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The study’s findings come at a time when dermatologists are looking for effective options for severe acne patients, according to study author Leon Kircik, M.D.

Topical ivermectin cream, 1% (Soolantra, Galderma) represents an advance in treatment for rosacea, offering superior efficacy and tolerability compared with previously available therapies, says Jeffrey S. Fromowitz, M.D., who spoke at the Orlando Dermatology Aesthetic & Clinical Conference.

Because of its benefits, ivermectin is also changing the treatment paradigm for rosacea, shifting the goal to targeting “clear” status for patients rather than settling for “near”.

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Each of the following companies have made a strong commitment to the advancement of patient care. Their support today will elevate our understanding of skin diseases and disorders, and clear the path for new therapies. We are grateful for their contributions and their confidence in the Foundation.

**2019 PLATINUM BENEFACORS ($200,000 OR MORE)**

- Galderma
- Sun Dermatology
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Our eyes are on the future

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

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

The Dermatology Foundation is a 501(c)3 charitable organization. Contributions are deductible to the extent provided by law.
INDICATION
ODOMZO® (sonidegib) is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

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

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

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

See full Prescribing Information for ODOMZO.

INDICATIONS AND USAGE

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

WARNINGS AND PRECAUTIONS

WARNING: EMBRYO-FETAL TOXICITY

See full Prescribing Information for complete boxed warning.

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

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

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

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

DOSAGE AND ADMINISTRATION

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

CYP3A inducers: Avoid strong and moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

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

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

LACTATION

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

PEDIATRIC USE

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

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

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Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

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PLR-00105
IMPORTANT SAFETY INFORMATION (continued)

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

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

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

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

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

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

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

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

Please see additional Important Safety Information on the front cover and Brief Summary of Prescribing Information, including Boxed WARNING, inside the front cover.
COMBINING A 40-MG DOXYCYCLINE DOSE (Oracea, Galderma) with a topical containing adapalene 0.3% and benzoyl peroxide 2.5% (Epiduo Forte, Galderma) is an effective and safe treatment option for severe acne, according to a single-center pilot study of 20 patients, published September 2019 in the Journal of Drugs in Dermatology.1

The study’s findings come at a time when dermatologists are looking for effective options for severe acne patients, according to study author Leon Kircik, M.D., who spoke at the Orlando Dermatology Aesthetic & Clinical Conference. It’s a revolution in atopic dermatitis therapy that promises to treat patients of all ages and suffering from every aspect of the disease—from rashes, itch and sleep disturbances, to secondary effects, like anxiety and depression, he says.

New target is clear
Topical ivermectin creates a new treatment paradigm

Because of its benefits, ivermectin is also changing the treatment paradigm for rosacea, shifting the goal to targeting “clear” status for patients rather than settling for “near clear.” IVERMECTIN CONTINUES ON PAGE 37 ▶

Dr. Eichenfield

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on the cover

ACNE
Oral + topical improve severe acne

ROSACEA
Ivermectin creates new Tx paradigm

ATOPIC DERMATITIS
PIPEDLINE POTENTIAL
EXPERT POINTS TO PROMISING THERAPIES
Better disease control

New agents, guidelines offer hope

MIKE HENNESSY, SR.

DISEASE BURDEN is a significant concern with many dermatologic conditions. Patients face both financial and social challenges, and physicians face the often resulting challenge of therapeutic adherence. Additionally, while research shows that there is much going on with drug development, significant numbers of patients report that their disease negatively impacts their lives, underscoring the need to find ways to improve disease control.

There is an unprecedented array and steady stream of newer agents in various phases of drug development for atopic dermatitis, as Lawrence Eichenfield, M.D., notes on page 1. Researchers are studying approved drugs in younger patients and, with the introduction of new topical and systemic therapies, there is hope that physicians can now better minimize the impact of the disease, he says.

In addition, newly published joint clinical guidelines for children with psoriasis (page 18), offer insight into better managing children with psoriasis, offering guidance on the psychosocial burden of the disease as well as how to screen for comorbidities in this population.

While room for improvement exists in patient satisfaction, the therapeutic pipeline in these areas is strong and encouraging. We hope that the reports in this issue on drug development in atopic dermatitis, psoriasis and acne/rosacea as well as recent clinical guidelines provide you a basis for continuing to improve your care of patients with these conditions.

MIKE HENNESSY, SR., CHAIRMAN AND FOUNDER OF DERMATOLOGY TIMES’ PARENT COMPANY, MJH LIFE SCIENCES.
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.
HUMIRA CITRATE-FREE
Prescribe it for your new and existing HUMIRA patients

YOU CAN HELP HER GO FORWARD

Use in Adolescents

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

Safety Considerations (cont’d)

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

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

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

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

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

Discontinue HUMIRA if a patient develops a serious infection or sepsis. Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection.

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

- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria. Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycobacteria are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.
- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

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

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

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

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

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

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

- Postmarketing cases of acute and chronic leukemias 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.

HYPERSENSITIVITY

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

HEPATITIS B VIRUS REACTIVATION

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

NEUROLOGIC REACTIONS

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

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

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

AUTOIMMUNITY

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

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the in utero exposed infant. The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA in utero is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (≥10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

References:

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

Please see Brief Summary of full Prescribing Information on the following pages.
**DISCUSSION**

HUMIRA® (adalimumab) is indicated for the treatment of moderate to severe rheumatoid arthritis (RA). HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) and for reducing signs and symptoms and inducing clinical remission in patients with active ulcerative colitis. HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with Crohn's disease. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in patients with psoriasis. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in patients with ankylosing spondylitis and is also approved for reducing signs and symptoms and inducing clinical remission in patients with active psoriatic arthritis.

**INDICATIONS AND USAGE**

**Rheumatoid Arthritis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms, improving physical function, and reducing the rate of Structural Damage in adult patients with moderately to severely active rheumatoid arthritis (RA) whose disease is inadequately controlled with one or more DMARDs, including tumor necrosis factor (TNF) blockers.

**Juvenile Idiopathic Arthritis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

**Psoriatic Arthritis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms, improving the progression of structural damage, and improving physical function in adults with psoriatic arthritis.

**Psoriasis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms in adults with active plaque psoriasis who have a history of inadequate response or intolerance to prior systemic therapy.

**Ankylosing Spondylitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in adult patients with active ankylosing spondylitis.

**Ulcerative Colitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderate to severe ulcerative colitis who have failed prior conventional therapy.

**Pediatric Crohn's Disease**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease.

**Malignancy**

HUMIRA® (adalimumab) is indicated for reducing the risk of tuberculosis (TB) in adult patients who are at increased risk of TB and who are unable to use other TB prophylaxis.

**Indications for HUMIRA® in Ps (Psoriasis)**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms of Ps and for reducing the rate of skin lesion development.

**Indications for HUMIRA® in PsA (Psoriatic Arthritis)**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms in adult patients with PsA with a history of inadequate response or intolerance to prior systemic therapy.

**Indications for HUMIRA® in AS (Ankylosing Spondylitis)**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in adult patients with active AS.

**Indications for HUMIRA® in Juvenile Idiopathic Arthritis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in patients with active JIA.

**Indications for HUMIRA® in Juvenile Idiopathic Arthritis with Uveitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in patients with JIA with uveitis.

**Indications for HUMIRA® in Crohn's Disease**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with active Crohn's disease.

**Indications for HUMIRA® in Ulcerative Colitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderate to severe ulcerative colitis.

**Indications for HUMIRA® in Ankylosing Spondylitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in adult patients with active AS.

**Indications for HUMIRA® in Juvenile Idiopathic Arthritis with Uveitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in patients with JIA with uveitis.

**Indications for HUMIRA® in Crohn's Disease**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with active Crohn's disease.

**Indications for HUMIRA® in Ulcerative Colitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderate to severe ulcerative colitis.

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**Indications for HUMIRA® in Juvenile Idiopathic Arthritis with Uveitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in patients with JIA with uveitis.

**Indications for HUMIRA® in Crohn's Disease**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with active Crohn's disease.

**Indications for HUMIRA® in Ulcerative Colitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderate to severe ulcerative colitis.

**Indications for HUMIRA® in Ankylosing Spondylitis**

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**Indications for HUMIRA® in Juvenile Idiopathic Arthritis with Uveitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in patients with JIA with uveitis.

**Indications for HUMIRA® in Crohn's Disease**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with active Crohn's disease.

**Indications for HUMIRA® in Ulcerative Colitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderate to severe ulcerative colitis.

**Indications for HUMIRA® in Ankylosing Spondylitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in adult patients with active AS.

**Indications for HUMIRA® in Juvenile Idiopathic Arthritis with Uveitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in patients with JIA with uveitis.

**Indications for HUMIRA® in Crohn's Disease**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with active Crohn's disease.

**Indications for HUMIRA® in Ulcerative Colitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderate to severe ulcerative colitis.

**Indications for HUMIRA® in Ankylosing Spondylitis**

HUMIRA® (adalimumab) is indicated for reducing signs and symptoms and improving clinical remission in adult patients with active AS.
In pediatric patients treated with adalimumab with moderate to severe active Crohn’s disease (CD) and who also had a history of non-infectious uveitis, the proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 7.5% and 8.4%, respectively. The difference between the proportions of major birth defects among the adalimumab-treated and the untreated infants was not statistically significant.

**Human Data**

In a placebo-controlled randomized study of 152 women with rheumatoid arthritis (RA) who received adalimumab during pregnancy, the proportion of women who delivered a live-born infant with a major birth defect was 7.5% (9/121) in the adalimumab group and 8.4% (10/121) in the placebo group. The difference between the proportions of major birth defects among the adalimumab-treated and the untreated infants was not statistically significant.

**Postmarketing Experience**

A total of 122 CD patients 16 years of age or older with an indication for adalimumab who had received adalimumab during pregnancy were treated in six cases of pregnancy or maternal/fetal risk. The proportion of major birth defects among these patients was 3.2% (4/122) in the adalimumab group and 5.0% (6/122) in the placebo group. The difference between the proportions of major birth defects among the adalimumab-treated and the untreated infants was not statistically significant.

**Risk Summary**

Adalimumab is a humanized monoclonal antibody that neutralizes tumor necrosis factor alpha (TNF-α), a cytokine that plays a role in the pathogenesis of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, and psoriasis. The safety and efficacy of adalimumab have been evaluated in controlled clinical trials and postmarketing studies in pediatric patients with Crohn’s disease, pediatric patients with JIA, and adult patients with uveitis.

**Carcinogenesis**

Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential of the drug. In a 2-year study of adalimumab in mice, adalimumab was not found to be carcinogenic.

**Mutagenesis**

No in vitro or in vivo tests conducted in adalimumab-treated mice or rats indicated that adalimumab is mutagenic or clastogenic.

**Impairment of Fertility**

No specific studies have been conducted to evaluate the effects of adalimumab on fertility in males or females. However, the effects of adalimumab on fertility in males or females have not been observed in preclinical studies.

**Use in Specific Populations**

**Pediatric Use**

Adalimumab has been studied in pediatric patients with Crohn’s disease, JIA, and uveitis. In pediatric patients with Crohn’s disease, adalimumab was well tolerated and effective, and the safety profile in pediatric patients was similar to the safety profile in adults. In pediatric patients with JIA, adalimumab was well tolerated and effective, and the safety profile in pediatric patients was similar to the safety profile in adults. In pediatric patients with uveitis, adalimumab was well tolerated and effective, and the safety profile in pediatric patients was similar to the safety profile in adults.

**Precautions**

Adalimumab should be used cautiously in patients with a history of severe infections, particularly those with a history of recurrent or persistent infections, or who have a history of prolonged infection. Adalimumab should be used with caution in patients who are immunocompromised or who have a history of immunosuppression, such as patients with HIV/AIDS, patients with lymphoma, or patients with malignancy.

**Drug Interactions**

Adalimumab is not expected to interact with cytochrome P450 enzymes or other drugs that are metabolized by cytochrome P450 enzymes. Adalimumab is not expected to interact with other drugs that are metabolized by cytochrome P450 enzymes, such as methotrexate, azathioprine, cyclosporine, or mycophenolate mofetil.

**Adverse Reactions**

Adalimumab is associated with a risk of serious infections, including tuberculosis, listeriosis, and pneumocystis pneumonia, and the risk of serious infections increases with the duration of treatment. Adalimumab is associated with a risk of serious infections, including tuberculosis, listeriosis, and pneumocystis pneumonia, and the risk of serious infections increases with the duration of treatment.

**Laboratory Abnormalities**

Laboratory abnormalities associated with adalimumab treatment include increased hepatic enzymes and increased blood counts for neutrophils and eosinophils.

**Nonclinical Toxicology**

Adalimumab is a potent inhibitor of TNF-α, which has anti-inflammatory properties. Adalimumab has been shown to reduce the incidence of infections in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn’s disease. Adalimumab has been shown to reduce the incidence of infections in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn’s disease.

**Other Information**

Adalimumab is supplied as a sterile, lyophilized powder for subcutaneous injection. The recommended dose of adalimumab is 40 mg subcutaneously every other week.

**Dosage and Administration**

The recommended initial dose for patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn’s disease is 40 mg subcutaneously every other week. The recommended initial dose for patients with psoriasis is 80 mg subcutaneously at weeks 0 and 2, followed by 40 mg subcutaneously every other week.

**Human Data**

Adalimumab has been studied in 192 pediatric patients with Crohn’s disease in one double-blind study (Study PCD-I). A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster. In adult patients, a total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

**Other Adverse Reactions**

Adalimumab has been studied in 464 adult patients with psoriasis who were treated with adalimumab and had an infection while receiving HUMIRA in Study PCD-I. The safety profile for patients with psoriasis who were treated with adalimumab and had an infection while receiving HUMIRA in Study PCD-I was similar to the safety profile in patients with psoriasis who were treated with adalimumab and had an infection while receiving HUMIRA in Study PCD-I.

**Treatment of Infections**

In patients with infection while receiving HUMIRA, the infection should be treated before discontinuing HUMIRA. The infection should be treated before discontinuing HUMIRA. The infection should be treated before discontinuing HUMIRA. The infection should be treated before discontinuing HUMIRA. The infection should be treated before disconnecting HUMIRA.
One of the hardest things I ever say to a patient is: “I am sorry, but there is no treatment for your condition.”

In this world of scientific dominance, it is hard for the patient to imagine that there are no options — or that all possible options have been exhausted without success. Failure as a physician is difficult. I want to run and knock on the door of the nearest pharmaceutical company and tell them that I have a patient who I need to help!

“Could you develop something that would make me a better physician in the eyes of my patient?” I’d ask.

“Could you do it quickly? Because my patient is in pain with accompanying emotional distress. This situation is very important to both my patient and me! Please do something!”

I find it a sobering thought that I could do little as a dermatologist without prescription medications. I rely on excellent pharmaceuticals to provide excellent results that will, in turn, allow my patient to see that I really am an excellent dermatologist.

There is no doubt that I am dependent on innovation in the pharmaceutical industry to advance my ability to treat patients. However, the innovation in dermatology is now coming through other areas of medicine laterally.

For example, many biologics were originally developed for rheumatology and introduced for psoriasis indications. These same biologics are being tested for other dermatology indications, like atopic dermatitis and hidradenitis suppurativa. This type of drug development still results in excellent dermatologic treatments, but we need to encourage primary pharmaceutical interest in dermatologic indications.

It has been discouraging to see a number of exciting dermatology start-ups disappear following financial problems or failed phase 3 studies.

Topical dermatology drug development faces higher hurdles than any other area of medicine. Oral medications are much easier to develop because a true pill placebo can be developed. In topical drug development, there is no true placebo thus our studies are vehicle-controlled instead of placebo-controlled.

In many cases, the vehicle functions as a less effective active, raising the bar to demonstrate statistical superiority for the vehicle/active over the vehicle alone. This encourages drug formulators to make less-desirable vehicles to minimize the vehicle effect; however, topical drugs would be much more aesthetically pleasing, tactfully elegant and efficacious if this were a nonissue.

Topical drug development is a hurdle for many pharmaceutical companies, requiring the encouragement and support of dermatologists.

It is sad that we are currently experiencing a proliferation of new generics in dermatology instead of new innovator drugs. The price of topical dermatologics has skyrocketed. A topical brand acne antibiotic sold for $25 a bottle during my residency and now the generic bottle sells for $400. Indeed, there has been some inflation, but the efficacy of the medication is unchanged.

Many existing and new generic companies are examining the profit margin now possible on topical drugs and entering dermatology. While interest in dermatology is positive, innovator drugs are critical to the advancement of our specialty. I recently had a conversation with the head of research and development for a generic dermatology company. He had been in his position for 25 years and noted that there had been a steady stream of innovator topicals in dermatology for generic development, but this had now changed. He was not sure where his next generic was coming from and had even considered attempting to encourage his company to become a drug innovator!

I do remember 25 years ago attending the winter American Academy of Dermatology meeting with three to four new product launches annually. There was tremendous proliferation in new corticosteroid molecules of varying potency with many different vehicles to choose from,
allowing customization for body area. Now, I am forced to use the first-line covered formulary corticosteroid for all indications and body areas. I feel like printing prescription pads with the three basic formulary-approved, low copay drugs that I am able to use and simply circling the one the patient is to receive.

Topical innovation is still occurring with the promise of new topical JAK inhibitors, which would be similar to the development of topical corticosteroids in terms of advancing dermatology. Inflammation reduction without skin atrophy! However, this type of innovation in topicals needs to be encouraged.

I hope this editorial is a call to action for dermatologists to be supportive of efforts by pharmaceutical companies on our behalf. This relationship has become strained in recent years by governmental regulation, corporate scandals and rising pharmaceutical prices.

The fact remains, however, that we are dependent on better drugs to be better dermatologists. We should be willing to help identify unmet medical needs, areas of opportunity and promising technologies. We should also offer our opinions and input on formulation and efficacy. Only through collaborative efforts can we guide the development of drugs needed for excellence in our specialty.
Can I pay a patient to leave my practice?

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’s patient has seen him for body exams, eczematous dermatitis and acneiform eruptions for more than a decade. No matter what he does, she is not happy. She has expressed her discontent to his staff and to him. On numerous occasions, she has refused to pay insurance co-pays and deductibles. He has written off thousands of dollars over the course of three years. Finally, he sends her a letter discharging her from the practice.

She responds by saying she will “destroy him” on social media if he does not allow her to see him. Dr. Derm responds by offering her $1,000 to never come back to the practice. She files a complaint with the state Board of Medical Examiners over the ethics of such a practice. Is he in trouble?

In reality, most patients do like their dermatologists. Unfortunately, that is not the case with all patients.

Dr. Derm treated his patient within the standard of care. His treatment, by all means, was good. Yet, this patient became disrespectful to the doctor and his staff. He felt it was worth paying her $1,000 to go away. He had nothing else to offer her medically, and he wanted to be left in peace and tend to his other patients who valued his time.

In “real life” people are paid for doing something: for an action or activity or labor. But in medicine (dermatology), not always.

At times, the government paid farmers to not grow crops. Why? To balance supply and demand in the marketplace; to achieve a policy objective.

Zappos, the shoe retailer, pays new employees to quit. That program, called Pay to Quit, extended the offer to its newest employees within the first few weeks post-hiring. Employees had to first be hired — so they were eminently qualified. Zappos would pay the new hires $1,000 to quit. Very few took the company up on its offer. Amazon, which purchased Zappos in 2008, came up with a similar type of program.

The company annually makes an offer to pay fulfillment center associates up to $5,000 to leave. The offer starts at $2,000 for employees who have been at the company for one year, and it increases by $1,000 for each year of employment. However, those who accept the offer can never work at Amazon again, according to CNBC.

“We want people working at Amazon who want to be here,” Amazon spokesperson Melanie Eshes told CNBC Make It. “In the long-term, staying somewhere you don’t want to be isn’t healthy for our employees or for the company.”

Amazon tells CNBC that they don’t accept employees to accept the offer. In fact, the memo is headlined: “Please Don’t Take This Offer,” founder and CEO Jeff Bezos tells the news outlet.

But, monetary payments can enhance employee engagement and may be cost-effective in the long run, says Michael Burchell, workplace culture expert and author of the book “The Great Workplace: How to Build It, How to Keep It and Why It Matters.”

Employee engagement tends to be about commitment to stay and discretionary effort. While Pay to Quit may not necessarily push employees to work harder, he tells CNBC, it does address the issue of commitment to stay.

Disengaged employees cost their company about 34% of their salary, according to a Gallup poll. A disengaged employee making $50k/year costs his company $17k in lost productivity. So, there’s a strong business rationale for paying disengaged workers to leave. (Of course, one can always fire that employee. But, the pay-to-quit option “smokes out” those employees who may never have reached the threshold of being noticed for their detrimental effect.) So, it’s a short-term cost with hope of a long-term benefit.

Does this principal apply to the management of a disgruntled patient who is loud, aggressive, disrespectful and angry (assuming there is nothing medically different that can be done for him/her)? This is always hard to evaluate. If nothing else, there is a “psychic cost,” if not an actual economic cost to Dr. Derm.

It makes sense that some dermatologists want to pay select patients to quit.

The obvious problem: patient abandonment is a serious issue in medicine. Before terminating a relationship with a patient, Dr. Derm may be required to ensure continuity of care. Patient dismissal letters can save time and money — and potential lawsuits. Dr. Derm’s payoff may be acceptable as long as there is no abandonment.
There are key differences between skin activities that occur during the day and night.

NEW CONCEPTS: Body rhythm moisturizers

by ZOE DIANA DRAELOS, MD

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

What are body rhythms?

The concept of body rhythms has been popularized as important in overall health. These rhythms are fluctuations in mental, physical and emotional well being based on the clock related to the day/night cycle, hormones, meals, sleep/wake cycle, adrenal gland production, thyroid gland and clock genes. The study of the body circadian rhythm is known as chronobiology with studies of the body’s inner clock dating back to the 18th century.

There are three types of chronobiology rhythms: infradian rhythms, ultradian rhythms, and circadian rhythms. Infradian rhythms last more than 24 hours and are repeated only every few days, weeks or months and represent such activities as female menses. Ultradian rhythms are shorter than 24 hours and often last several hours, such as ingestion of food. Finally, circadian rhythms last 24 hours with distinctive day/night cycles.

What are circadian rhythms?

Circadian rhythms are endogenous and adjusted to the local environment by cues called zeitgebers, meaning “time giver” in German. The 2017 Nobel Prize in physiology or medicine was awarded for research in molecular mechanisms controlling circadian rhythms in fruit flies. In humans, the circadian clock is in the suprachiasmatic nucleus, located in the hypothalamus. PER1 and PER2 genes are expressed in the suprachiasmatic nucleus representing the primary circadian pacemaker in the human brain.

These circadian rhythms are also important in the skin with robust autonomic clocks in keratinocytes, fibroblasts, melanocytes, mast cells and hair follicles. Important skin functions affected by circadian rhythms include free radical production and neutralization, DNA damage and repair, keratinocyte/fibroblast differentiation and proliferation, and barrier and immune functioning.

What are circadian rhythm-based moisturizers?

There are key differences between skin activities that occur during the day and night. During the day, the skin has the highest pH, sebum production and thickness with the lowest cell proliferation. Conversely, during the night, the skin has the highest DNA repair, cell proliferation, barrier permeability, skin penetration, blood flow, moisturizer loss and the lowest barrier recovery rate. This has led to the development of moisturizers to address the diurnal variation in skin needs and a new concept in cosmeceuticals.

A very obvious example of a circadian rhythm-based moisturizer would be the inclusion of sunscreen. Sunscreen-containing moisturizers should be worn during the day and not at night based on daytime sun exposure. Since the skin barrier permeability is higher at night, more occlusive moisturizer formulations should be used to include products with less water and more oils. Occlusive ingredients include petrolatum, mineral oil, and shea butter. Since sebum production is higher during the day, oil control ingredients such as talc or kaolin should be placed in daytime products. Also, since the skin pH is higher during the day, oil control ingredients such as talc or kaolin should be placed in daytime products. Also, since the skin pH is higher during the day, it may be worthwhile to make daytime formulations slightly more acidic to lower pH. These are examples of how cosmeceuticals can be modified to address the circadian rhythm concept.
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Current systemic agents used to treat AD aren’t doing enough to alleviate disease burden.

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

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

Study underscores need to improve disease control

LISETTE HILTON | Staff Correspondent

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

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

“[The study] shows that the standard of care with currently available topical, oral systemic and phototherapies is clearly inadequate...”

Jonathan I. Silverberg, M.D., Ph.D., MPH, associate professor of dermatology, medical sciences and preventive medicine at the Feinberg School of Medicine, Northwestern University, Chicago.

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

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

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

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

Most participants (63.6%) reported using topical corticosteroids in the last month, while 11.4% used systemic corticosteroids and 5.1% had used systemic immunosuppressants in the last month, according to the baseline monthly data.

“Regardless of AD severity, 38% of patients who had received systemic agents in the past six months reported that they had not experienced remission in the prior 12 months,” the authors write.

Data from the Patient-Oriented Eczema Measure (POEM), a seven-item measure of symptom frequency in the past week, revealed that 52.6% of participants reported moderate to very severe symptoms in the short term. More than 34% of patients indicated they experienced one to four days of disrupted sleep in the last week. Severe atopic dermatitis patients fared worse in those two outcomes.

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

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

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

References:

Basis for standardized care

WHITNEY J. PALMER | Contributing editor

As one of the most common dermatological conditions of childhood, atopic dermatitis affects between 10% and 20% of pediatric patients. Knowing how to most effectively treat these individuals is critical to ensuring the best possible outcomes. However, no clear framework exists to guide dermatologists and other pediatric providers on the optimal therapeutic methods.

To ensure patients receive standardized care, a team led by Adrian Pona, M.D., a dermatologist with Wake Forest University School of Medicine, investigated not only which providers most frequently treat children with atopic dermatitis, but which medications they most commonly prescribe. Findings were published in the Journal of Drugs in Dermatology.1

“The most important thing to understand is that we have guidelines for atopic dermatitis,” he says. “We’ve got guidelines on how to manage it appropriately, and we want to see if healthcare providers are adhering to those guidelines.”

Following treatment recommendations is critical, he says, because relapse and treatment failure rates for atopic dermatitis are high, frequently leading children and their families to suffer bodily discomfort, as well as psychological and financial detriment. And, in many cases, this condition can continue into adulthood, making long-term successful management even more vital.

EXAMINING OPTIONS

To determine who treats these patients most often, Dr. Pona’s team examined 10.4 million ambulatory medical records from the National Ambulatory Medical Care Survey from 2006 to 2015. According to the records, male and female patients sought atopic dermatitis treatment equally. White children accounted for approximately 71% of patients even though the condition proportionately affected African-American and Asian-American children more, five out of every 1,000 and seven out of every 1,000, respectively.

The records also revealed children with atopic dermatitis receive treatment from a variety of providers. While pediatricians are the most common physician, seeing 31% of cases, dermatologists address 27% of cases, and family physicians see 11% of these patients. Other providers, including emergency room doctors, urgent care physicians, nurse practitioners, and physician assistants, account for the remaining 31% of cases.

Based on study results, pediatricians are the specialists that see the most atopic dermatitis cases, but dermatologists are the specialists that see the most such cases per physician.

This data also underscores the importance of all providers in the treatment and management of atopic dermatitis. The onus of providing therapy doesn’t just fall to the dermatologist, he says. “We need to know who is seeing these patients so we can be sure they’re adhering to dermatology guidelines or that they’re adhering to the American Academy of Pediatrics guidelines,” he says. “Are we all prescribing the same medication? For example, are primary care and family physicians also prescribing the same things as dermatologists?”

COMMONLY USED MEDICATIONS

According to the study results, topical corticosteroids are the most common medication class recommended for children with atopic dermatitis, and dermatologists are the most likely provider to prescribe the most potent of these medications, Dr. Pona says. Specifically, providers prescribe triamcinolone as their first-line drug, suggesting it in 25% of office visits. Most frequently, it is prescribed for patients between the age of 2 and 7, as well as over the age of 18, emerging as an initial therapy in 9% and 7% of cases, respectively.

Hydrocortisone is the second most commonly prescribed topical corticosteroid at 19%, and it is most often recommended for children under one year and between the age of 8 and 18. Its lower potency makes it an attractive treatment option for this age group. Providers can also turn to several similar medications. For example, desonide is prescribed in 6% of patients, clobetasol in 4%, fluocinolone in 2%, and desoximetasone in 1%.

Alongside topical corticosteroids, Dr. Pona says, providers also employ moisturizers as an effective atopic dermatitis treatment. Study results revealed that physicians recommend pimecrolimus cream during 6% of office visits. It’s important to note, though, he adds, that because moisturizers are not considered drugs, no definitive instructions for prescribing patterns for healthcare providers exist.

Additionally, Dr. Pona cautions providers about the use of second-generation antihistamines, including cetirizine, to treat atopic dermatitis. Although these drugs were the second most commonly prescribed medications for this patient population, using them to manage the condition is not recommended. There’s currently little evidence to support their efficacy, he says.

Ultimately, Dr. Pona hopes the findings from this study can be used to guide further atopic dermatitis treatment.

“This information acts as a reference to what the nature of managing atopic dermatitis will be in the future,” he says. “It’s a reference that we will use to manage and follow the guidelines for our future patients. And, it will help us know — in the next decade — if they’re still adhering to the recommended guidelines.”

References:
Pipeline for atopic dermatitis full of potential

**EXPANDING INDICATIONS**

Researchers are studying approved atopic dermatitis drugs in younger patients, according to Dr. Eichenfield, chief of pediatric and adolescent dermatology at Rady Children’s Hospital San Diego, and professor of dermatology and pediatrics at the University of California San Diego School of Medicine.

**Quick TAKES**

*Expert: Atopic dermatitis therapy is undergoing a revolution.*

A pipeline holds promise for patients of all ages.

Pfizer recently announced that it completed a study of topical crisaborole (Eucrisa) in atopic dermatitis patients younger than two years. “It appeared safe, but we haven’t yet heard the details of the data and the status of expanded specific indication for use of crisaborole under age two,” says Dr. Eichenfield, who also is on the National Eczema Association’s Scientific Advisory Committee.

The FDA has approved dupilumab (Dupixent, Sanofi and Regeneron Pharmaceuticals), an interleukin (IL)-4 and IL-13 blocker, in adults and patients ages 12 to 17 years with moderate-to-severe atopic dermatitis.

“Studies have been completed down to six years of age, and they’re finishing studies down to under two years,” Dr. Eichenfield says. “The community is well aware that we have children across the ages that have very severe disease. Historically, there have been no systemic drugs, other than corticosteroids, approved for pediatric and adolescent atopic dermatitis until the approval of dupilumab age 12 and older.”

**PIPOLINE OF POTENTIAL**

Dr. Eichenfield points to an unprecedented array and steady stream of newer topical and systemic agents that are in various phases of drug development.

“We continue to see portions of the data as they move along from phase 2 to phase 3 trials,” he says.

There are two IL-13 inhibitors well under development: tralokinumab (Leo Pharma) and lebrikizumab (Dermira).

“This brings forward the intriguing question of whether they’re going to be as effective or less effective than IL-4 and IL-13 blocker [like dupilumab]. They may be more selective. There are differences in how the drugs work in terms of how they block IL-13 signaling. We’re awaiting those studies,” Dr. Eichenfield says.

Yet another biologic target in atopic dermatitis is IL-31. IL-31 blocker nemolizumab (Calderma) has been in clinical studies.

“We’re waiting for further results to see how that could potentially be a niche therapy for moderate-to-severe disease,” Dr. Eichenfield says.

Immune targeted therapies in the pipeline include GBR380, an OX40 immunoglobulin G antibody. This immune checkpoint receptor appears to be important in T-cell activity, according to Dr. Eichenfield. There are two companies developing OX40 inhibitors for atopic dermatitis: Kyowa Hakko Kirin and Glenmark Pharmaceuticals.

“This will be a relatively specific immune target but whether it has broader immunosuppression is unknown until we see the clinical trial results,” according to Dr. Eichenfield.

There are several Janus kinase (JAK) inhibitors by many drug companies being studied for atopic dermatitis. JAK inhibitors are small molecule medications—more traditional type oral drugs that are not antibody based. The JAK-signal transducer and activator of transcription (STAT) pathway appears important in a variety of inflammatory diseases, including atopic dermatitis. This pathway is also being studied for alopecia areata and vitiligo treatment, according to Dr. Eichenfield.

The three JAK inhibitor drugs that are furthest along in development for atopic dermatitis are Eli Lilly and Company drug baricitinib; Abbvie’s upadacitinib; and Pfizer’s abrocitinib.

“They have selectivity to different JAK pathways as well as differences in other aspects of drug metabolism. Those differences may influence their efficacy and side effect profiles,” Dr. Eichenfield says. “We’re aware that some of the JAK inhibitors used to treat other diseases, such as tofacitinib (Xeljanz, Pfizer), have received safety warnings because of systemic side effects including venous thrombosis. There are potential effects that may require standard blood work monitoring. As we go forward assessing these drugs, we’ll be assessing safety.”

Interestingly, companies are developing topical JAK inhibitors. Some think topical formulations might minimize the chance of systemic side effects, Dr. Eichenfield says.

“The furthest along that we’ve seen phase 2 and phase 3 trials are for topical ruxolitinib (Incyste) and topical delgocitinib (Leo Pharma),” he says.

In other topical news, DS Biopharma has developed the investigational topical lipid-based product 5% DS107 cream to use along with topical corticosteroids to maintain results from topical corticosteroids and potentially discontinuing their use.

Tapinarof cream (Dermavant), a topical aryl hydrocarbon receptor modulating agent (TAMA) topical, is a novel treatment being developed for psoriasis and atopic dermatitis, according to Dr. Eichenfield.

“There are other drugs that are in earlier stages of development. It’s an interesting diverse landscape for medications,” he says. “We know that we need more drugs to treat atopic dermatitis, as we have increasing evidence of the impact of moderate-to-severe disease and its association with high rates of comorbidities and other health effects, including ADHD [attention deficit hyperactivity disorder], anxiety, depression and more. We also know that many patients have been undertreated due to concerns about topical steroids and corticosteroid phobia. With the introduction of new topical and systemic therapies, we have the promise that we can minimize the disease’s impact on individuals.”

**Disclosures:**

Dr. Eichenfield has consulting and/or research ties to Allergan, Almirall, Dermira, DS Laboratories, Galderma, Glenmark, Incyte, LEQPharma, Lilly, Novan, Otsuka Pharmaceuticals Co., Pfizer, Sanofi Regeneron, Ortho Dermatologics, Valiant.
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Guidelines establish management pearls for kids

ILYA PETROU, M.D. | Staff Correspondent

A collaborative effort between the American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) has led to the first joint guidelines of care for the treatment and management of pediatric patients with psoriasis.1

Similar to guidelines for adults with psoriasis, clinicians need to be aware of the comorbidities that can occur in the pediatric psoriasis population. However, one expert believes that much more attention needs to be given to the psychosocial impact of psoriasis on kids.

“The last AAD psoriasis guidelines that addressed juvenile pediatric psoriasis came out a little over 10 years ago,” says Alan Menter, M.D., chairman, division of dermatology, Baylor University Medical Center, Dallas and co-author of the new guidelines.

“The current guidelines, in collaboration with the National Psoriasis Foundation, are a much more extensive review and include everything we have learned in the treatment and management of psoriasis over that time. We now know more acutely that the quality of life (QoL) of pediatric psoriasis patients can be severely impacted, and this needs to be more seriously addressed by healthcare providers going forward,” he says.

Approximately one-third of psoriasis cases begin in childhood and adolescence; so, it is necessary to screen for these comorbidities and address them early to minimize their long-term impact. It has become clear that psoriasis can no longer be considered only a cutaneous disease, but an inflammatory systemic disease with far-reaching implications, Dr. Menter says.

“The multiple systemic comorbidities found, primary care physicians, pediatricians, rheumatologists and dermatologists should mutually consult on the best treatment approach, and depending on the various comorbidities found, interdisciplinary involvement is typically the best course of action,” Dr. Menter says.

“Clinicians should try to spend more time with their pediatric psoriasis patients during the consult to carefully assess comorbidities, help improve symptoms and increase the quality of life of patients, Dr. Menter says. A multidisciplinary involvement is typically the best approach, and depending on the various comorbidities found, primary care physicians, pediatricians, rheumatologists and dermatologists should mutually consult on the best treatment and management plan for the individual patient.2

Reference:

Disclosures: Dr. Menter reports no relevant disclosures.
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“What I like about this particular meeting is that it’s so intimate and it’s so interactive. You have the opportunity to ask questions of the panelist and have this whole interaction about their experience. I really like that because it’s about sharing what everybody is actually doing in their practices, not just evidence-based but anecdotal and experiential.”
- CHYTRA ANAND, MD

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A primer on interleukin-29

Practical implications of cytokine’s role in pathogenesis

CHERYL KRADER, B.S. PHARM | Staff Correspondent

Interleukin-29 (IL-29) is a newly discovered cytokine that has become the subject of increased research attention for its role in inflammation and inflammatory autoimmune disorders and therefore as a target for novel therapeutic development.

In a recently published paper, researchers provided a review of current knowledge regarding IL-29, including information about its binding, signaling, expression, biologic functions, association with inflammatory autoimmune disorders and therapeutic potential. In presenting the information, the authors state that they hope it will contribute to future research on IL-29, provide some clues regarding the role of IL-29 in inflammatory autoimmune diseases and provide implications for clinical treatment.

“Based on the accumulating evidence that indicates IL-29 has a role in the pathogenesis of inflammatory autoimmune disorders, researchers suggest that the development of the autoimmune diseases might be suppressed by interventions that reverse abnormal IL-29 expression.”

AN IL-10 CYTOKINE

IL-29 is a type 3 interferon and belongs to the IL-10 family, which includes a total of nine cytokines. Like all type 3 interferons, IL-29 mediates signal transduction by binding to its receptors, IL-28R1 and IL-10R2, that are expressed in dendritic cells, T cells, intestinal epithelial cells, leukemia cells and melanoma cells.

Binding of IL-29 activates downstream signaling pathways, including via the JAK-STAT pathway, that leads to the production of a number of inflammatory cytokines and chemokines and also has been shown to result in apoptosis of melanoma cells.

In addition to its antitumor activity, studies indicate that IL-29 has antiviral and immunoregulatory activity, including roles in innate and adaptive immunity. For example, IL-29 stimulation has been shown to enhance toll-like receptor (TLR) 7/8-mediated B cell proliferation, induce immunoglobulin G and immunoglobulin M production by B cells, and induce IL-10 signaling events in macrophages.

It also regulates the production of inflammatory cytokines from monocytes, plasmacytoid dendritic cells, neutrophils and T cells, and inhibits T cell differentiation. In addition, IL-29 is released by mast cells, induces mast cell infiltration, and regulates the release of various cytokines from mast cells.

The antiviral activity of IL-29 has been shown in studies of its effects on keratinocytes. IL-29 induced expression of TLR3 in keratinocytes as well as expression of interferon-induced by herpes simplex virus type 1, protecting the keratinocytes from viral attack.

INFLAMMATORY AUTOIMMUNE DISEASES

Expression of IL-29 has been shown to be dysregulated in atopic dermatitis, psoriasis and other inflammatory autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, Sjögren’s syndrome and systemic sclerosis. In patients with psoriasis, IL-29 expression was found to be upregulated in lesional skin, and the levels of IL-29 expression correlated with antiviral protein expression. Compared with healthy controls, patients with psoriasis were also found to have higher serum levels of IL-29. In addition, IL-29 expression was shown to be increased in the skin of patients with atopic dermatitis compared with healthy controls.

Studies of patients with rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, Sjögren’s syndrome, Hashimoto’s thyroiditis and systemic sclerosis also show increased expression of IL-29 in the serum, whereas a decreased level of IL-29 expression was seen in ocular fluid of patients with juvenile idiopathic arthritis-associated uveitis compared with ocular fluid from controls with idiopathic uveitis.

In an animal model, injection of IL-29 into the skin induced local expression of C-X-C motif chemokines 10 and 11 and T cell infiltration, leading to skin swelling. In psoriatic lesional skin, neutralization of IL-29 with an anti-IL-29 antibody resulted in downregulation of antiviral protein expression.

Based on the accumulating evidence that indicates IL-29 has a role in the pathogenesis of inflammatory autoimmune disorders, researchers suggest that the development of the autoimmune diseases might be suppressed by interventions that reverse abnormal IL-29 expression. Recognizing, however, that the pathogenesis of inflammatory autoimmune diseases is complex, the authors noted that further studies are needed to understand the role and therapeutic effects of IL-29.

References:

A study showing differences in baseline characteristics between responders to anti-tumor necrosis factor (anti-TNF) therapy and insufficient responders may be helpful to dermatologists as they consider treatment for patients with moderate-to-severe psoriasis, according to the investigators.

The research analyzed data from patients enrolled in the Corrona Psoriasis Registry. In an adjusted analysis, female gender was the only baseline characteristic that was independently associated with a decreased likelihood of achieving a response to anti-TNF therapy at six months. However, a number of other imbalances were noted at enrollment between the responders and patients who had an insufficient response to anti-TNF therapy. The investigators suggested that awareness of these differences may help clinicians identify patients with moderate-to-severe psoriasis whose needs may not be met by an anti-TNF agent and who, instead, may benefit from a different mechanism of action.

Providing information to explain the background for conducting the study, researchers note that anti-TNF agents are often used as first-line biologic treatment for psoriasis. They wrote, “Switching or discontinuing anti-TNFs has significant implications for clinical and economic outcomes in patients with psoriasis; therefore, real-world studies that characterize patients on the basis of response to therapy would provide valuable information to help healthcare providers.”

To conduct a “real-world” study, they extracted data from the prospective Corrona Psoriasis Registry, which enrolls adults diagnosed with psoriasis by a dermatologist who started or switched to and continued a systemic or biologic agent within the previous 12 months that has an FDA-approved indication for treating psoriasis. Patients were included in the analysis if they had moderate-to-severe disease, defined as affected body surface area (BSA) ≥3%, entered into the registry between April 2015 and June 2018 upon starting anti-TNF therapy, and had at least one six-month follow-up visit. Patients were identified as insufficient responders if, at six months, their affected BSA was ≥3% or improved <75% from baseline. Patients who had discontinued or were switched from their initial anti-TNF agent were also classified as insufficient responders.

Data were included for 180 patients who were nearly equally comprised of insufficient responders (89 patients, 49.4%) and responders (91 patients, 50.6%). The two groups were compared for demographic characteristics (age, gender, race, ethnicity, body mass index) and baseline disease-related and clinical variables (duration of psoriasis and psoriatic arthritis, comorbidities, Investigator’s Global Assessment, BSA, Psoriasis Area Severity Index, and prior use of biologics) as well as patient-reported outcomes from a variety of questionnaires.

In the statistical analysis that adjusted for baseline differences, females were approximately 50% less likely to achieve a response to anti-TNF therapy compared with males (odds ratio = 0.534, 95% confidence interval = 0.289 to 0.988; P = 0.046). The researchers note that there have been few previous studies investigating differences in response to anti-TNF agents based on patient gender.

However, they identified two previous papers—one involving patients with psoriasis and another analyzing data from patients with psoriatic arthritis—that also reported better response in males than females.

Of the differences found at registry entry between the responders and the insufficient responders in the unadjusted analysis, the investigators say that it was particularly notable that the anti-TNF responders reported better dermatology-related quality of life and according to the data collected by nearly all of the other patient-reported outcome tools, were slightly less impaired by their psoriasis.

Identifying small sample size and short follow-up duration as limitations of their study, researchers call for larger studies to better characterize significant differences between anti-TNF responders and insufficient responders.

References:

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

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

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Quick TAKES

The incidence of adverse events rises with the number of laser skin treatments.

Adverse events can include prolonged erythema and edema and, particularly in skin of color, postinflammatory hyperpigmentation.

Adjunctive treatments may improve results while reducing downtime.

Adjunct therapies may support fractional CO₂

JOHN JESITUS | Staff Correspondent

A lthough the fractional ablative CO₂ laser is a first-line treatment for acne scarring, the potential for side effects from repetitive treatments leaves room for improvement with additive therapies, according to a recent review. However, its authors add, adjunct options ranging from pharmaceuticals to platelet-rich plasma (PRP) require further study.

When treating acne scars with laser alone, the incidence of adverse events rises with the number of treatments, say authors led by Yun Zhu Mu, M.D., department of dermatology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China. These adverse events can include prolonged erythema and edema and, particularly in skin of color, postinflammatory hyperpigmentation. The review appeared in Dermatologic Therapy.

Options ranging from isotretinoin and topical steroids to devices, stem cells and PRP may potentially improve results while reducing downtime. Regarding PRP, small studies have shown significant improvement in acne scarring and post-treatment side effects in combination with fractional CO₂ laser. However, Mu et al. note that in two recent studies, adding topical PRP prolonged postprocedural erythema and edema.2,3 Interpreting such mixed results is difficult, says Ashish C. Bhatia, M.D., who was not involved with the review. There could be variations in the type of PRP used or in patients treated. Because PRP uses each person’s autologous plasma-derived growth factors, he adds, results are inherently difficult to generalize. Dr. Bhatia is associate professor of clinical dermatology at Northwestern University Feinberg School of Medicine, Chicago. He also is co-director of dermatologic, laser and cosmetic surgery and medical director for dermatologic research at Oak Dermatology in Chicago.

Mu et al. highlight two studies showing that combining intense pulsed light (IPL) with fractional CO₂ yielded better therapeutic effects with diminished redness versus laser alone. Subcutaneous incision releases tethering beneath a scar’s surface and loosens scar fibers that are fixed to the dermis as a first step in treating atrophic acne scars. In a 50-patient study, combining subcision with fractional CO₂ laser achieved statistically significant improvements over laser alone. In another study, the “cure rate” of combination therapy was 54.7% vs 43% for laser-only treatment (P<0.001). However, the combination treatment side had a higher incidence of hyperpigmentation and bruising.

Combining RF energy with fractional CO₂ adds the effect of a temperature increase in the upper layers of the dermis. This temperature increase produces a firming and compacting effect, write Mu et al. A 10-patient study showed more pronounced clinical improvement and faster healing with fewer side effects and pigmentation changes in the combination treatment group. But due to the study’s small size, the authors reserve judgment on this combination.

“The two areas where I see the most promise are fractional CO₂ combined with radiofrequency microneedling and with subcision,” Dr. Bhatia says. Like fractional laser therapy, he says, these technologies have demonstrated acne scar- ring efficacy on their own. Their mechanisms of action also complement that of laser resurfacing.

“Fractional CO₂ does a good job from the surface down. Basically you’re drilling little micrometer holes in the scar-type collagen in a pattern, and the depth is based on the energies used,” he says.

This process vaporizes some of the scar tissue while remodeling existing collagen and stimulating new collagen growth around the micro-channels. That improves the surface texture, along with more superficial and intermediate remodeling of the actual scars,” says Dr. Bhatia. “In some cases, you can see improvement in pigmentation as well.”

Conversely, he notes, subcision targets fibrous bands of scar tissue that tether down scars, creating undulations of the overlying skin.

“So if you release those bands from underneath, that takes care of the deeper structural issue,” Dr. Bhatia says.

After subcision, he often injects hyaluronic acid or calcium hydroxyapatite fillers to help normalize contour of the overlying skin. Conversely, he says, RF microneedling penetrates to a prescribed depth and heats tissue from underneath, making it a good choice for remodeling non-tethered acne scars at medium and deeper depths.

References

Disclosures:
Dr. Bhatia is a Cutera investigator, speaker and consultant and Solta Medical consultant.
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Topical probiotics may improve acne lesions

Ingrid Torjesen | Staff Correspondent

Probiotics applied topically could promote a positive bacterial balance on the skin similar to how oral probiotics increase diversity of flora in the gut, and this may improve skin conditions like acne, say authors of a recent review published in *Experimental Dermatology*.1

Few studies have investigated the potential benefits of probiotics in acne management, but what data exist suggest they could be useful for acne as well as other inflammatory skin diseases, write authors Rebecca Knackstedt, M.D., of the department of plastic surgery, Cleveland Clinic, and Thomas Knackstedt, M.D., of the department of dermatology, MetroHealth, Cleveland.1

The intestinal microflora is known to have an impact on gut health, as well as wider systemic inflammation and disease. Some large meta-analyses have found that probiotics may be able to decrease the incidence of infections and need for antibiotics while improving wound healing, markers of inflammation and cholesterol levels. Oral probiotics have also demonstrated efficacy in treating other skin conditions, such as atopic dermatitis and rosacea.

The skin microflora plays a similarly crucial role in regulating inflammation and the immune response. Dysregulation of both the innate and adaptive immune systems has been implicated in the pathogenesis of acne. Activation of toll-like receptors and CD14 by *Cutibacterium* enables upregulation of inflammatory cytokines, such as TNF-α, IL-1β and IL-8, which allows for the development of acne lesions, and can also trigger the adaptive immune system through Th1 cells and the humoral immunity.

*Cutibacterium*, the pathogen implicated in acne, is a commensal organism in healthy patients, but its presence alone is not responsible for the condition. Two strains — ribotype 4 and ribotype 5 — have been shown to only be present in patients with acne and may play a role in pathogenesis by an unclear mechanism.2

One prospective trial has looked at the use of oral probiotics (a combination of *Lactobacillus acidophilus, Lactobacillus delbrueckii* and *Bifidobacterium bifidum*), either alone or in combination with antibiotics, to treat acne patients and found the combination reduced the lesion numbers significantly.2

“…the studies that have been done in acne and other inflammatory and infectious conditions indicate that probiotics could positively impact these disease states.”

Rebecca Knackstedt, M.D.
Cleveland Clinic, Cleveland

Thomas Knackstedt, M.D.
MetroHealth, Cleveland

“Future studies should elucidate if probiotics should be utilized in concert with antibiotics to provide better disease control,” Drs. Rebecca Knackstedt and Thomas Knackstedt tell *Dermatology Times*. “When used for their anti-inflammatory properties in dermatological conditions, it is advisable to use sub-antimicrobial drug dosing. These lower dosages achieve anti-inflammatory efficacy while minimizing disruption of intestinal flora.”

Patients with acne treated with topical probiotics including *L. plantarum* and cell-free supernatant from *Enterococcus faecalis* have also been found to experience a reduction in lesion concentration, erythema and pathogenic bacteria load with an improvement in the skin barrier.

“…as acne is associated with an overgrowth of pathogenic bacteria, and the mainstays of therapy are often antibiotics, topical probiotics could restore a more desired microflora to decrease acne lesions without systemic side effects,” Drs. Rebecca Knackstedt and Thomas Knackstedt write.

Probiotics, including the commensal bacteria *Streptococcus thermophilus, Vitreocilla filiformis, Staphylococcus hominis, Staphylococcus epidermidis* and *Lactobacillus johnsonii*, have also been shown to have an impact in the treatment of atopic dermatitis. According to the review, atopic dermatitis is associated with alterations in the skin microflora, such as an abundance of *S. aureus*, which has been linked to T-cell dysfunction, reduced antimicrobial peptides, more severe allergic reactions and disruptions in the skin barrier.

The relationship between beneficial and pathogenic skin bacteria and their mediators is complex and not fully understood. The skin microflora is individualized, changes frequently in response to a variety of factors, and, as a result, not all probiotics will work for all patients, the doctors conclude.

Optimal dosing and strains have yet to be determined, they write. The most effective strategy may combine topical and oral therapy.

“There is a paucity of well-done studies investigating the role that probiotics, topical or oral, may have on the evolution of acne. However, the studies that have been done in acne and other inflammatory and infectious conditions indicate that probiotics could positively impact these disease states,” Drs. Rebecca and Thomas Knackstedt say. “More well-done studies are required to help determine the role that probiotics could have in mitigating acne and other dermatologic conditions.”

References:


Severe acne responded to combined topical treatment

FROM PAGE 1

clinical associate professor of dermatology at the Icahn School of Medicine at Mount Sinai, New York, and medical director of Physicians Skin Care and DermResearch in Louisville, Ky.

“Severe acne can be difficult to treat, and we’re looking for the best combinations. We use oral antibiotics but want to avoid oral antibiotics in order not to increase antibiotic resistance, which is a real issue,” Dr. Kircik said.

Current acne guidelines encourage judicious use of conventional systemic antibiotics, noting concerns of antibiotic resistance. These guidelines recommend multimodal treatment approaches that target inflammation, address hyperkeratinization and provide antibacterial effects. And guidelines endorse using topical retinoids and benzoyl peroxide for most acne patients, especially patients receiving oral antibiotics, according to the study.

Dermatologists use oral antibiotics in acne treatment not because of the drugs’ antimicrobial properties, but rather for anti-inflammatory properties. Oracea is a 40 mg anti-inflammatory dose of doxycycline that does not have an antibiotic effect and has no risk for development of bacterial resistance associated with its use, according to Dr. Kircik.

“Oracea is already approved for rosacea. So, we looked at it if it would work for acne, which might benefit from its anti-inflammatory effect,” Dr. Kircik says. “In combination, we used a topical product, which, in this case, is Epiduo Forte Gel.”

The regimen, which includes a sub-anti-microbial doxycycline dose with anti-inflammatory properties, as well as topical benzoyl peroxide and adapalene, with anti-inflammatory and anti-comedogenic properties, complies with current recommendations for severe acne treatment, according to the paper.

Dr. Kircik studied 20 patients, ages 18 and older, including men and women of both white and African American races who had severe acne. Each used the combination and after an initial acne screening at Dr. Kircik’s practice, returned for follow-up visits at weeks four, eight and 12. He instructed patients to apply the gel once daily, at night—a regimen he continues to use.

All the patients had an Investigator Global Assessment (IGA) score of 4 at baseline, indicating severe disease. By week four of the open-label study, 75% of patients had a one-grade IGA improvement; 40% of patients had a two-grade improvement, indicating mild acne; and 10% had a three-grade improvement, meaning almost clear. At 12 weeks, 95% had a three-grade improvement or more from baseline.

Patients experienced significant reductions in inflammatory lesion, non-inflammatory lesion and nodule counts beginning at week four and continuing for the study’s duration, according to Dr. Kircik.

Best candidates include severe acne patients that don’t want to be on long-term oral antibiotics or on isotretinoin.

For example, inflammatory lesion counts fell 35% by week four, 62% by week eight and 80% from baseline at week 12.

“By week four, the percentage of patients with 0 nodules was 70% compared to baseline of 20%,” according to the study.

While treatment was generally well-tolerated, six patients had adverse events. Generalized sunburn, sunburn on the face and nausea occurred in three patients and might have been a result of the study medications, according to Dr. Kircik.

Best candidates for the combination treatment include severe acne patients that don’t want to be on long-term oral antibiotics or on isotretinoin, he says.

“The combination does work quite effectively,” Dr. Kircik says. “However, we have to be aware of the shortcomings of this study — that this was an off-label study in 20 people. It’s open label so everybody is going to get better somehow. But there is some signal that this combination might work in severe acne patients.”

Disclosure:

Dr. Kircik has served as an investigator, consultant or speaker for Almirall, Botanix, Cassiopea, Foamix, Galderma, Mayne Pharma, Novartis, Ortho Dermatologics and Sun Pharma. Galderma funded this study.

References:

1. Kircik L. Anti-Inflammatory Dose Doxycycline Plus Adapalene 0.3% and Benzoyl Peroxide 2.5% Gel for Severe Acne. J Drugs Dermatol. 2019;18(9):924-927.

Leon Kircik, M.D., Icahn School of Medicine, Mount Sinai, New York
An IL-23 inhibitor for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

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**RAPID**
Co-primary endpoints of PASI 90 and sPGA 0/1 at Week 16, including improvement 4 weeks after first dose.

**CLEAR**
The majority of patients achieved PASI 100 at Week 52.

**4 DOSES PER YEAR**
Reliable 3-month dosing after 2 initiation doses at Weeks 0 and 4 (150 mg per dose).

**Study Design:** UltIMMa-1 (N=506) and UltIMMa-2 (N=491) were replicate phase 3, randomized, double-blind, placebo- and active-controlled studies to evaluate the efficacy and safety of SKYRIZI (150 mg) vs placebo at Week 16 and ustekinumab at Week 52 in adult patients with moderate to severe plaque psoriasis. Co-primary endpoints were PASI 90 and sPGA 0/1 at Week 16 vs placebo in each study. Analysis conducted using non-responder imputation (NRI) method.
Efficacy Results from Ultimma-2

Participants received treatment at Week 0, 4, and every 12 weeks thereafter.

Week 16 - After 2 Doses

- sPGA 0/1
  - SKYRIZI 150 mg (n=294): 84%
  - USTEKINUMAB (n=99): 75%
  - PLACEBO (n=98): 51%

- PASI 90
  - SKYRIZI 150 mg (n=294): 62%
  - USTEKINUMAB (n=99): 47%
  - PLACEBO (n=98): 24%

- PASI 100
  - SKYRIZI 150 mg (n=294): 51%
  - USTEKINUMAB (n=99): 24%
  - PLACEBO (n=98): 2%

Week 52 - After 5 Doses

- PASI 90
  - SKYRIZI 150 mg (n=294): 81%
  - USTEKINUMAB (n=99): 51%
  - PLACEBO (n=98): 30%

- PASI 100
  - SKYRIZI 150 mg (n=294): 60%

Ultimma-1 Results:

Week 16: sPGA 0/1: SKYRIZI 88% (n=304), ustekinumab 63% (n=100), placebo 8% (n=102). PASI 90: SKYRIZI 75%, ustekinumab 42%, placebo 5%. PASI 100: SKYRIZI 36%, ustekinumab 12%, placebo 0%. Week 52: PASI 90: SKYRIZI 82%, ustekinumab 44%. PASI 100: SKYRIZI 56%, ustekinumab 21%.

Active Comparator

The ustekinumab used as a biologic active control in Ultimma-1 and Ultimma-2 was sourced from the European Union. Comparability between non-US-approved ustekinumab and US-approved ustekinumab has not been established.

Warnings and precautions include infections, tuberculosis, and immunizations. No labeled warnings and precautions on malignancy, IBD, or depression.

Important Safety Information

Indication

SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Infection

- SKYRIZI™ (risankizumab-rzaa) may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.
- In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with SKYRIZI.

Pre-Treatment Evaluation for Tuberculosis (TB)

- Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Immunizations

- Prior to initiating SKYRIZI, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with SKYRIZI.

Adverse Reactions

- Most common (≥1%) adverse reactions associated with SKYRIZI include upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections.

Please see the Brief Summary of the Full Prescribing Information on the following page.

References:

SKYRIZI™ (risankizumab-rzaa) injection, for subcutaneous use

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Infections (see Warnings and Precautions)

Clinical Trials Experience

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

A total of 8244 adults were treated with SKYRIZI in clinical development studies in plaque psoriasis. Of these, 2234 subjects were treated with SKYRIZI in phase 1-3 clinical studies. Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than in the placebo group through Week 16. Table 2 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical studies.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>SKYRIZI (n = 2001)</th>
<th>Placebo (n = 1992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea†</td>
<td>170 (8.5)</td>
<td>52 (2.6)</td>
</tr>
<tr>
<td>Influenza†</td>
<td>150 (7.5)</td>
<td>32 (1.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infections†</td>
<td>125 (6.3)</td>
<td>75 (3.8)</td>
</tr>
<tr>
<td>Upper respiratory infections†</td>
<td>113 (5.7)</td>
<td>51 (2.6)</td>
</tr>
<tr>
<td>Pharyngitis†</td>
<td>95 (4.8)</td>
<td>21 (1.1)</td>
</tr>
<tr>
<td>Sinusitis†</td>
<td>45 (2.3)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Oral infections†</td>
<td>43 (2.2)</td>
<td>12 (0.6)</td>
</tr>
<tr>
<td>Influenza-like reactions†</td>
<td>39 (2.0)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>38 (1.9)</td>
<td>19 (0.9)</td>
</tr>
<tr>
<td>Nasopharyngitis†</td>
<td>30 (1.5)</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Sinusitis†</td>
<td>26 (1.3)</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>Influenza‡</td>
<td>21 (1.1)</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>Infectious gastroenteritis‡</td>
<td>20 (1.0)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infections‡</td>
<td>15 (0.8)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Upper respiratory infections‡</td>
<td>10 (0.5)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

†Includes respiratory tract infections, nasopharyngitis, sinusitis, oral infections, pharyngitis, sinusitis, tonsillitis.
‡Includes respiratory tract infections, nasopharyngitis, pharyngitis, tonsillitis.

Table 2. Adverse Drug Reactions Occurring at a Rate of at Least 1% in Subjects on SKYRIZI and Placebo through Week 16

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>SKYRIZI (n = 2001)</th>
<th>Placebo (n = 1992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>432 (21.6)</td>
<td>309 (15.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>338 (17.0)</td>
<td>161 (8.6)</td>
</tr>
<tr>
<td>Influenza†</td>
<td>303 (15.2)</td>
<td>67 (3.4)</td>
</tr>
<tr>
<td>Sinusitis†</td>
<td>122 (6.1)</td>
<td>24 (1.2)</td>
</tr>
<tr>
<td>Oral infections†</td>
<td>118 (5.9)</td>
<td>17 (0.9)</td>
</tr>
<tr>
<td>Influenza-like reactions†</td>
<td>113 (5.7)</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>100 (5.0)</td>
<td>50 (2.5)</td>
</tr>
<tr>
<td>Nasopharyngitis†</td>
<td>94 (4.7)</td>
<td>23 (1.2)</td>
</tr>
<tr>
<td>Sinusitis†</td>
<td>84 (4.2)</td>
<td>14 (0.7)</td>
</tr>
<tr>
<td>Influenza‡</td>
<td>76 (3.8)</td>
<td>18 (0.9)</td>
</tr>
<tr>
<td>Infectious gastroenteritis‡</td>
<td>74 (3.7)</td>
<td>14 (0.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infections‡</td>
<td>69 (3.5)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Upper respiratory infections‡</td>
<td>58 (2.9)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

†Includes respiratory tract infections, nasopharyngitis, sinusitis, oral infections, pharyngitis, tonsillitis.
‡Includes respiratory tract infections, nasopharyngitis, pharyngitis, tonsillitis.

Conditions for Use of the Medication Guide

Consistently instruct patients in the technique of needle and syringe disposal. Instruct patients or caregivers in the technique of needle and syringe disposal.

PATIENT COUNSELING INFORMATION

Advising the patient or caregiver to read the FDA-approved patient labeling Information Guide and Instructions for Use before starting SKYRIZI therapy and to refer the Medication Guide such that the prescription is reviewed. Advise patients of the potential benefits and risks of SKYRIZI.

Infections

Skin infections that SKYRIZI may lower the ability of skin immune system to fight infections. Instruct patients of the importance of continuing any hygiene to the skin such as provided with wound-dressing devices.

SKYRIZI differs from other treatments in that it can cause infections. Although serious infections are rare, they can occur during treatment with SKYRIZI. SKYRIZI should be discontinued if a patient develops any symptoms of an infection. [see Warnings and Precautions] administered subcutaneously.

Instruct patients or caregivers to perform the first self-injection under the supervision and guidance of a qualified healthcare professional for training in administration and administration of SKYRIZI. infused weekly for the first 16 weeks of treatment.

PATIENT COUNSELING INFORMATION

Advising the patient or caregiver to read the FDA-approved patient labeling Information Guide and Instructions for Use before starting SKYRIZI therapy and to refer the Medication Guide such that the prescription is reviewed. Advise patients of the potential benefits and risks of SKYRIZI.
Rhinophyma treatment, prevention strategies

CHERYL KRADER, B.S. PHARM | Staff Correspondent

Rhinophyma is a cosmetically deformative condition with unmet needs — both in understanding etiology and in treatment options, says Deborah S. Sarnoff, M.D., clinical professor of dermatology, NYU Langone School of Medicine, New York, and director of dermatologic surgery, Cosmetique Dermatology, Laser & Plastic Surgery, New York.

**Quick TAKES**

Rhinophyma is a disfiguring condition with deleterious psychosocial and functional consequences, and its pathogenesis remains unclear.

Various treatments can reduce redness, but only surgical interventions can improve the deformity.

Medications targeting fibroblasts hold interest as future treatment.

“Rhinophyma is a very embarrassing and humiliating problem with enormous negative psychosocial implications resulting from its disfigurement and alleged association with alcohol use, and it can also have functional consequences, interfering with breathing, sleeping, eating, drinking and, even, vision,” Dr. Sarnoff says. “In recent years there have been some medical advances for masking and controlling the redness associated with rhinophyma, but surgery is still the only option for correcting the deformity.”

Although rosacea is much more common in women, men with rosacea are at greater risk to develop rhinophyma than their female counterparts. In addition, rhinophyma is seen more often in Caucasians than in other racial groups, and particularly in Caucasians with very fair skin.

“A reason for these differences is not known. They suggest there may be a hormonal or genetic component contributing to rhinophyma, and other theories propose Demodex mites, ultraviolet light exposure, heat, vitamin deficiency and alcohol or caffeine use may be causative or exacerbating factors,” Dr. Sarnoff says.

“Likely, the etiology is multifactorial,” she adds.

The phymatous changes are thought to result from unregulated superficial vasodilation and vascular instability, leading to lymph extravasation into surrounding tissues. Chronic edema from accumulating lymph incites an inflammatory reaction that results in fibrosis and sebaceous hyperplasia.

“In people who wear eyeglasses, pressure from the nose pads may particularly restrict lymph drainage and explain the localization of phymatous changes to the lower two-thirds of the nose,” Dr. Sarnoff observes.

**TREATMENT OPTIONS**

Vascular-specific lasers or intense pulsed light treatment targeting blood vessels can be used to reduce redness and telangiectasias. Medical treatments that can help relieve redness include topical ivermectin, brimonidine, and oxymetazoline as well as oral aspirin, clonidine, and propranolol.

Surgery using physically destructive techniques, however, remains the only option for tissue contouring. Preferred approaches include the bloodless heated scalpel technique, radiofre-
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Faster symptom relief

MORGAN PETRONELLI | Assistant Editor

Combination therapy may offer faster relief to some patients with moderate-to-severe rosacea, according to patients enrolled in a randomized, multicenter, parallel-group, investigator-blind, 12-week comparative clinical trial that recruited 273 adults with severe rosacea and was conducted across 39 sites in the United States, Canada, Hungary, Poland and Czech Republic.

Participants applied IVM once daily in the evening in conjunction with taking either DMR or placebo (PBO) once a day in the morning. They were also instructed to apply rosacea skin care products during the trial, including Cetaphil Redness Relieving Foaming Face Wash (Cetaphil) and SPF 20 sunscreen (SPF 30 in Europe).

Twenty-two study participants dropped out during the trial (13 from IVM + placebo and nine from IVM + DMR), resulting in 251 completing treatment. Reasons for early discontinuation were adverse events (5), subject’s request (9), pregnancy (4), lost to follow-up (1) and other (3).

Additionally, the combination therapy increased the number of participants who achieved 100% lesion reduction (17.8% versus 7.2% [P = .006]) and reached an Investigator’s Global Assessment (IGA) score of 0 (11.9% versus 5.1% [P = .045]) at week 12.

Both the combination and monotherapy decreased the Clinician’s Erythema Assessment (CEA) score, Dermatology Quality Index (DLQI), flushing episodes, stinging, ocular symptoms and burning.

“A surprising outcome from this study was the improvement in ocular signs and symptoms. Despite instructions to avoid application of IVM to the eyelid area, both treatments resulted in a significant reduction in ocular signs and symptoms,” write Schaller et al.

Additionally, the study’s authors write the occurrence of treatment-related adverse events for combination therapy (4.4%) was lower compared to monotherapy (7.2%).

Despite positive results, the authors note limitations included the lack of a control group and that the 12-week trial period restricted the analysis of possible future recurrences or improvements of the combination therapy.

“Combination therapy may offer faster and significant improvement of lesion counts and symptoms when compared to monotherapy,” the authors conclude.

References:


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"The ability to induce remission and eliminate the need for daily use of medication is an important outcome for patients with any chronic disease."

Jeffrey Fromowitz, Boca Raton, Fla.

Ivermectin changes treatment landscape for patients with rosacea

Ivermectin represents a unique treatment for reducing inflammatory lesions of rosacea and is thought to exert its benefit via dual mechanisms. First, ivermectin has anti-inflammatory activity, decreasing both the cellular and humoral immunity pathways that are thought to be involved in the development of rosacea. In addition, ivermectin is a vermicidal agent, killing Demodex mites that have been implicated in rosacea pathophysiology and may drive inflammation.

In both pivotal trials that led to the approval of topical ivermectin, the medication demonstrated statistical superiority compared with vehicle control in both co-primary endpoints that looked at the percentage of subjects achieving clear or almost clear in the Investigator Global Assessment at week 12 and the absolute change in inflammatory lesion count from baseline to week 12.

Other studies provide evidence comparing topical ivermectin with other treatments for papulopustular rosacea. A European pharmacoeconomics study comparing ivermectin cream, 1% with metronidazole cream, 0.75% reported statistically significant differences favoring ivermectin for having better efficacy and tolerability. Another study examining the long-term efficacy and safety profiles of ivermectin, metronidazole cream, and azelaic acid gel, 15% showed ivermectin offered both superior efficacy and better tolerability than the other topical agents, reported Dr. Fromowitz.

In the study comparing topical ivermectin and metronidazole cream, the percentage of patients achieving success without relapse requiring retreatment was found to be 33% greater in the ivermectin versus metronidazole group. In addition, the mean time to relapse was 30 days longer in the ivermectin group, or stated another way, patients using ivermectin benefited with an average of 30 more treatment-free days.

“One ability to induce remission and eliminate the need for daily use of a medication is an important outcome for patients with any chronic disease,” Dr. Fromowitz adds.

Disclosure: Dr. Fromowitz has received speaking and consulting fees from Galderma.
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An experimental vaccine being studied in patients with stage IIB and IIC melanoma is demonstrating positive outcomes in recurrence-free survival and a favorable adverse event profile, one expert says.

The experimental vaccine offers hope to a patient population in need of more effective therapies with far fewer and more tolerable adverse events, particularly when compared with currently available therapies for this patient population, says Craig L. Slingluff Jr., M.D., professor of surgery, director of the human immune therapy center and co-leader of the cancer therapeutics program, UVA Cancer Center, Charlottesville, Va.

"Interferon is the only treatment that is currently approved for stage IIB and IIC melanoma after surgery," he says. "Because of its associated toxicity and the variability in the benefit seen in different trials, however, a need for better treatment options perhaps in the form of a vaccine could prove very useful in this subgroup of patients."

The MAVIS (Melanoma Antigen Vaccine Immunotherapy Study) clinical trial is an ongoing multicenter, double-blind, placebo-controlled, phase 3 clinical study investigating seviprotilt-L (Polynoma LLC), an experimental allogenic, polyvalent, partially purified shed melanoma antigen vaccine derived from three proprietary human melanoma cell lines. It is designed to stimulate the patient's humoral and cellular immune responses.

Researchers are examining the safety and efficacy of the vaccine with primary endpoints of RFS and overall survival (OS) in patients with American Joint Committee on Cancer (AJCC) stage IIB/C, IIIA, IIIB/C melanoma.

"I think that what we have achieved so far with the seviprotilt-L vaccine is major progress for melanoma vaccines."

Craig L. Slingluff Jr., M.D., UVA Cancer Center, Charlottesville, Va.
at high risk of recurrence after definitive surgical resection.

A total of 347 subjects, aged 18 to 75 years, were randomized 2:1 to receive seviprotimut-L 40 mcg or placebo, administered intradermally every two weeks divided into five injections, then monthly divided into four injections, then every three months to month 24. Patients were stratified by stage (IIB/C, IIIA, IIIB/C).

The analysis of subgroups based on pre-planned stratification suggested an enhanced RFS for seviprotimut-L in subjects with stage IIB and IIC melanoma, as well as those under 60 years of age.

Moreover, seviprotimut-L was also very well tolerated by subjects, akin to those patients who received placebo. Adverse events were mild, localized and transient in nature following topical treatment.

“I think that what we have achieved so far with the seviprotimut-L vaccine is major progress for melanoma vaccines. A lot of the other studies that are currently underway are very much early development trials looking for earlier signals. Our study is a randomized, placebo-controlled trial that has shown promise for benefit in this particular subgroup of melanoma patients for which current treatment options are suboptimal and need to be improved,” Dr. Slingluff says.

In view of the toxicities associated with the currently used therapies for melanoma, Dr. Slingluff says that there is a definite niche in which novel vaccines like seviprotimut-L could fit for melanoma patients with stage IIB and IIC following surgical resection. There are immune therapies with checkpoint blockade that are currently approved for patients with advanced disease, as well as those with resected stage III and IV disease; however, there is nothing approved for stage II disease.

“The toxicity associated with checkpoint blockage is not very high, but it can be significant. Moreover, there can be serious toxicities that are long-term, which I think have to be balanced against the potential benefit for patients with stage II disease who are at lower risk than patients with stage III disease,” Dr. Slingluff says.

The experimental seviprotimut-L vaccine with its low toxicity profile and proven benefit in the randomized trial just for stages IIB and IIC makes it very appealing in that sub population as well. According to Dr. Slingluff, this opens a clear path forward to do a randomized trial that focuses on that subset of patients.

“There is no other truly effective treatment that addresses stages IIB and IIC following surgery. I think clinical trials remain good options for patients with stage II disease and, hopefully, this low toxicity vaccine approach will be available to patients soon,” Dr. Slingluff says. 

Disclosure: Dr. Slingluff reports no relevant disclosures.
**Quick TAKES**

Newer cancer therapy with a sound concept could prove beneficial for skin malignancies in the future.

CART-cell therapy involves genetically altering a patient's T cells so they bind to the patient's cancer cells.

Therapeutic benefits have been seen in kids with acute lymphocytic leukemia.

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**Standard of care progresses**

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

Though still considered controversial, several evolving treatment and management plans for primary cutaneous melanoma are making their way into the mainstream and challenging more traditional approaches.

“The standard of care for primary cutaneous melanoma may slowly be changing in light of the recent advancements and positive outcomes we are seeing with Mohs surgery, slow Mohs and new genetic molecular tests for diagnosis and prognosis of the tumor,” says M. Laurin Council, M.D., FAAD, FACMS, associate professor of dermatology, John T. Milliken department of internal medicine, Washington University School of Medicine, St. Louis.

Mohs surgery is generally accepted for melanoma in situ on the head and neck; however, the consensus is not as clear when it comes to invasive cutaneous melanoma, she says. A wide local excision of invasive melanoma with margins from 1 cm to 2 cm remains the standard of care; but, recent data indicate that Mohs surgery can achieve treatment outcomes equal, if not better than, the traditional wide local excision technique in early-stage invasive melanoma, she says.

Moreover, Mohs surgery used in invasive melanoma has also been shown to result in lower recurrence rates compared to a standard wide local excision, especially on the head and neck.

Removing a melanoma with these wide margins can be challenging in certain areas, such as the eyelid or nose where less tissue is available. In these areas, Dr. Council says that surgeons may rely on the disclaimer in current guidelines that allows for removing less tissue in these complex areas. The National Comprehensive Cancer Network (NCCN) guidelines state that a surgeon may modify margins for an individual due to anatomic or functional considerations.

“Many Mohs surgeons today are adjusting their focus and believe that the importance is not necessarily the size of the margin; rather, that you clear the entire primary tumor,” she says. “Accordingly, the ‘standard margin’ can change depending on the individual case, and treatment outcomes can be achieved that are comparable to those of the traditional wide local excision technique.”

Some obstacles remain for clinicians who may want to offer Mohs surgery to their patients, Dr. Council adds. Not all centers are set up for immunohistochemistry, and not all histotechnicians are comfortable cutting sections very thinly to be able to perform the immunostaining.

Although most Mohs surgeons likely do not offer traditional Mohs surgery for melanoma, Dr. Council says they do often perform “slow Mohs” for melanoma, which is a variation in which the tumor is removed and processed with permanent sections (instead of frozen) in a manner that allows for complete evaluation of the margins.

“Using Mohs surgery for primary melanoma still remains somewhat controversial because there are some surgeons who are taking less than a 1 cm margin, which is considered the standard of care, wherever possible,” Dr. Council says.

For prognostic purposes, genetic tests such as DecisionDx-Melanoma test (Castle Biosciences, Inc.) and the SkylineDx (currently in trials) can help indicate whether a tumor is at high or low risk for metastasizing sometime in the future.

Ideally, the thought is that these molecular assays could be implemented instead of necessarily performing a sentinel lymph node biopsy (SLNB).

According to Dr. Council, SLNB is also slowly evolving because of recent data showing the same survival for melanoma patients who received SNLB with and without complete lymphadenectomy. As a result, some surgeons may do SNLB for prognostic information Dr. Council said, but they will not necessarily go back and perform a complete lymphadenectomy.

“Particularly for melanoma of the head and neck, where the lymphatic drainage is more variable and there is a higher rate of false negativity, perhaps a genetic test would be more appropriate,” Dr. Council says. “As the SLNB is an imperfect test, there is a vacuum to fill and a genetic test that is superior in outcomes and less invasive than SNLB could be ideal. Ultimately, with our choices, we hope to minimize the morbidity for patients and give them equivalent or superior outcomes.”

**Disclosure:**

Dr. Council reports that she is a consultant for Sanofi-Genzyme/Regeneron.

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Risk Skin Lightening

LISSETTE HILTON | Staff Correspondent

Unscrupulous skin lightening practices are becoming a problem in the United States, according to dermatologist Arianne Shadi Kourosh, M.D., MPH. She says she has seen more patients using skin lightening creams that have unsafe and unregulated ingredients that patients purchase over the counter or overseas.

“Unless these patients bring these creams to their dermatologists’ practices, we don’t necessarily know that they’re using creams with ingredients that we don’t recommend putting on the face,” says Dr. Kourosh, director, Pigmentary Disorder and Multietnic Skin Clinic, Massachusetts General Hospital.

The problem became more evident in 2018 when a male patient presented with the desire to lighten his skin for cultural reasons and had been getting intravenous (IV) glutathione infusions at a U.S. skin lightening clinic. Glutathione infusions have questionable skin lightening efficacy and are considered unsafe, she says.

“IV glutathione infusions can damage the thyroid, kidney as well as cause life-threatening drug reactions, such as Stevens-Johnson syndrome,” Dr. Kourosh says.

She convinced the patient to stop the infusions. However, she found skin lightening clinics touting questionable and medically unsound treatments increasing in prevalence in the United States. In one case, FDA alleged Flawless Beauty, LLC, marketed unapproved, mis-labeled and dangerous drugs, singling out the company’s injectable skin whitening products. In 2017, a federal judge ordered the company to stop selling and recall the skin whitening products and other beauty products, according to a September 27, 2017 article on UPI.com.3 She also discovered a billboard for products, according to a September 27, 2017 article ordered the company to stop selling and recall the skin whitening products. In 2017, a federal judge...
Post-op wound care critical

Expert’s regimen following aggressive resurfacing procedures

JOHN JESITUS | Staff Correspondent

Maximizing results and safety of aggressive resurfacing procedures requires painstaking post-procedural care, says Dallas-based plastic and reconstructive surgeon A. Jay Burns, M.D. His favorite postoperative wound dressing is no longer available; so he says he has had to reconfigure this portion of his treatment regimen to include gas-permeable silicone gels.

Without meticulous postoperative wound care, the most careful, well-researched resurfacing technique will fail. He shared an anecdote following a teaching experience in France many years ago at which he said he resurfaced to 600-800 µ deep in places. Years later, the French surgeon hosting the conference told him he no longer performed such aggressive procedures because the two patients that Dr. Burns had treated developed thick post-procedural scarring along the mandible. He asked if the post-procedural care was carried out as he had shown but was told the patients were left to scab.

“Can you imagine going that deep and just letting them scab up?” he asks.

Dr. Burns says he was a huge fan and frequent user of Flexan (Polymedical Industries) occlusive dressing, which is no longer produced.

His post-procedural regimen, described in January 2019 in Plastic & Reconstructive Surgery, includes applying Flexan after aggressive erbium:YAG resurfacing. On postoperative day one, he would remove the flexible sheet, meticulously debride the underlying skin and replace the existing dressing. On day three, he would debride again and instruct patients whose wounds were healing well to use petrolatum or an EltaMD (Colgate-Palmolive) post-laser kit to keep the skin moisturized. At that point, the only water, Beiersdorf AG) would suffice. He says petrolatum or Aquaphor (petrolatum plus Aquaphor) are not absorbed through the skin or gastrointestinal tract, he adds, and they’re hydrophobic, antimicrobial, bacteria-tropic and highly biocompatible.

Dr. Burns prefers gas-permeable gel over sheet dressing, formulates his say, because sheeting leaves coverage gaps when applied over uneven surfaces.

“But the liquid goes on then gets into every crevice. And when it dries, it makes a structural barrier that is gas-permeable,” he says. “As I began to think about it, it’s a lot like Flexan. It has similar properties. It causes less pain and less buildup of heat because it breathes. And it promotes faster healing and infection control.”

Thicker gel options provide less occlusion, but greater binding capability for open wounds and de-epithelialized skin, such as a superficial second-degree burn, he says. Conversely, less viscous options provide more occlusion for partially epithelialized skin and skin post-fractionated procedures.

In a 20-patient post-microneedling study, Stratamed performed significantly better than petrolatum in terms of erythema (p<0.001) and patient preference (p<0.008). Dr. Burns attempted to perform a 10-patient, split-face study of Stratamed versus petrolatum after full-field laser resurfacing. However, he had to stop after seven patients due to overwhelming patient and nurse preference for the silicone gel. He may never publish the results.

“I just needed to know what to do because I needed a new dressing. But it was pretty powerful,” he says.

Given the depths to which he performs laser resurfacing, adds Dr. Burns, seeing less redness three weeks post-procedure was an unexpected surprise with the silicone gel. If such products work after full-field ablation, he explains, perhaps they will provide similar advantages after fractional ablative treatments. Granted, says Dr. Burns, gas-permeable silicone gel may not be the only answer.

After gaining additional experience with Stratamed, he says, it performs excellently in the early exudative phase.

“But at three or four days, I have some patients who look like they’ve got wrinkles because it’s not moist enough, even if they supplement the silicone with water spraying. At that point, the only thing I know to do is to go back to petrolatum, just for two to three days to get them through that really dry inflammatory phase.”

References:

Disclosures:
Dr. Burns is a consultant for Sciton.
Review: PDL may improve nonvascular conditions

JOHN JESTUS | Staff Correspondent

T he 595 nm pulsed dye laser (PDL) may provide an effective option for nonvascular conditions, such as scars, acne and molluscum contagiosum, according to a recent review. However, evidence from large, randomized controlled trials makes drawing firm conclusions difficult.

Researchers led by Emily Forbat, MBBS, of the dermatology unit at Warwick Hospital in Warwick, U.K., reviewed a total of 84 studies and concluded that PDL has demonstrated efficacy in acne, scar remodeling and prevention, post-filler bruising, nail psoriasis, low-risk basal cell carcinoma and warts.1 Some studies, however, showed no significant differences between PDL and more conventional regimens. Additionally, variable results have emerged in plaque psoriasis. The review appeared online in April 2019 in the Journal of Cosmetic Dermatology.

“While the review is a good collection and summarization of a lot of studies,” says Emmy Graber, M.D., MBA, who was not involved with the study, “there’s a paucity of large-scale, randomized, controlled studies looking at the pulsed dye laser for nonvascular indications. So it’s very hard to draw conclusions from this study.” She is president of the Dermatology Institute of Boston and an affiliate clinical instructor at Northeastern University.

Forbat et al. reviewed 12 acne studies, but these studies included fewer than 400 patients total. Among the indications reviewed, Dr. Graber says, “My big takeaway from this paper is that the pulsed dye laser can be used for many different dermatologic conditions. But it’s best used in the indications for which it’s tried.”

For example, a 30-patient split-face study showed that two sessions twice weekly for eight weeks produced no significant improvement over no treatment at all.2

For scarring, the review included studies that compared PDL to other lasers and light sources including erbium, fractional CO2, KTP, Nd:YAG, low-level laser and intense pulsed light (IPL), along with botulinum toxin. While all treatment modalities demonstrated improvement in scar outcomes, write Forbat et al., most studies showed no significant improvement between treatment arms.

Nevertheless, Dr. Graber says that by including 23 scar studies, the paper reflects the clinical reality that scarring is the most frequent nonvascular indication for which dermatologists use PDL.

“We know that there are some other types of lasers that work as well. But this paper further emphasizes that the pulsed dye laser is an effective means for treating scars. That’s one of the sound conclusions that can be drawn.”

Molluscum lesions are often difficult to treat, she says. “There’s no ideal therapy in that many of the treatment approaches either hurt or leave scars. Utilizing the pulsed dye laser is an interesting approach and worth considering if a patient fails or is not a candidate for other therapies. However, the review does not support a conclusion that PDL should be first-line treatment, she adds.

Outcomes varied when treating striae. One study showed slight improvement in treating mature striae twice monthly for up to two years; another found that both PDL and IPL improved the appearance of striae, and that early striae rubra (SR) fared better with both treatments. In the latter study, PDL was found to significantly increase collagen 1 expression versus IPL.3

Forbat et al. say this difference could make PDL preferred if larger studies support this finding.

Dr. Graber says, “My big takeaway from this paper is that the pulsed dye laser can be used for many different dermatologic conditions. But it’s best used in the indications for which it’s tried and true. Such as erythema, telangectasias, rosacea and port wine stains.”

References:

Disclosures:
Dr. Graber has received research funding from Selvacis.

While the review is a good collection and summarization of a lot of studies, there’s a paucity of large-scale, randomized, controlled studies looking at the pulsed dye laser for nonvascular indications. So it’s very hard to draw conclusions from this study.”
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