXI under maximal clinical use conditions. Because of low systemic exposure, it is not expected that maternal use of ZILXI will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with ZILXI. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during organogenesis induced skeletal malformations in fetuses at systemic exposures of 2,000 and 1,300 times, respectively, the maximum recommended human dose (MRHD based on AUC comparison) of ZILXI (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

• Data: Animal Data: Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (2,000 and 1,300 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (680 times the systemic exposure at the MRHD based on AUC comparison).

• Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (1,700 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

• Lactation: Risk Summary: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with ZILXI.

• Pediatric Use: The safety and effectiveness of ZILXI for the treatment of inflammatory lesions of rosacea have not been evaluated in pediatric patients.
• Geriatric Use: There were 278 subjects aged 65 or older in the clinical trials of ZILXI (16.6% of 1,678 subjects). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY

• Carcinogenesis, Mutagenesis, Impairment of Fertility: In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride was associated in both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females. Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.
• Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (27,500 times the systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (10,000 or 27,500 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis. Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

• HANDLING: Allow the can to warm to room temperature before first use. Shake well before use.
• WARNING: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).

For more information, including the FDA-approved Prescribing Information, go to www.ZILXI.com or call 1-844-375-3673.

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Novel device characterizes mite infestations

CHERYL GUTTMAN KRADER BS PHARM | Staff Correspondent

Experience evaluating fluorescence-advanced videodermatoscopy (FAV, Adamo Srl) for characterization of Demodex mites suggests that it can be a useful tool in the clinical evaluation and management of patients with Demodex-related skin diseases, according to investigators who used FAV to describe the morphological features of Demodex infestation and compared them with results using reflectance confocal microscopy (RCM) in a recently published paper.

“FAV is a commercially available, noninvasive, real-time, videodermoscopy system that is both affordable and easy to use,” says Diego Fernandez-Nieto, M.D., Department of Dermatology Ramón y Cajal University Hospital, Madrid, Spain.

“Our study shows that with its high magnification (500x), the device enables observation of different parts of Demodex mites and counting of the number of mites present at each follicle,” he says. “Furthermore, it allows faster estimation of mite density compared with the use of RCM that has been tested as a noninvasive alternative to standardized superficial skin biopsy (SSSB) for detecting and quantifying Demodex. Considering its advantages and capabilities, we believe that FAV could have a role for detecting Demodex infestation and evaluating response to treatments targeting the mites and that it will be adopted for many other applications in the future.”

The FAV system is manufactured in several different versions that are designed to be suitable for videodermatoscopy, videocapillaroscopy, videotrichoscopy, and even videoentomology. Fernandez-Nieto notes that it is mainly used for evaluating melanocytic and non-melanocytic skin cancers. In those applications, it has the added benefit of being able to evaluate the vascularization pattern due to the high absorption and afterwards emission of fluorescence by the hemoglobin at the wavelength of the probe (405 nm ± 5 nm), he says.

“FAV has also been used for skin evaluation in fungal and parasitic infections, including scabies. We had access to this new technology for skin examination during a trial period at our center. Because of its versatility, high amplification and especially because it allows rapid visualization, we were interested in studying its ability to characterize Demodex,” he tells Dermatology Times.

The evaluation was performed in six patients with clinical suspicion of having a Demodex-related disease, including three individuals with pityriasis folliculorum and three with papulopustular rosacea. All of the patients had undergone previous SSSB that documented the presence of >5 mites/cm².

As reported by Dr. Fernandez-Nieto and colleagues, under FAV the Demodex mites were identified within the hair infundibulum as “roundish bright structures” when they were vertically oriented. Mites positioned at an oblique angle were seen as tubular dark structures surrounded by a whitish halo. The researchers note that the latter description corresponds to the appearance of the mites on RCM and that the whitish halo represented the mite’s exoskeleton.

Adjustment of the FAV system’s penetration depth made it possible to visualize the mite’s opisthosa and gnathosoma, including the gut cells within the opisthosa, and to estimate mite length.

“The FAV system allows counting of individual mites. With its field of view of 340 micrometers, mite density can be estimated quickly with just a few movements of the probe,” Dr. Fernandez-Nieto says. “We believe it is an equally reliable but easier and faster method than RCM or SSSB to evaluate mite density.”

Disclosure: Dr. Fernandez-Nieto has no relevant financial interest to disclose.

Reference:
Inflammatory lesions treatment available

MORGAN PETRONELLI | Assistant Editor

A new treatment for inflammatory lesions of rosacea in adults is now on the market with the recent announcement from VYNE Therapeutics (formerly Menlo Therapeutics), that their newly United States Food and Drug Administration (FDA)-approved 1.5% topical minocycline foam, FMX103 (ZILXI, VYNE Therapeutics), is now available in pharmacies nationwide.

Minocycline is a broad-spectrum antibiotic within the tetracycline family that possesses anti-inflammatory properties. FMX103 is specifically equipped with VYNE’s proprietary Molecule Stabilizing Technology (MST) that helps deliver the drug through a foam-based vehicle along with coconut and soybean oil for added moisturization, according to the company.

Oral minocycline has been on the market for numerous years for acne vulgaris but is now being developed into a topical formulation to treat both acne and rosacea. Previously, a 4% topical minocycline foam (Amzeez) developed by VYNE’s now wholly-owned subsidiary Foamix Pharmaceuticals Ltd. was approved by the FDA for treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in pediatric patients and adults on Oct. 18, 2019.1

In May 2020, FMX103 became the first FDA-approved topical minocycline treatment for rosacea.1

“This is the only product containing minocycline approved by the FDA for rosacea,” says Iain Stuart, Ph.D., chief scientific officer of VYNE. “The availability of a novel topical formulation of this molecule underscores our efforts to provide innovative treatment options for patients who suffer from difficult to treat skin conditions.”

The approval follows positive results from two randomized, multicenter, vehicle-controlled, double-blind clinical trials that enrolled 1,522 patients 18 years and older. During the trials, patients with rosacea-related papules and pustules were given either FMX103 or vehicle daily for 12 weeks.

FMX103 met all co-primary endpoints in both trials, which included an absolute mean change inflammatory lesions counts from baseline at week 12 and a proportion of patients who achieved an Investigators Global Assessment (IGA) score of clear (0) or almost clear (1) with a minimum of a two-grade decrease from baseline at week 12. The 1.5% topical minocycline foam also demonstrated superiority over vehicle and a statistically significant decrease in inflammatory lesion count and IGA success.2

Additionally, erythema was investigated during the trials, with 40.9% and 48.3% of FMX103 patients being clear or almost clear of erythema at week 12.2

Tolerability of the drug was assessed with scores of mild or none at application site at application site at week 12. While no serious treatment-related adverse events (TRAEs) were reported, the most prevalent adverse reaction during the trials was diarrhea, which was reported by 21% of FMX103 patients compared to vehicle, respectively.3

“Patients and physicians have been seeking new treatment options for rosacea, a condition that can be difficult to treat, leaving many patients dissatisfied and, in some cases, switching treatments multiple times or discontinuing altogether,” says David Domzalski, CEO of VYNE. “By combining a unique topical delivery system for minocycline with strong efficacy and tolerability, ZILXI is positioned to address a very challenging skin condition in a way that could change treatment considerations for rosacea.”

VYNE announces the annual list price for FMX103 will be $485 per 30-gm canister. The company says they are currently working with commercial insurance companies to align contracts to help expand access to the topical.1

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3. Menlo Therapeutics Receives FDA Approval of ZILXI™ (minocy-
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Although the pathophysiology of atopic dermatitis (AD) is being increasingly understood, ideal treatment approaches remain challenging, particularly in patients with more severe disease. A recent paper presented an update on the current and potential therapeutic approaches for AD ranging from various biologics to small-molecule drugs such as the Janus kinase (JAK) inhibitors.

Atopic dermatitis is one of the most common chronic inflammatory skin diseases and is estimated to occur in 7-10% of adults and 5-10% of children. Two major mechanisms are thought to promote the chronic inflammation of the skin, namely a genetically determined impairment of the barrier function of the skin triggered by mutations in barrier and structural proteins, respectively, as well as a genetically determined immunological disbalance characterized by an enhanced TH2 response accompanied by the production of inflammatory cytokines such as interleukin (IL) IL-4 and IL-13.

Cyclosporine has long been considered to be the only systemic medical therapy available for patients with AD but more recently, dupilumab, an antibody against the IL-4/IL-13 receptor has also found its use in patients with moderate to severe AD symptoms.

“Dupilumab is the first effective and very well tolerated biologic available for treatment of moderate-to-severe atopic dermatitis. Numerous other biologics are currently under clinical investigation and may expand the range of therapies for treatment of atopic dermatitis in the future.”

Margitta Worm, M.D., professor of the Department of Dermatology and Allergology, Charité - University Medical Center Berlin, Berlin, Germany

Biologics, small molecule drugs expand AD options

Dupilumab, JAK inhibitors are leading the way, but a number of other treatments are in clinical trials.

ILYA PETROU, M.D. | Staff Correspondent

Although the pathophysiology of atopic dermatitis (AD) is being increasingly understood, ideal treatment approaches remain challenging, particularly in patients with more severe disease. A recent paper presented an update on the current and potential therapeutic approaches for AD ranging from various biologics to small-molecule drugs such as the Janus kinase (JAK) inhibitors.

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As the first approved biologic for the treat-
Baricitinib, PF01, and ASN are the most advanced oral JAK inhibitors to date. They interfere with intracellular signaling pathways.

In a recent phase 3 trial, dupilumab demonstrated comparable positive outcomes in adults with atopic dermatitis (AD). The researchers found that 32% of the patients achieved a SCORing Atopic Dermatitis (SCORAD) 75 and 67% achieved a SCORAD of 50 after three months of dupilumab therapy. At the six-month follow-up, the SCORAD improved more than 60%. Moreover, the researchers found that the affected body surface area was significantly reduced from 42.17% to 9.9%.

According to the researchers, approximately 90% of patients who receive dupilumab adhere to the therapy. Although infections of the skin are commonplace in atopic dermatitis patients, particularly in moderate-to-severe cases, data has shown no increased risk of skin infections in patients on long-term dupilumab therapy.

A mosaic of other cytokine inhibitors and cytokine antagonists currently in clinical development for the treatment of AD include antibodies against IL-13, IL-31, oxazolone (OX)40, thymic stromal lymphopoietin (TSLP) and TSLP receptor, IL-33, IL-22, as well as IL-17. Of these agents, the furthest advanced in development is tralokinumab, an antibody directed against IL-13 that blocks the IL-13 signaling pathway. The phase IIb trial showed a significant reduction in the Eczema Area and Severity Index (EASI) in patients with moderate-to-severe AD, demonstrating response rates of up to 70% for EASI 50 and up to 40% for EASI 75. Lebrikizumab, another antibody against IL-13, has also demonstrated comparable positive outcomes in a recent phase 3 trial.

JAK inhibitors are small molecules used to interfere with intracellular signaling pathways. The most advanced oral JAK inhibitors to date include baricitinib, PF01, and ASN. They have been shown to be effective in the treatment of moderate-to-severe AD and to benefit from a rapid onset effect. The initial phase 2 clinical trial data revealed an efficacy between 60-82% with respect to EASI 50. Of note, the side efficacy profile appears to be broader when compared to dupilumab. However, the researchers observed increased incidence in infections, particularly the herpes virus.

“"The side effect profile demonstrates that infections are more common and that certain lab parameters are altered under therapy, necessitating more intensive patient monitoring," say the study authors. “JAK inhibitors may, therefore, be particularly beneficial for short-term interval treatment of patients with AD.”

Topical JAK inhibitors have also been developed and are currently in clinical trials including tofacitinib, delgocitinib, and ruxolitinib. Initial data in patients with moderate to severe AD show response rates of 70-80% after a mean treatment time of four weeks. Similar promising initial clinical data is also being seen in children with AD, demonstrating moderate-to-clinical efficacy and a good tolerability.

“"For example, the prospects of a patient severely affected with atopic dermatitis would be treatment with a biologic and a topical JAK inhibitor in the future," say the study authors. "Future studies are required to characterize in detail the selection of specific substances for individual patients and the optimal duration of therapy."
Aquaphilus Dolomiae demonstrates skin soothing properties

Researchers have found that Aquaphilus Dolomiae, a flagellated bacterium, facilitates soothing and calming of the skin.
Skin microbiota takes part in the control of cutaneous inflammation. In skin diseases such as atopic dermatitis (AD), cutaneous dysbiosis and the emergence of *Staphylococcus aureus* contribute to the pathophysiology of the disease. Researchers wrote in a study published in November 2016 in *Pharmaceutical Biology,*" new therapeutic approaches consist in topical application of natural products able to counteract *S. aureus* effects through activation of resident immune cells producing anti-inflammatory cytokines such as IL-10.

When they studied possible immunosuppressive properties of Aquaphilus Dolomiae extract, they found that hydrotherapy, otherwise known as water baths, counteracted *S. aureus* secretome in the skin of children with atopic dermatitis. Aquaphilus Dolomiae is extracted, then fermented. The researchers concluded Aquaphilus Dolomiae could ease atopic dermatitis severity. Years later, a study published in the *Journal of Inflammation Research,* researchers looked at the effects of Avène on dendritic cells, which help control immune response. They discovered the hydrotherapy’s immunomodulatory potential.

Bacteria play a major role in wound repair, secreting molecules that can activate cell multiplication and stimulate skin repair. The biofilm helps to protect that wound from invasion and helps to keep that balance between symbiotic and pathogenic bacteria, according to Ted Lain, M.D., M.B.A., dermatologist and chief medical officer of Sanova Dermatology, with practices throughout Texas and Louisiana.

The Aquaphilus Dolomiae in Avène Thermal Spring Water is previously unrecognized bacteria that only survives in the deepest, pure, crystalline waters. "This is a gram-negative highly flagellated bacteria, which is rich in molecules that support cell differentiation and keratinocyte migration for fibroblast proliferation," Dr. Lain said.

Research published in 2011 in the *Journal of the European Academy of Dermatology and Venereology* touted Avène Thermal Spring Water key component and specific properties. 

The clinical efficacy of the Water was demonstrated at the Hydrotherapy Center in chronic and disabling diseases such as atopic dermatitis but also in various settings in medical and post-dermatology procedures such as photodynamic therapy or photothermolysis...

Avène Thermal Spring Water is a key component."

Researchers assessing the efficacy of keratinocyte migration conducted an in vitro study incubating human keratinocytes in two environments. One was exposed to Aquaphilus Dolomiae ferment filtrate, the other was in an untreated environment. They found keratinocyte migration and skin repair was 2.5 times faster in the Aquaphilus Dolomiae environment, according to the "Wound Healing: Inspiration from the Intestine and a New Postbiotic Active Ingredient" white paper including 2019 data on file at Pierre Fabre Research Institute.

Authors of the same white paper cited an in vitro study looking at measuring antimicrobial peptide human beta-defensin 2 (hBD-2) expression in an environment with 3ug/mL Aquaphilus Dolomiae Ferment Filtrate exposure versus an untreated environment or one with sucralfate. They found hBD-2 increased by 2,121.3% compared to skin exposed to the other two environments, which showed no significant antimicrobial peptide expression. Avène Thermal Spring Water only contains the natural spring water which is bottled at the source in Avène, France.

"There are no parabens, preservatives, alcohol, etc. It only contains the water," Dr. Lain said.

The water begins as rain water and makes the 50-year journey through the Cévennes Mountains in Avène. It travels through the mountainous soil and rocks to collect in the underground spring, enriched with trace elements, silica, calcium and magnesium. It eventually comes in contact with a microorganism Aquaphilus Dolomiae, which Avène first identified in 2001.

The Water’s soothing properties have been used for decades in patients for decades as a treatment for atopic dermatitis and psoriasis at the Avène Hydrotherapy Center, located near the spring.

"Dermatologists can easily incorporate this water as a spray to be applied after gentle cleansing, advising patients to allow the water to evaporate before moving on to the next steps in their treatment plan. Alternatively, the spray could be applied directly to inflamed or affected skin to soothe and calm the skin," Dr. Lain said. "Avène Thermal Spring Water should be used as adjunctive care alongside your normal skin routine. Its soothing and softening effects are beneficial and can help care for all skin types including, sensitive, hypersensitive and irritated skin."
I encourage clinicians to look at the more real-world data where patients are using some topical steroids with their biologic.”

Eric L. Simpson, M.D., Oregon Health & Science University, Portland
For clinicians who treat patients with atopic dermatitis

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**Risankizumab outperforms secukinumab at one year**

**JOHN JESITUS | Staff Correspondent**

In the IMMerge phase 3b trial against secukinumab, risankizumab met both of its primary endpoints — noninferiority at week 16 and superiority at week 52 — with no new safety signals.

“Although we know we have many efficacious treatments for psoriasis,” says principal investigator Richard B. Warren, BSc, MBChB (Hons), FRCP, Ph.D., “it is important to be able to decide which drug is best used where, and which drugs are better than others. Therefore, head-to-head studies are important.” Improving patients’ quality of life requires identifying treatments with greater efficacy and dosing convenience, he adds. Prof. Warren is a dermatologist at The Dermatology Centre, Salford Royal NHS Foundation Trust and The University of Manchester, United Kingdom.

IMMerge phase 3b was a randomized, open-label (both arms), efficacy assessor-blinded study that evaluated the interleukin (IL)-23 inhibitor risankizumab against secukinumab, which blocks IL-17A. Investigators randomized 164 and 163 patients with moderate-to-severe plaque psoriasis, respectively, to the following regimens:

- **Risankizumab**: 150 mg (two 75 mg subcutaneous injections at baseline, week four and every 12 weeks thereafter)
- **Secukinumab**: 300 mg (two 150 mg subcutaneous injection at baseline, weeks one through four, and monthly thereafter).

The most notable baseline characteristics in both groups, Prof. Warren says, were a significant level of prior biologic use (62 patients/37.8% and 58 patients/35.6% for risankizumab and secukinumab, respectively) and a high proportion of patients with body weight above 100 kg (52 patients/31.7% and 54 patients/33.1%, respectively).

At week 52, the proportions of patients in the risankizumab and secukinumab arms who completed the study were 151 (92.1%) and 135 (82.8%), respectively. The dropout rate in the secukinumab arm was driven by slightly higher rates of adverse events (five patients/3.1%) and lack of efficacy (seven patients/4.3%) in this arm, he says. The corresponding figures for risankizumab were one patient (0.6%) in each category.

Among primary endpoints, the proportions of patients in the risankizumab and secukinumab arms who achieved Psoriasis Area and Severity Index (PASI) 90 at week 16 were 74% and 66%, respectively (this endpoint had a 12-point margin for noninferiority). PASI 90 rates at week 52 were 87% and 57%, respectively (P<0.001).

Ranked secondary endpoints at week 52 also favored risankizumab. Specifically, 66% of patients in this group achieved PASI 100, versus 40% for secukinumab. Additionally, 88% of risankizumab-treated patients achieved static physician global assessment (sPGA) scores of zero or one (clear or almost clear), versus 58% in the secukinumab arm (P<0.001 in PASI and sPGA analyses).

Overall, the number of treatment-emergent adverse events (TEAEs) was similar across both groups, about 70%. TEAEs leading to drug discontinuation were more common in the secukinumab arm — 4.9%, versus 1.2% for risankizumab.

Through 52 weeks, three serious infections occurred in the risankizumab arm (1.8% of patients), versus none in the secukinumab arm. However, says Prof. Warren, the study’s relatively small size could account for this apparent disparity. “We can get numerical imbalance when we have smaller numbers of patients within a study. Therefore, safety is best contextualized across the whole study programs for various drugs.”

In the UltIMMa-1 and UltIMMa-2 phase 3 trials, 4/588 risankizumab-treated patients (0.7%) and 52.2 Ustekinumab-treated patients experienced serious infections between weeks 16 and 52.

“Ustekinumab-treated patients experienced a similar rate of serious infections. IMMerge 52-week data also reflect two major adverse cardiovascular events in the risankizumab cohort. “It’s important to highlight that both of those patients had significant risk factors for cardiovascular disease, and neither event was deemed to be related to the study drug.”

Overall, Prof. Warren says, risankizumab demonstrated noninferiority to secukinumab at week 16, and superiority at week 52.

**Disclosures:**
Prof. Warren has been an investigator, consultant, speaker and/or has received research grants from AbbVie, Almirall, Amgen, Arena Pharmaceuticals, AveXis, Bausch Health, Janssen, Blistar/Mylan/Opadrix, Celgene, Eli Lilly, Janssen, UCB, Novartis, Pfizer and UCB.

**References:**
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*In the ERASURE study at Week 12, 82% of patients in the COSENTYX 300-mg arm (n=245) achieved a PASI 75 response and 65% of patients achieved IGA 0 or 1 vs 4% and 2% in the placebo group (n=248), respectively. In the FIXTURE study at Week 12, 76% of patients in the COSENTYX 300-mg arm (n=327) achieved a PASI 75 response and 62% of patients achieved IGA 0 or 1 vs 5% and 3% in the placebo group (n=328), respectively. In the FUTURE 2 study, for patients with active psoriatic arthritis treated with COSENTYX 300 mg (n=100), 150 mg (n=100), or placebo (n=98), ACR20 response at Week 24 was 54%, 51%, and 15%, respectively. In the ERASURE (N=738) and FIXTURE (N=1306) studies, among the patients who chose to participate (39%) in assessments of patient-reported outcomes, improvements in signs and symptoms related to itching, pain, and scaling at Week 12 compared with placebo were observed using the Psoriasis Symptom Diary.

† NBRx share as prescribed by rheumatologists, allocated using Symphony Health patient longitudinal data to limit product use to ICD-10 codes for PsA and/or PsO.

NBRx is the IQVIA NPA New to Brand® measure showing the volume of prescriptions associated with first-time patient use of a product.

ACR=American College of Rheumatology; ICD-10=International Classification of Diseases, Tenth Revision; IGA=Investigator’s Global Assessment modified 2011; PASI=Psoriasis Area Severity Index; PsA=psoriatic arthritis; PsO=plaque psoriasis.

INDICATIONS

COSENTYX® (secukinumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

COSENTYX is indicated for the treatment of adult patients with active psoriatic arthritis.

COSENTYX is indicated for the treatment of adult patients with active ankylosing spondylitis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

COSENTYX is contraindicated in patients with a previous serious hypersensitivity reaction to secukinumab or to any of the excipients.

Please see additional Important Safety Information on reverse.

Please see Brief Summary of full Prescribing Information on the following pages.
**WARNINGS AND PRECAUTIONS**

**Infections**

COSENTYX may increase the risk of infections. In clinical trials, a higher rate of infections was observed in subjects treated with COSENTYX compared to placebo-treated subjects. In placebo-controlled clinical trials in patients with moderate to severe plaque psoriasis, higher rates of common infections such as nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%), and mucocutaneous infections with candida (1.2% versus 0.3%) were observed with COSENTYX compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis and ankylosing spondylitis. The incidence of some types of infections appeared to be dose-dependent in clinical studies.

Exercise caution when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and COSENTYX should be discontinued until the infection resolves.

**Pre-treatment Evaluation for Tuberculosis**

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX. Do not administer COSENTYX to patients with active TB infection. Initiate treatment of latent TB prior to administering COSENTYX. Consider anti-TB therapy prior to initiation of COSENTYX in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving COSENTYX should be monitored closely for signs and symptoms of active TB during and after treatment.

**Inflammatory Bowel Disease**

Caution should be used when prescribing COSENTYX to patients with inflammatory bowel disease. Exacerbations, in some cases serious, occurred in patients treated with COSENTYX during clinical trials in plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX. In an exploratory study in 59 patients with active Crohn’s disease, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group. Patients who are treated with COSENTYX should be monitored for signs and symptoms of inflammatory bowel disease.

**Hypersensitivity Reactions**

Anaphylaxis and cases of urticaria occurred in patients treated with COSENTYX in clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of COSENTYX should be discontinued immediately and appropriate therapy initiated.

The removable cap of the COSENTYX Sensoready® pen and the COSENTYX prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals. The safe use of the COSENTYX Sensoready pen or prefilled syringe in latex-sensitive individuals has not been studied.

**Vaccinations**

Prior to initiating therapy with COSENTYX, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with COSENTYX should not receive live vaccines. Non-live vaccinations received during a course of COSENTYX may not elicit an immune response sufficient to prevent disease.

**MOST COMMON ADVERSE REACTIONS**

Most common adverse reactions (>1%) are nasopharyngitis, diarrhea, and upper respiratory tract infection.


Please see additional Important Safety Information on the previous page. Please see Brief Summary of full Prescribing Information on the following pages.
COSENTYX® (secukinumab) injection, for subcutaneous use

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
1.1 Plaque Psoriasis
COSENTYX® is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

1.2 Psoriatic Arthritis
COSENTYX® is indicated for the treatment of adult patients with active psoriatic arthritis.

2 CONTRAINDICATIONS
COSENTYX® is contraindicated in patients with a previous serious hypersensitivity reaction to secukinumab or to any of the excipients.

5 WARNINGS AND PRECAUTIONS
5.1 Infections
COSENTYX® may increase the risk of infections. In clinical trials, a higher rate of infections was observed in COSENTYX® treated subjects compared to placebo-treated subjects. In placebo-controlled clinical trials in patients with moderate to severe plaque psoriasis, higher rates of common infections such as nasopharyngitis (11.4% versus 8.8%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with candida (0.2% versus 0.3%) were observed in COSENTYX® compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis and ankylosing spondylitis.

5.2 Pre-treatment Evaluation for Tuberousclerosis
Evaluate patients for tuberculous (TB) infection prior to initiating treatment with COSENTYX®. Do not administer COSENTYX® to patients with active TB infection. Initiate treatment of latent TB prior to administering COSENTYX®. Consider anti-TB therapy prior to initiation of COSENTYX® in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving COSENTYX® should be monitored closely for signs and symptoms of active TB during and after treatment.

5.3 Inflammatory Bowel Disease
Caution should be used when prescribing COSENTYX® to patients with inflammatory bowel disease. Exacerbations, in some cases serious, occurred in COSENTYX® treated patients during clinical trials in plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX®. In an exploratory study in 59 patients with active Crohn’s disease, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group. Patients who are treated with COSENTYX® should be monitored for signs and symptoms of inflammatory bowel disease.[See Adverse Reactions (6.1)].

5.4 Hypersensitivity Reactions
Anaphylaxis and cases of urticaria occurred in COSENTYX® treated patients in clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of COSENTYX® should be discontinued immediately and appropriate therapy initiated.[See Adverse Reactions (6.1)].

5.5 Risk of Hypersensitivity in Latex-sensitive Individuals
The removable cap of the COSENTYX® Sensoready pen and the COSENTYX prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals. The safe use of COSENTYX® Sensoready pen or prefilled syringe in latex-sensitive individuals has not been studied.

5.6 Vaccinations
Prior to initiating therapy with COSENTYX®, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with COSENTYX® should not receive live vaccines. Non-live vaccinations received during a course of COSENTYX® may not elicit an immune response sufficient to prevent disease.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail elsewhere in the labeling:

• Infections (see Warnings and Precautions (5.3)).
• Inflammatory Bowel Disease (see Warnings and Precautions (5.3)).
• Hypersensitivity Reactions (see Warnings and Precautions (5.4)).

6.1 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.

Plaque Psoriasis
A total of 2430 plaque psoriasis patients were treated with COSENTYX® in controlled and uncontrolled clinical trials. Of these, 1641 subjects were exposed for at least 1 year. Four placebo-controlled phase 3 trials in plaque psoriasis subjects were pooled to evaluate the safety of COSENTYX® in comparison to placebo up to 12 weeks after treatment initiation, in Trials 1, 2, 3, and 4. In total, 2017 subjects were evaluated (919 to COSENTYX® 300 mg group, 692 to COSENTYX® 150 mg group, and 406 to placebo group). [See Clinical Studies (14) in the full prescribing information].

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the COSENTYX® groups than the placebo group during the 12-week placebo-controlled period of the placebo-controlled trials.

Table 1: Adverse Reactions Reported by Greater Than 1% of Patients with Plaque Psoriasis Through Week 12 in Trials 1, 2, 3, and 4

<table>
<thead>
<tr>
<th>COSENTYX®</th>
<th>300 mg (N = 691)</th>
<th>150 mg (N = 692)</th>
<th>Placebo (N = 694)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>79 (11.4)</td>
<td>80 (12.3)</td>
<td>60 (8.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28 (4.1)</td>
<td>18 (2.6)</td>
<td>10 (1.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17 (2.5)</td>
<td>22 (3.2)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>10 (1.4)</td>
<td>10 (1.4)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>9 (1.3)</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>8 (1.2)</td>
<td>7 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>8 (1.2)</td>
<td>8 (1.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Rinfitanolate</td>
<td>8 (1.2)</td>
<td>8 (1.2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Adverse reactions that occurred at rates less than 1% in the placebo-controlled period of Trials 1, 2, 3, and 4 through Week 12 included: sinusitis, conjunctivitis, canker sores, genital herpes, pruritus, rhinorrhea, gastroenteritis, pharyngitis, conjunctivitis, impetigo, folliculitis, urinary tract infection, and neutropenia.

Infections
In the placebo-controlled period of the clinical trials in plaque psoriasis (a total of 1382 subjects treated with COSENTYX® and 884 subjects treated with placebo up to 12 weeks, 1302 patients received COSENTYX® compared with 28.7% of subjects treated with COSENTYX® compared with 18.8% of subjects treated with placebo. Serious infections occurred in 0.4% of patients treated with COSENTYX® and in 0.3% of patients treated with placebo (See Warnings and Precautions (5.3)).

Over the entire treatment period (a total of 3430 plaque psoriasis subjects treated with COSENTYX® for up to 52 weeks for the majority of subjects), infections were reported in 47.5% of subjects treated with COSENTYX® (0.5 per patient-year of follow-up). Serious infections were reported in 1.2% of subjects treated with COSENTYX® (0.015 per patient-year of follow-up).

Phase 3 data showed an increasing trend for some types of infection with increasing serum concentration of secukinumab. Candida infections, herpes infections, skin infections, and infections requiring treatment increased as serum concentration of secukinumab increased.

Neutropenia was observed in clinical trials. Most cases of secukinumab-associated neutropenia were transient and reversible. No serious infections were associated with cases of neutropenia.

Inflammatory Bowel Disease
Cases of inflammatory bowel disease, in some cases severe, were observed in clinical trials with COSENTYX®. In the placebo psoriasis program, with 3430 psoriasis patients exposed to COSENTYX® over the entire treatment period for up to 52 weeks (2725 patient-years), there were 3 cases (0.11 per 100 patient-years) of exacerbation of Crohn’s disease, 2 cases (0.08 per 100 patient-years) of exacerbation of ulcerative colitis, and 2 cases (0.08 per 100 patient-years) of new onset ulcerative colitis. There were no cases in placebo patients (N = 793, 176 patient-years) during the 12 week placebo-controlled period.

One case of exacerbation of Crohn’s disease was reported from long-term non-controlled portions of ongoing clinical trials in plaque psoriasis (see Warnings and Precautions (5.3)).

6.2 Non-Live Vaccines
Patients treated with COSENTYX® may receive non-live vaccinations. Healthy individuals who received a single 150 mg dose of COSENTYX® 2 weeks prior to vaccination with a non-U.S. approved group C meningococcal polysaccharide conjugate vaccine and a non-U.S. approved inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive COSENTYX® prior to vaccination. The clinical effectiveness of meningococcal and influenza vaccines has not been assessed in patients undergoing treatment with COSENTYX® (see Warnings and Precautions (5.3)).

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. The immunogenicity of COSENTYX® was evaluated using an electrochemiluminescence-based bridging immunosassay. Less than 1% of subjects treated with COSENTYX® developed antibodies to secukinumab in up to 52 weeks of treatment. However, this assay’s limitations in detecting anti-secukinumab antibodies in the presence of seukinumab therefore the incidence of antibody development might not have been reliably determined. Of the subjects who developed antidrug antibodies, approximately one half had antibodies that were classified as neutralizing. Neutralizing antibodies were not associated with loss of efficacy.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (incovalence) in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to COSENTYX® with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS
7.1 Live Vaccines
Patients treated with COSENTYX® may not receive live vaccinations (see Warnings and Precautions (5.6)).

7.2 Non-Live Vaccines
Patients treated with COSENTYX® may receive non-live vaccinations. Healthy individuals who received a single 150 mg dose of COSENTYX® 2 weeks prior to vaccination with a non-U.S. approved group C meningococcal polysaccharide conjugate vaccine and a non-U.S. approved inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive COSENTYX® prior to vaccination. The clinical effectiveness of meningococcal and influenza vaccines has not been assessed in patients undergoing treatment with COSENTYX® (see Warnings and Precautions (5.3)).
7.3 CYP450 Substrates
The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation.

Results from a drug-drug interaction study in subjects with moderate to severe psoriasis showed no clinically relevant interaction for drugs metabolized by CYP3A4.

Upon initiation or discontinuation of COSENTYX in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed (see Clinical Pharmacology (12.3) in the full prescribing information).

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Limited available human data with COSENTYX use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In an embryo-fetal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of secukinumab during organogenesis at doses up to 30 times the maximum recommended human dose (MRHD) (see Data).

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data
Animal Data
An embryo-fetal development study was performed in cynomolgus monkeys with secukinumab. No malformations or embryo-fetal toxicity were observed in fetuses from pregnant monkeys that were administered secukinumab weekly by the subcutaneous route during the period of organogenesis at doses up to 30 times the MRHD (on a mg/kg basis at a maternal dose of 150 mg/kg).

A pre- and post-natal development toxicity study was performed in mice with a murine analog of secukinumab. No treatment related effects on functional, morphological or immunological development were observed in fetuses from pregnant mice that were administered the murine analog of secukinumab on gestation days 6, 11, and 17 and on postpartum days 4, 10, and 16 at doses up to 150 mg/kg/dose.

8.2 Lactation
Risk Summary
It is not known whether secukinumab is excreted in human milk or absorbed systemically after ingestion. There are no data on the effects of COSENTYX on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for COSENTYX and any potential adverse effects on the breastfed child from COSENTYX or from the underlying maternal condition.

8.4 Pediatric Use
Safety and effectiveness of COSENTYX in pediatric patients have not been evaluated.

8.5 Geriatric Use
Of the 3430 plaque psoriasis subjects exposed to COSENTYX in clinical trials, a total of 230 were 65 years or older, and 32 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 years and older was not sufficient to determine whether they responded differently from younger subjects.

10 OVERDOSAGE
Doses up to 30 mg/kg intravenously have been administered in clinical trials without dose-limiting toxicity. In the event of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

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T2020-09
Skin of color patients lacking in psoriasis trials

LISETTE HILTON | Staff Correspondent

An overwhelming majority of subjects in phase 3 psoriasis clinical trials are Caucasian, leaving unanswered questions about how one’s ethnicity or race might impact the safety and efficacy of today’s psoriasis treatments, according to a research letter published August 7 in the British Journal of Dermatology.

Psoriasis impacts people with all skin colors. Studies on U.S. adults suggest psoriasis affects about 3.6% of Caucasians, 1.9% of African Americans and 1.6% of Hispanics. Up to 0.47% of Asians are thought to have psoriasis, according to East and Southeast Asian population studies.

Researchers have found evidence that patients’ ethno-racial backgrounds might impact how they respond to biologics and other treatments, according to the authors.

“... evidence has shown that non-white ethnicity is associated with a reduced likelihood of responding to biologics up to one year...”

In general, studies have shown that about 20% of new medications demonstrate inter-racial/ethnic variability in efficacy and safety profiles, dosing, pharmacokinetics, pharmacogenetics and other factors.

“Phase 3 clinical trials provide important large-scale safety and efficacy data on novel treatment options. The inclusion of non-white patients in clinical trials is critical as it can inform tailored treatment algorithms and the development of educational resources and support groups,” according to the authors.

An example of how diversity in research can impact treatment algorithms is in hypertension. While black people are at increased risk of developing hypertension, there wasn’t enough data to make evidence-based treatment decisions for black patients until the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial, in which more than a third of subjects were black. Data from the trial led to specific treatment recommendations for black patients that are in the Joint National Commission hypertension treatment guidelines, according to the research letter.

University of California, San Francisco, researchers reviewed the ClinicalTrials.gov database looking for completed phase 3 clinical trials of plaque psoriasis in adults before May 8, 2020.

They identified 82 phase 3 clinical trials evaluating psoriasis treatments from topicals to systemic and biological medications, representing nearly 49,000 patients. When they analyzed enrolled subjects’ ethnicities and races, the researchers found 62 of the studies reported on subjects’ ethno-racial information, with 64.5% of those studies reporting comprehensive race and ethnicity data.

Nearly 86% of subjects in those 62 studies were white, according to the research letter.

Considering the global burden of psoriasis, which is estimated between 0.91% to 8.5% of the population, the inclusion of 14.2% non-white subjects in phase 3 psoriasis studies severely underrepresents adults with skin of color with the skin disease. That’s particularly true when it comes to black subjects, who made up 3.09% of subjects in those phase 3 psoriasis trials.

Increasing clinical trial diversity is a critical goal, the authors wrote.

An amendment in the Health Revitalization Act, which went into effect in 2017, requires researchers to report subjects’ race and ethnicity in National Institutes of Health (NIH)-funded trials.

Psoriasis trial researchers should consistently report safety and efficacy data sub-analyses by ethnicity and race, regardless of the funding source.

On a bigger scale, new strategies are needed that focus on diversifying clinical trials and data registries, such as implementing goals specifically aimed at recruiting people of color; employing people and involving organizations in marginalized communities to help with recruitment efforts; and funding translation services when necessary in recruitment and informed consent processes, they wrote.

Disclosures:
None

Reference:
Quick TAKES

- Positive predictive value (PPV) of 60% was achieved for the highest-risk group.
- 40-GEP test clearly differentiates tumors into three classes.
- Results indicate tumor biology could be a factor in predicting SCC metastasis.

Gene expression profile test predicts metastatic risk

ILYA PETROU, M.D. | Staff Correspondent

In a recent study,1 researchers developed and validated a 40-gene expression profile (40-GEP) test to help improve the clinician’s ability to identify patients with primary cutaneous SCC at high risk for metastatic disease.

“SCC is an area of cutaneous oncology where we have a large knowledge gap in terms of being able to predict which SCC tumors can be cured with local destructive techniques or surgery alone, and trying to identify those tumors that are going to go on and metastasize and may benefit from further intervention and surveillance,” says Ashley Wysong, M.D., M.S., associate professor and chair of the Department of Dermatology, University of Nebraska Medical Center, Omaha, Nebraska.

“The implementation of a validated gene expression profile test for SCC could significantly impact the treatment planning and prognosis of many of these high-risk SCC tumors,” adds Wysong.

In the prospectively designed study, researchers collected archival formalin-fixed paraffin-embedded primary cutaneous SCC tissue and clinicopathologic data (n=586) from 23 different independent centers across the United States. They then developed a GEP profile using a discovery cohort (n=202) and validated in a separate, then developed a GEP profile using a discovery cohort (n=324).

Wysong and her fellow researchers started with approximately 150 genes taken both from the literature as well as independent findings from all of the various labs involved in the development of the assay. They used deep machine learning to narrow that to a group of 40 genes found to be most predictive of metastasis of SCC.

The prognostic 40-GEP test stratified high-risk cutaneous SCC patients into classes based on metastatic risk: Class 1 (low-risk), Class 2A (high-risk), and Class 2B (highest-risk). Data showed that for the validation cohort, the three-year metastasis-free survival rates were 91.4%, 80% and 44%, respectively. An improvement over current staging systems, results also showed that a positive predictive value (PPV) of 60% was achieved for the highest-risk group (Class 2B). However, negative predictive value, sensitivity and specificity were comparable to staging systems.

“The 40-GEP test was able to clearly differentiate tumors into three classes which we believe are clinically relevant going forward. When used in conjunction with current staging systems, the GEP test could have a profound impact on the treatment and management of higher-risk cutaneous SCC tumors,” Dr. Wysong says.

Following in the footsteps of gene expression profile testing successfully used in melanoma, this 40-GEP test is the first test of its kind available for SCC. According to Dr. Wysong, GEP testing should be considered for high-risk SCCs in any patient with at least one high-risk feature such tumor size greater than 2 cm, depth beyond subcutaneous fat or > 4 mm, moderate-to-poor differentiation, perineural invasion, site of prior radiation therapy or chronic inflammation, recurrent tumors and immunosuppressed patients.

“Clinical staging used in cutaneous oncology has advanced over the last 10 years, and we are getting better at utilizing patient-specific and histologic risk factors to help determine the risk for nodal metastasis,” she says. “Nevertheless, determining which tumors will metastasize remains challenging. I believe tumor biology is an important component that needs to be addressed.”

Going forward, Dr. Wysong says the goal is to try to implement and integrate the 40-GEP test further with clinical and histologic risk factors and try to identify those groups where the GEP testing could be beneficial.

“This is an extremely exciting time for SCC and cutaneous oncology as a whole. I think the integration of GEP data and tumor biology into our current clinic and histologic staging models is momentous,” she says. “We are at the cusp of personalized medicine and state-of-the-art oncology care for individual SCC patients.”

Disclosure:
Dr. Wysong reports no relevant disclosure.

Reference:
A breakthrough for patients with advanced CSCC

LIBTAYO® is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.1

79% of responders (50 out of 63 patients) reached a DOR of ≥6 months2,2*: 54% of responders (34 out of 63 patients) reached a DOR of ≥12 months2,2*

ORR: 63 out of 137 patients (95% CI, 37%-55%)1,2

*Median duration of follow-up was 11.1 months for combined CSCC in Study 1540.2* See additional study design details below.1

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and usually occur during treatment; however, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1–blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-mediated pneumonitis: Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%), and Grade 2 (1.3%). Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg/day or equivalent. Pneumonitis resolved in 62% of patients. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated colitis: Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%). Colitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥40 mg/day or equivalent. Colitis resolved in 80% of patients. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated hepatitis: Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%). Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg/day or equivalent. Hepatitis resolved in 64% of patients. Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases to more than 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated endocrinopathies: Withhold LIBTAYO if clinically necessary for Grade 2, 3, or 4.

Adrenal insufficiency: Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%)

Hypophysitis: Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis

Hypothyroidism: Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%); no patients discontinued hormone replacement therapy

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
**Important Safety Information (continued)**

**Warnings and Precautions (continued)**

**Severe and Fatal Immune-Mediated Adverse Reactions**

*Immune-mediated endocrinopathies (continued):*

- **Hyperthyroidism:** Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%). Hyperthyroidism resolved in 38% of patients.

- **Type 1 diabetes mellitus:** Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%).

*Immune-mediated nephritis with renal dysfunction:*

Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%). Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients.

*Immune-mediated dermatologic adverse reactions:*

Immune-mediated dermatologic reactions, including erythema multiforme and pemphigus, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%). In addition, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥40 mg/day or equivalent. Nephritis resolved in all patients. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0–1) after corticosteroid taper.

*Other immune-mediated adverse reactions:*

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO or were reported with the use of other PD-1–blocking and PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0–1) after corticosteroid taper.

- **Neurological:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/ myelitis gravis, Guillain-Barré syndrome, nerve paresis, and autonomic neuropathy

- **Cardiovascular:** Myocarditis, pericarditis, and vasculitides

- **Oral:** Ulcers, irritis, and other oral inflammatory toxicities. Some cases can be associated with retinal detachment. Various Grades of visual impairment to include blindness can occur. If ulcers occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss

- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, and duodenitis

- **Musculoskeletal and connective tissue:** Myositis, rhabdomyolysis, and associated sequelae, including renal failure, arthritis, and polymyalgia rheumatica

- **Haematological and immunological:** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, and solid organ transplant rejection

**Adverse reactions**

- **Serious adverse reactions occurred in 35% of patients.** Serious adverse reactions that occurred in ≥2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia. The most common Grade 3–4 adverse reactions (≥2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia.

- **Embryo-fetal toxicity**

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

**Use in specific populations**

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO

- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

*Results as of data cutoff October 27, 2017.

†This patient also had cranial lesions that were included in the calculation of best percent change in target lesion(s). Those images are not included here.


To learn more about LIBTAYO, speak with your sales representative or visit LIBTAYOhcp.com.
LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE
LIBTAYO® is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (lCSCC) who are not candidates for curative surgery or curative radiation.

2 CONTRAINDICATIONS

Early identification and management are essential to ensure safe use of PD-1/PD-L1 blocking antibodies.

3 WARNINGS AND PRECAUTIONS

None.

4 ADVERSE REACTIONS

The most common adverse reactions reported in at least 20% of patients were fatigue, rash, diarrhea, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%).

5.2 Infusion-Related Reactions

Severe infusion-related reactions occurred in ≤2% of patients receiving LIBTAYO [see Adverse Reactions (6.1)]. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see Dosage and Administration (2.2)].

5.3 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]

- Infusion-Related Reactions [see Warnings and Precautions (5.2)]

5.1 Clinical Trials Experience

The data described below reflect exposure to LIBTAYO in 219 patients with advanced CSCC in two open-label, single-arm, multicohort studies (Study 1423 and Study 1540), including 98 patients with mCSCC (nodal or distant), 65 patients with lCSCC, and 71 patients with other advanced solid tumors. LIBTAYO as a single agent or in combination with chemotherapy or radiation was administered intravenously at doses of 1 mg/kg every 2 weeks to 1 mg/kg every 4 weeks to 1 mg/kg every 6 weeks. Patients with mCSCC (nodal or distant) had a median age of 65 years (range 29 to 89 years), 61% male, 83% white, and 9% Hispanic. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (range 38 to 96 years), 63% male, 96% white, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash, diarreal, skin infections, and pneumonia.

The following table summarizes the adverse reactions that occurred in >10% of patients and Table 2 summarizes adverse reactions that occurred in ≥2% of patients receiving LIBTAYO.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=219</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and Administration Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 summarizes the adverse reactions that occurred in >10% of patients and Table 2 summarizes adverse reactions that occurred in ≥2% of patients receiving LIBTAYO.

Table 1: Adverse Reactions in ≥2% of Patients Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=219</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and Administration Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 summarizes the adverse reactions that occurred in >10% of patients and Table 2 summarizes adverse reactions that occurred in ≥2% of patients receiving LIBTAYO.
Table 1: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1548 (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO N=219</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Abnormality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

Table 2: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>2</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
</tbody>
</table>

Toxicity was graded per NCI CTCAE v4.03.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADA) were tested in 467 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.1% using an electrochemiluminescent (ECL) bridging immunoassay; 0.2% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1)). There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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.

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1- and PD-L1 knockout mice.

Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO (see Use in Specific Populations (8.1)).

Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)).

Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

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

8.5 Geriatric Use

The safety and effectiveness of LIBTAYO have not been established in elderly patients.
According to researchers, each of the studies in the review had a high risk of bias in at least one of the four QUADAS-2 areas. Key concerns include participant selection and lack of representation of skin of color and special sites.

**References**


**Disclosures**

No relevant disclosures were reported.

**Quick Takes**

Researchers conducted a critical appraisal of a systematic review of six different smartphone apps and found little evidence that they are effective in self-monitoring or skin cancer detection.

According to researchers, each of the studies in the review had a high risk of bias in at least one of the four QUADAS-2 areas. Key concerns include participant selection and lack of representation of skin of color and special sites.

**Smartphone apps not effective in skin cancer risk**

**Algorithms and study methodology need improvement.**

**ILA PETROU, M.D. | Staff Correspondent**

A recent review of a study evaluating the use of algorithm-based smartphone applications (apps) to assess skin cancer risk found that the currently available technologies used in this niche still need improvement to be effective. As such, clinicians and their patients should be wary of relying on these apps when assessing skin cancers.

The incidence of skin cancers is on an alarming rise, with up to 3 million occurring worldwide. Melanomas account for approximately 4% of skin cancers and are responsible for 75% of deaths. That underscores the necessity for self-monitoring and earlier detection which can impact survival outcomes from melanoma. Algorithm-based smartphone apps used for skin cancer diagnosis are designed to potentially help facilitate early detection of otherwise aggressive life-threatening skin cancers, allowing patients to seek further medical assessment of suspicious lesions in a timely fashion.

Researchers from the University of Manchester recently conducted a critical appraisal of the systematic review performed by Freeman et al. which evaluated algorithm-based smartphone apps used to assess the risk of skin cancer in suspicious skin lesions. The systematic review included nine studies that evaluated six different identifiable smartphone apps. Of these, six studies verified results by using histology or follow-up, with five studies evaluating the detection of melanoma and one study evaluating the SkinVision app, designed to detect other skin cancers such as basal cell carcinoma (BCC) and SCC as well as premalignant conditions. Three studies, all evaluating the SkinVision app, verified results by using expert recommendations for whether further investigation or intervention should be pursued. Two included diagnoses for all types of premalignant and malignant lesions, and one study did not report the expert diagnosis.

“Freeman et al produced a high-quality systematic review, showing that there is little evidence that smartphone apps can be useful in self-monitoring and detection of skin cancer at present,” write Zenas Zee Ngai Yiu, M.D., and colleagues, Dermatology Centre, Salford Royal NHS Foundation Trust, NIHR Manchester Biomedical Research Centre, University of Manchester, Manchester Academic Health Science Centre, Manchester, U.K.

The overall results of the Freeman paper show variable and unreliable test accuracy across the selected smartphone apps. According to the researchers, the systematic review was well conducted and reported. Investigators used QUADAS-2, a validated tool to assess diagnostic accuracy studies, to assess study quality. They found that each included study had a high risk of bias in at least one of four QUADAS-2 domains.

Of the studies included in the review, the researchers note that the selectively recruited participants were not fully representative of the general population. Seven studies recruited patients who were already selected for excision of suspicious lesions or undergoing assessment of their skin conditions by dermatologists. Moreover, the researchers found it ambiguous as to whether skin of color and special sites, such as acral skin and nails, were represented adequately.

“Without a focus on whether the patient sample is generalizable to the population, including an adequate representation of different skin colors and body sites, algorithms risk producing biased results,” the researchers wrote.

When evaluated in a representative sample for the target population, the positive predictive value (PPV) of the algorithms can prove useful as a screening tool. However, this was not reported or extracted in the systematic review. According to the researchers, any given screening test will likely have a higher PPV for common skin cancers and a lower PPV with a high false positive rate in a disease of lower prevalence, i.e. melanoma.

“This may have a low impact on improving patient survival from melanoma but a high adverse effect of increasing overdiagnosis, unnecessary healthcare visits and potentially procedures, increasing use of scarce healthcare resources,” say the researchers.

To improve upon smartphone apps used for skin cancer diagnosis, the researchers suggest that future studies and systematic reviews for these reports on the presence of industry funding and the PPV where appropriate, highlight whether special body site images were included in the training and validation datasets and report whether the proportion of participants of skin color reflects the target population.

**Disclosures**

No relevant disclosures were reported.

**References**


Mohs micrographic surgery presents challenges in kids

ILYA PETROU, M.D. | Staff Correspondent

Although Mohs micrographic surgery (MMS) has long been established as a safe and effective therapeutic modality for the treatment of a variety of skin tumors in adults, little is known regarding its use in children and adolescents. A recent review study looked at the unique challenges encountered when employing this technique in the pediatric population and highlighted how clinicians can best circumvent these obstacles in order to help facilitate the appropriate use of Mols in children.

Typically performed in an outpatient setting, Mohs involves surgical excision and intraoperative assessment of tumor margins by the surgeon. The procedure is characterized by real-time histopathologic margin control and the ability to spare healthy tissue, particularly in cosmetically sensitive areas, resulting in better cosmetic outcomes as well as high cure rates. Although occurring less commonly than in adults, aggressive cutaneous tumors are also seen in children and Mohs can provide significant advantages in terms of margin control and minimization of surgical margins.

“In the pediatric population, this can be especially beneficial given the patients’ small body surface areas, and tissue preservation can be instrumental in helping to avoid functional and cosmetic morbidity. Mohs has not yet become first-line treatment in the pediatric population for challenging skin tumors. As such, I believe there needs to be an increased awareness amongst dermatologists and pediatricians who care for these patients regarding the benefits of Mohs as well as the challenges that are particular to this age group and how these challenges can be best overcome to provide optimal patient care,” says Hanieh Zargham, M.D., Division of Dermatology, Montreal General Hospital, McGill University Health Center, Montreal, Canada.

Dr. Zargham and colleague Amor Khachemoune, M.D., recently performed a comprehensive systematic review of the PubMed and EMBASE electronic databases including English, Spanish and French language literature articles that reported on the clear specification of the use of “slow Mohs” and “modified Mohs,” and the use of this technique in patients younger than 18 years of age. In the final analysis, 87 articles were identified that included 111 patients ranging in age from 6 weeks to 17 years (median age 11 years), and a total of 123 resected tumors. A predisposing comorbidity was noted in 10 percent of patients (n=11) with the most common being xeroderma pigmentosum (n=3). The most common tumor treated was dermatofibrosarcoma protuberans (n=62), followed by basal cell carcinoma (n=30), and most common location of lesions was the head and neck, followed by the trunk and extremities.

Data showed that 12 patients underwent general anesthesia, 7 had local anesthesia, and one patient had conscious sedation, while all other articles did not specify the means of anesthesia. Three patients reported complications consisting of a cellulitis, a seroma and a minor wound dehiscence and only one patient had a recurrence noted at 44 months post-op. The researchers found that the most commonly cited challenges in the application of Mohs in the pediatric population included patient cooperation, concerns for safety of prolonged general anesthesia, availability of a Mohs surgery service in the pediatric setting, and access to a histopathology lab experienced in MMS sectioning.

Performing any surgical procedure, especially a longer one such as Mohs, can be particularly difficult in children and each age group has their own unique set of challenges. There are several challenges regarding the procedural logistics of Mohs in children however, according to Dr. Zargham, the biggest one may be the unpredictability of patient cooperation, especially when performed under local anesthesia.

“We believe children are usually upset about being restrained, older children usually have an anticipation of pain that can lead to anxiety and an unwillingness to cooperate, which can make the process difficult and impact time constraints of the surgical staff and healthcare facilities,” Dr. Zargham says.

Screening a child’s psychological and developmental status prior to a preoperative consultation is important in assessing likelihood of cooperation. According to Dr. Zargham, clinicians should remember that there are several different pharmacological (i.e., injection techniques minimizing pain) and non-pharmacological approaches to facilitate patient cooperation. To the latter, the combination of swaddling and sweet solutions as well as hypnosis with imagery can be used to immobilize infants and toddlers during surgery, and distraction methods can be used for older children.

If the procedure cannot be performed under local anesthesia, then the discussion about general anesthesia can be undertaken. In these cases, multidisciplinary planning including dermatologists, pediatricians and other healthcare workers involved in the care of the child, preoperative imaging, “slow Mohs,” and using multiple cryostats for larger tumors can all be helpful in decreasing procedure time. In addition, using “slow Mohs” with permanent sections is helpful when access to an MMS lab is limited.

“There may be numerous challenges to overcome when performing Mohs in children but we need to have a better understanding of these challenges and really think about practical ways how some of these challenges can be overcome so that we can facilitate the appropriate use of Mohs in children and provide the best patient care to our pediatric patients,” Dr. Zargham says.

Disclosures
No relevant disclosures were reported.

Reference
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FEB 4 - 7 2021
Robotic-controlled laser advances body contouring

CHERLY GUTTMAN KRADER | Staff Correspondent

The new 1064-nm laser for non-contact body contouring introduces robotics into aesthetic surgery and brings advantages for increased efficiency and precision, said Jill Waibel, MD, at the virtual annual meeting of the American Society for Dermatologic Surgery.

Dr. Waibel described the technology (eon FR, Dominion Aesthetic Technologies) and presented the results from the clinical trial that supported FDA clearance of the device.

“This novel system delivers the laser energy with a precision-controlled, motorized, articulated arm and is the first of its design to treat abdominal adiposity,” said Dr. Waibel, medical director and owner, Miami Dermatology and Laser Institute, Miami, FL.

“It offers easy application and the ability to treat the entire abdomen in just 1 hour. Patients have no postprocedural downtime, and in early experience their satisfaction has been high. Considering these features, I believe this new device provides a promising solution to current barriers in noninvasive body contouring treatment.”

SOPHISTICATED TECHNOLOGY

The robotic arm on the laser was inspired by the remote-controlled mechanical arm found on the Space Shuttle (Canadarm). Because of its repeatable, accurate motion, the treatment head is maintained at a uniform distance from the skin and traverses the abdomen at a constant speed. The device also incorporates an innovative and patent pending proprietary jet impingement cooling system.

“We know that treatment with the 1064-nm wavelength is effective for lipolysis, but with manually operated devices there is no way to control whether the energy is delivered long enough or too long, which can cause excessive or suboptimal heating,” Dr. Waibel said.

“This system reduces human error and delivers energy that effectively activates apoptosis while minimizing patient discomfort.”

CLINICAL TRIAL RESULTS

Dr. Waibel was one of three investigators participating in the premarketing study that evaluated the laser. Eligible patients had a body mass index ≤30 kg/m² and ≥25 mm thickness of adipose tissue on the abdomen.

A total of 36 patients were enrolled. They ranged in age from 18 to 70 years and had Fitzpatrick skin types I-V. Each patient was treated at a single session on the lower abdomen in a designated 150 cm² on each side.

The primary outcome was based on a blinded evaluation of fat reduction judged on clinical photographs by three independent raters at week 12 post-treatment. The results showed a preference for the week 12 appearance versus baseline for 94.4% of the image pairs. Consistent with those results, 95% of patients reported visible reduction in fat and overall improved appearance.

Secondary outcomes included ultrasound measurement of fat thickness, which showed a 21.6% reduction, and circumferential measurements, which showed a 3.40 mm reduction.

“All patients had a >1 inch average reduction in circumference with a range of up to 4 inches,” Dr. Waibel reported.

Pain during the procedure was reported by 9 (25%) patients. Nodules, which Dr. Waibel noted are the result of an inflammatory response following fat necrosis and fairly common after lipolysis with any 1064-nm laser, developed in four patients (11.1%) and were self-limiting. No adverse events were reported at the 12-week follow-up visit.

PLATFORM REFINEMENTS

Dr. Waibel said that the device used in the premarketing trial was a prototype model. Refinements found in the commercially available system have resulted in increased efficacy and better patient comfort. The changes include an increase in the energy setting that as reported by Thomas Fiala, MD, in a postmarketing study, led to a 26.3% reduction in ultrasound-measured fat thickness.

In addition, the company addressed pain during the procedure by increasing cooling at the points where the robotic arm turns to change direction at the end of a pass.

“There is the potential for a ‘hot spot’ to develop when the treatment head turns a corner, and some patients reported pain in association with that phenomenon. However, their discomfort was generally mild, on the order of a 2 or 3 out of scale of 10,” said Dr. Waibel.

Disclosures:

Dr. Fiala and Suzanne Kilmer, MD, also participated as investigators in the premarketing study of the laser.

Dr. Waibel is on the advisory board for Dominion Aesthetic Technologies and an advisor, consultant, and/or clinical trial investigator for other aesthetic laser companies.
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As an antioxidant, it may decrease the production of reactive oxygen species and free radicals as well as damage from ultraviolet radiation and may even have a protective effect from ultraviolet radiation and may even have a protective effect. It helps to decrease the damage from ultraviolet radiation and may even have a role in promoting hair growth through its effect on the enzyme 5-alpha reductase. It is increasing found in makeup, cosmetics, creams, and cosmeceuticals due to its ability to penetrate the tough skin barrier and its high biologic activity.

CAFFEINE'S ROLE AND BENEFITS

So what concentrations of caffeine are potentially beneficial, and normally incorporated into skincare? The average amount of caffeine normally present in commercially available, over-the-counter skincare products is around roughly 3%. Further investigation is needed to evaluate whether a higher concentration is needed. Further exploration. The hair follicle represents an important route whereby substances enter the skin. Caffeine is a model for a highly water-soluble compound, and thus is used frequently in experiments studying skin penetration. Interestingly, the thickness of the skin and occlusion have little impact on the ability of caffeine to penetrate the skin. However, the absorption rates of caffeine into select areas of the skin have regional differences. In certain areas, hair follicles have “weak spots” that allow hydrophilic substances such as caffeine to penetrate. This may, in turn, also encourage faster delivery of topical substances.

CAFFEINE AND CARCINOGENESIS

Caffeine has anti-carcinogenic properties. Through oral administration in black tea and green tea, it was found to have a possible inhibitory role in the development of malignancies. It has also been associated with up-regulation of tumor suppressor genes. Oral intake of caffeine has demonstrated an effect on the inhibition of UVB-induced carcinogenesis, thus supporting its role in sun protection. Further research has also shown that applying caffeine topically promotes apoptosis in sunburn cells in mice, some of which were pretreated with UVB radiation, further supporting its role in inhibition of carcinogenesis. Research has shown that applying caffeine topically decreases the amount of malignant and benign cutaneous tumors found in mice that were pretreated with UVB radiation. The use of topical caffeine results in increased apoptosis in squamous cell carcinomas and benign skin tumors. Additional research by the same team also demonstrated that topical use of caffeine may have a sunscreen-like effect on the skin and enhance UVB radiation-induced cell death, which has potential implications for its role in inhibiting the formation of sun-induced skin cancer. Given these findings, further investigation is needed to evaluate whether topical administration of caffeine has a possible role in the prevention of skin cancer and how much it can inhibit sunlight-induced photo damage in humans.

It is no surprise that many manufacturers have chosen to add small amounts of caffeine to their topical formulations, cosmetics, skincare, and cosmeceuticals products that are available on the market today. Given its potential to decrease the onset of skin cancer, decrease photo damage from UV exposure, and its role as an antioxidant, further investigations are needed to determine how effective it may be in these particular roles as a cosmeceutical and a nutriceutical in both oral and topical form. So far, supporting evidence shows caffeine may offer relief and benefits to a wide range of dermatologic and skin conditions when applied topically, with an added benefit of increased penetration into the skin barrier.

References:
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Steps are being taken to increase diversity and equity within the aesthetics field by Allergan Aesthetics, an Abbvie company, and Skinbetter Science through the launch of The DREAM Initiative. DREAM: Driving Racial Equity in Aesthetic Medicine, is focused on implementing measures to increase racial and ethnic diversity, equity, understanding, inclusion and respect within the plastic surgery and dermatology fields, according to the press release.

“We are inaugurating the DREAM Initiative with three important projects, which will immediately expand available resources to enhance the care of all patients, as well as to better diagnose and treat dermatologic conditions across the full spectrum of skin types and patients of color,” says Carrie Strom, senior vice president of Abbvie and president of Global Allergan Aesthetics.

With darker skin types being underrepresented in current medical education materials, leading to under- or misdiagnoses in patients with these skin types, both companies are joining forces to construct The National Racial Equity Medical Residency Curriculum.

In an effort to help students, faculty and staff in dermatology and plastic surgery residency programs, the curriculum is designed to assist with identification of implicit bias in clinical and academic settings while also demonstrating how to address bias when it occurs.

The DREAM Initiative will also sponsor the development of The Spectrum of Dermatologic Disease, a photo atlas textbook showing the characteristics of skin conditions across racial and ethnic skin types.

Additionally, the initiative plans on organizing Forces of Beauty Summits to recognize diverse beauty standards amongst various ethnic and racial groups to help aesthetic providers, companies and the media understand the aesthetic needs of all patients.  

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Although the neuromodulators with cosmetic indications that are used for facial rejuvenation represent different molecules and vary in some formulation aspects, the same core neurotoxin — botulinum toxin A (BTXA) — is responsible for their therapeutic action. All can be used “with great success” when the treatment is delivered by a trained clinician, says Seth Matarasso, M.D.

“When it comes to clinical impact, the BTXA products are more similar than dissimilar,” according to Dr. Matarasso, clinical professor of dermatology, University of California San Francisco, speaking at a session on neuromodulators which he co-directed at the American Society for Dermatologic Surgery (ASDS) Virtual Annual Meeting October 9. “Although individual clinicians may have a preference for a particular neuromodulator, I think all of the products are safe and effective when used in the right hands. I believe that many of the reported differences between these products can be related to the injector, not the injectable.”

Still, a closer look reveals some nuanced factors that can impact the decision.

Of the four neuromodulators with cosmetic indications, only onaBTXA (Botox Cosmetic, Allergan) is approved to treat all three aesthetic areas of the face: the glabella, peri-ocular crow’s feet and forehead lines from the frontalis muscle. IncoBTXA (Xeomin, Merz), aboBTXA (Dysport, Galderma), and prabTXA-xvs (Jeuveau, Evolus) currently only have U.S. FDA approval for the glabellar area and are used off-label in other facial areas.

There are reports that the treatment effect is less durable with incoBTXA compared with other BTXA products. Dr. Matarasso notes. However, he suggests the longevity of incoBTXA may be shortened as the result of improper reconstitution leading to suboptimal dosing.

“Some of the active ingredient in the incoBTXA vial can be trapped at the rim unless the reconstituted solution is adequately swirled after dilution. It is my opinion that the shorter duration of benefit associated with incoBTXA relates to patients not getting the appropriate dose,” he explained. He also notes that one benefit of incoBTXA is that unopened vials do not need to be refrigerated.

Based on his experience, discomfort during injection may be a little greater when using aboBTXA, Dr. Matassaro says. There is a basis for that observation considering that the reconstituted aboBTXA solution is a little more acidic than the other products, and the difference has been documented in split-face comparisons with another BTXA product. However, Dr. Matarasso says he does not believe there are any dramatic differences in product tolerability.

Clinical experience also indicates that aboBTXA may result in a “harder freeze” compared with onaBTXA.

“This may be my personal bias, but I find that patients maintain a bit more facial mobility after an onaBTXA injection. I have seen patients who reported noticing a difference when the neuromodulator they were being treated with was switched,” he said. “The difference may be explained by greater diffusion using aboBTXA.”

While observing that, in his experience, prabTXA-xvs has a slightly faster onset of action than other BTXA products, he questions the importance of the difference, which is only about 24 hours. On the flipside, the treatment effect may be a little briefer with prabTXA compared with the other neurotoxins, he added.

“Perhaps clinicians may encounter a patient who wants to see the benefit of the treatment right away, but I don’t believe that is a common occurrence nor do I think that there are any clinically relevant differences in time to onset or durability among the commercially available toxins,” says Dr. Matarasso.

Looking ahead, daxibTXA (Revance Therapeutics), which is not yet FDA-approved, is reported to have a longer duration of action than the available neuromodulators. Dr. Matarasso says, however, that he is somewhat skeptical about the difference and noted greater persistence is not always desirable.

“From a physiologic perspective, I don’t think it makes sense that the therapeutic effect of daxibTXA can be longer lasting. Perhaps the durability observed in the daxibTXA clinical trials is the result of the touch-ups that were allowed,” he explains. “Longer duration can be achieved with any of the toxins by increasing the number of units injected. But it is not something that we necessarily want considering that complications can occur even when treatment is done by a skilled injector.”

Dr. Matarasso rejects the idea of using certain products in a site-specific manner such that a patient may be treated with more than one neuromodulator to address lines in different areas of the face. “My concerns are that combining products can lead to confusion with dosing and with determining the agent that is responsible if a patient develops an adverse reaction,” he explains.

The bottom line: it is exciting to have multiple products to offer patients, and clinicians can choose confidently among them, says Dr. Matarasso. He hopes that the expansion in the neuromodulator space will spur more rigorous studies evaluating their efficacy, including comparative trials, and might even prompt manufacturers to reduce product costs.

Disclosure: Dr. Matarasso has served on advisory boards to Allergan, Galderma, and Revance.

References:
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2020 has certainly ushered in wholly unthinkable challenges! Like all of you, the Cosmetic Surgery Forum team has been facing them head-on and doing all we can to care for those around us and make a better community for us all.

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For more information, please contact: Natasha Mohr or Meg Housholder - info@CosmeticSurgeryForum.com - 402-697-6564
Many dermatologists caught up quickly, learning valuable lessons along the way. At the pandemic’s peak, dermatologists saw 57% of their patients remotely, a level commensurate with that of other specialties, according to the survey.1 “Telemedicine has been a complete lifesaver,” says Joel Schlessinger, M.D., Dr. Schlessinger, an Omaha, Nebraska-based board-certified dermatologist and cosmetic surgeon and CEO of LovelySkin.

One of the drivers for that dramatic uptick came from the federal government and various insurers who began waiving restrictions on telemedicine in mid-March to encourage quick adoption by healthcare providers.

“That’s exactly what we did,” says Adam Friedman, M.D., professor and interim chair of dermatology, George Washington School of Medicine and Health Sciences. “It’s very hard to make such a pivotal change in one’s practice. But we did a pretty good job.” Schlessinger adds that, with the help of his practice’s electronic medical records (EMR) vendor, Nextech, “We were up and running for telemedicine within three days of asking them about it.”

Offering telemedicine is one thing; optimizing it is another. First, Dr. Friedman’s practice got Zoom (Zoom Video Communications) licenses for all its team members, including residents. “It was a learn-as-you-go approach. We learned a lot of simple things that enhanced the experience, ensured timelines and got the most out of telemedicine as we went along,” he says. Initially, Dr. Friedman’s patients were reluctant. “This is something completely new to these patients — especially in certain populations who don’t have technology literacy or access to technology.”

To address that, Dr. Friedman’s schedulers use a script to help “sell” telemedicine. If a patient doesn’t understand the process, a staff member walks them through a typical telehealth appointment and explains how patient safety and information security are maintained. Still, glitches persist. For example, when a patient schedules a telehealth visit, a staff member immediately sends a detailed email explaining how to download and use Zoom. “They’re given all the information,” Dr. Friedman says. “But we found that, when you get to the time of the visit, the patient doesn’t understand the process before the appointment. The time required for this two-step process creates severe challenges for practices, says Dr. Schlessinger. “It was never as efficient as seeing the patient in the office, frankly.” For example, if the doctor identifies a suspicious mole during a telemedicine visit, the patient will need a second in-office visit for evaluation of the mole. Previously, that would have been addressed in a single appointment. The time required for this two-step process creates severe challenges for practices, says Dr. Schlessinger.

Now, says Dr. Schlessinger, telemedicine appointments are modestly profitable. His practice still sees five to 10 patients — such as those with acne, nonsurgical concerns or unwanted tattoos — daily this way.

Before the pandemic, all faculty were seeing patients every 15 minutes, often with double bookings, says Dr. Friedman. Depending on program year, residents saw patients every 20 or 30 minutes, also with double bookings. “With telehealth, you can’t do overbooks because you can only log into one telehealth visit at a time,” he says.

Initially, providers saw one remote patient every 30 minutes, and later every 20 minutes as comfort with the system grew. “Even though we were still able to have clinical productivity, it was a fraction of what we were pre-COVID-19.”

With loosened COVID-19 restrictions, Dr. Friedman now sees most patients on-site, although he says he hopes telemedicine is here to stay. On average, according to the physician survey, dermatologists expect to see 12% of their patients through teledermatology post-pandemic.

For Dr. Schlessinger, telemedicine visits likely will continue at least until the pandemic ends. “While we still haven’t reached the same numbers that we were doing overall, including both medical and cosmetic, the fact that we are running at a less dense schedule and approaching parity with our monthly revenue is encouraging. I don’t see us going back to full patient volume until we have a vaccine or things are significantly better.”

By John Schlemon

Reference:

Disclosures:
Dr. Friedman and Dr. Schlessinger report no relevant financial interests.
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