Dermatology Foundation
SHAPING THE FUTURE OF DERMATOLOGY

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Clinical Symposia—Seaside Chats

APRIL 8, 15, 22, 29

One hour beginning at 8 p.m. EDT
$100 for the 4 sessions

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Although COVID-19 has required us to postpone our annual DF Clinical Symposia at Naples, Florida until next year, we are pleased to offer you a high-quality virtual CME experience you can enjoy from your home.

Join your colleagues for a series of four standout educational sessions with live Q&A—each with one of dermatology's renowned experts—just like our Clinical Symposia programs. Each one-hour chat will deliver a 30-minute talk on a topic of central interest to dermatologists, residents, and physician assistants. The live Q&A that follows provides the opportunity for you and your colleagues to ask the questions you are eager to have answered.

To register visit dermatologyfoundation.org.

2021 VIRTUAL SEMINAR SCHEDULE

Thursday April 8, 2021 | 8 p.m. EDT

Jean L. Bolognia, M.D.

Professor of Dermatology
Yale School of Medicine

Melanoma: The Cutaneous Side Effects of Immune Checkpoint-Blocking Antibodies

- Learn to recognize cutaneous side effects of immune checkpoint-blocking antibodies, which can be divided into: (1) morbilliform, lichenoid, eczematous, and psoriasiform eruptions; (2) blistering disorders, in particular bullous pemphigoid; 3) severe cutaneous adverse reactions; (4) leukoderma; and (5) other, e.g., sarcoidosis, atypical squamous proliferations
- Become aware of the systemic side effects of immune checkpoint-blocking antibodies

Thursday April 15, 2021 | 8 p.m. EDT

Jim R. Treat, M.D.

Associate Professor of Clinical Pediatrics and Dermatology
Fellowship Director, Pediatric Dermatology
Children's Hospital of Philadelphia

An Update on Atopic Dermatitis

- Understand how the newest therapeutics can change management
- Recognize how debilitating atopic dermatitis can be emotionally

Thursday April 22, 2021 | 8 p.m. EDT

Adewole S. Adamson, M.D., M.P.P.

Assistant Professor
Division of Dermatology
Department of Internal Medicine
The University of Texas at Austin

Challenges and Opportunities in Addressing Health Disparities in Skin Cancer in Skin of Color Patients

- Understand the evidence about the role of photoprotection in skin cancer prevention in skin of color
- Understand disparities in patterns of care related to melanoma

Thursday April 29, 2021 | 8 p.m. EDT

Jeremy S. Bordeaux, M.D., M.P.H.

Professor of Dermatology
Case Western Reserve University
Director, Dermatologic Surgery and Melanoma Program
University Hospitals of Cleveland

When Mohs Surgery Really Matters

- Understand how the use of Mohs Micrographic Surgery can significantly reduce patient morbidity compared to other treatment options in specific clinical scenarios, including dermatofibrosarcoma protuberans, genital tumors, microcystic adnexal carcinoma, lentigo maligna, and eyelid tumors

The Yale School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Yale School of Medicine designates this live activity for a maximum of 4 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ATOPIC DERMATITIS
Biologics, inhibitors are in the pipeline, but will they be accessible, affordable?

ROSACEA
LL-37 studies could have implications in coronavirus research.

PSORIASIS
Positive results from three phase 3 novel drug trials could signal of year of innovation in treatment and management.

SKIN CANCER
Pediatric patients differ from adults in diagnosis, risk assessment, management of congenital melanocytic nevi, melanoma.

DermatologyTimes®

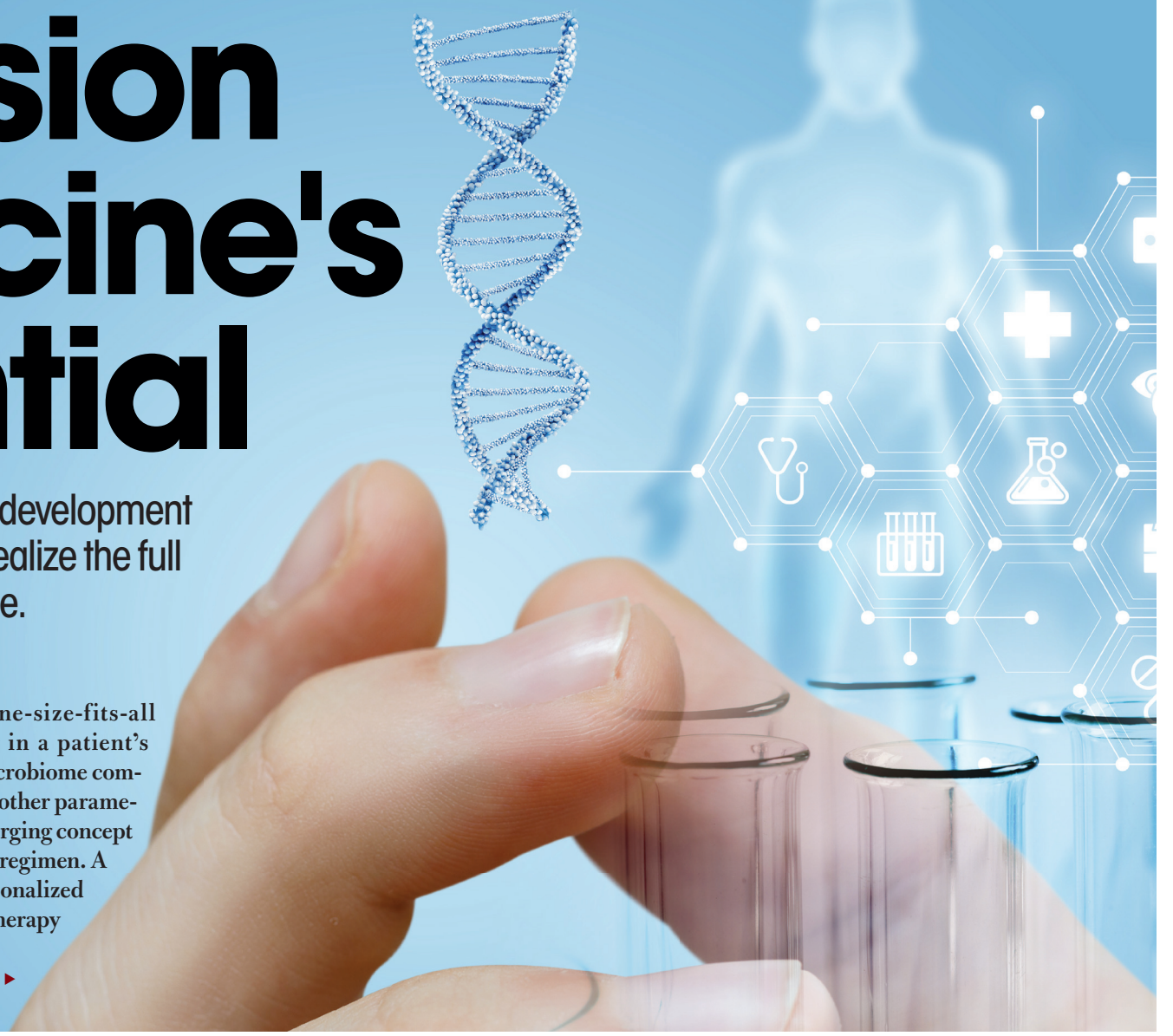
CLINICAL INSIGHTS THAT EXPAND EXPERTISE AND ADVANCE PRACTICE

Volume 42, Number 3 | **March 2021**

SPECIAL COVERAGE
Maui Derm Live + Maui Derm Connect 2021.

CLINICAL INSIGHTS

Precision Medicine's Potential



Additional research, product development are needed before patients realize the full benefits of precision medicine.

ILYA PETROU, MD | *Staff Correspondent*

Taking the polar opposite of a one-size-fits-all approach, clinicians now factor in a patient's genetic profile, medical history, microbiome composition, lifestyle, and diet, among other parameters. Known as precision medicine, this emerging concept helps guide clinicians on a patient's therapy regimen. A central goal of this model, once called "personalized medicine," is to predict early on if a given therapy will work for an individual patient.

PRECISION MEDICINE CONTINUES ON PAGE 51 ▶

ACNE

Topical Probiotics Show Promise in Trials

JOHN JESITUS | *Staff Correspondent*

LIKE THEIR ORAL COUNTERPARTS, topical probiotics show encouraging results in treating various dermatologic conditions, most notably acne and atopic dermatitis (AD). However, according to a recent review, with research still in its infancy, physicians and patients need additional data regarding topical probiotics' safety, efficacy, and mechanism of action in skin diseases.[1]

"In the last few years, we have seen a surge in studies about microbiota that stretch far beyond digestive health benefits," said author Katlein França, MD, PhD, assistant professor in the Dr Phillip Frost Department of Dermatology and Cutaneous Surgery at the Uni-

PROBIOTICS CONTINUES ON PAGE 23 ▶

ANTIAGING

New Modalities Revise Scars

MORGAN PETRONELLI | *Associate Editor*

THERE ARE A PLETHORA OF METHODS to treat the appearance of scars. From lasers and fillers to microneedling, physicians have an arsenal of modalities to choose from to help them and their patients achieve desired results.

Three expert dermatologists offered best-practice strategies for their preferred methods of scar treatment in a panel discussion at the 2021 ODAC Dermatology, Aesthetic & Surgical Conference held virtually January 14 through 17, 2021.[1] They discussed the outcomes possible with different approaches and

MODALITIES CONTINUES ON PAGE 49 ▶

zilxi™
(minocycline)
topical foam, 1.5%

Not an actual patient.

IT'S TIME MINOCYCLINE GOT

ON TOP OF ROSACEA

Take on inflammatory lesions of rosacea from the top down.
Visit ZilxiHCP.com to learn more.

INDICATIONS AND USAGE

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

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ZILXI should be used only as indicated.

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

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

IMPORTANT SAFETY INFORMATION, CONTINUED

- ***Teratogenic effects, inhibition of bone growth & permanent tooth discoloration:*** Use during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth.
- ***Clostridioides difficile associated diarrhea (CDAD):*** If CDAD occurs, discontinue ZILXI.
- ***Hepatotoxicity & metabolic effects:*** If renal impairment exists or if liver injury suspected, discontinue ZILXI.
- ***Central nervous system effects:*** Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.
- ***Intracranial hypertension:*** Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue ZILXI immediately if symptoms occur.
- ***Autoimmune syndromes:*** Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue ZILXI immediately if symptoms occur.

The first time minocycline has been approved for rosacea

Zilxi is the first and only topical minocycline proven effective in adult patients with inflammatory lesions of rosacea[1*]

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

Proven safe and well-tolerated on already-sensitive skin[1]

- The most commonly reported adverse reaction was diarrhea (1%)
- Zilxi was well-tolerated throughout the treatment period

Delivered in a gentle, proprietary foam vehicle

- Leverages Molecule Stabilizing Technology (MST)™ for stable topical delivery[2,3]
- Contains naturally moisturizing ingredients,[4] is surfactant-free, and does not contain drying agents, such as ethyl alcohol[1†]

IMPORTANT SAFETY INFORMATION, CONTINUED

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

Adverse Reactions

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

IGA=Investigator's Global Assessment

*Co-primary endpoints at Week 12 were: absolute change from baseline in inflammatory lesion count and IGA treatment success. IGA treatment success was defined as an IGA score of 0 or 1 (clear or almost clear) and at least a 2-grade improvement (decrease) from baseline. Patients were included if they had 15-75 facial lesions (papules and pustules), no more than 2 facial nodules, and an IGA score of moderate or severe (grade 3 or 4) (N=1522).[1]

†Zilxi 1.5% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol, and propellants (butane + isobutane + propane).[1]

REFERENCES: 1. ZILXI™ (minocycline) topical foam, 1.5% Prescribing Information. Bridgewater, NJ: Foamix Pharmaceuticals Inc; 2020. **2.** Hazot Y, et al. *J Anal Pharm Res.* 2017;4(5):00117. **3.** Tamarkin D. Foam: a unique delivery vehicle for topically applied formulations. In: Dayan N, ed. *Handbook of Formulating Dermal Applications: A Definitive Practical Guide.* Beverly, MA: Scrivener Publishing LLC; 2017:233-260. **4.** Lin TK, et al. *Int J Mol Sci.* 2017;19(1):70. doi: 10.3390/ijms19010070.

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

VYNE™ THERAPEUTICS

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

INDICATION

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

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ZILXI should be used only as indicated.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Flammability:** The propellant in ZILXI is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).
- **Teratogenic Effects:** Minocycline, like other tetracycline-class drugs, may inhibit bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.
- **Tooth Discoloration:** The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline drugs. Use of tetracycline drugs is not recommended during tooth development.
- **Inhibition of Bone Growth:** All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. Results of animal studies indicate that oral tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated orally early in pregnancy.
- ***Clostridioides difficile* Associated Diarrhea:** *Clostridioides difficile* associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
- **Hepatotoxicity:** Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use.
- **Metabolic Effects:** The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.
- **Central Nervous System Effects:** Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
- **Intracranial Hypertension:** Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concomitant use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Because intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.
- **Autoimmune Syndromes:** Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have presented shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including ZILXI.
- **Photosensitivity:** Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although ZILXI did not induce phototoxicity or photoallergic responses in human dermal safety studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using minocycline. If patients need to be outdoors while using ZILXI, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with ZILXI at the first evidence of sunburn.
- **Serious Skin/Hypersensitivity Reaction:** Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with oral minocycline use. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue ZILXI immediately.
- **Tissue Hyperpigmentation:** Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.
- **Development of Drug-Resistant Bacteria:** ZILXI has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using ZILXI, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of ZILXI, it should be used only as indicated.
- **Superinfection/Potential for Microbial Overgrowth:** Use of ZILXI may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue ZILXI and institute appropriate therapy.

ADVERSE REACTIONS

- **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In three (two Phase 3 and one Phase 2) multicenter, randomized, double-blind, vehicle-controlled trials, adult subjects applied ZILXI or vehicle once daily for 12 weeks. A total of 1,087 subjects were treated with ZILXI and 591 with vehicle. The majority of subjects were White (97%) and female (70%). Approximately 67% were non-Hispanic/Latino. The mean age was 50.0 years and ages ranged from 18 to 86 years.
- The most common adverse reaction reported by ≥1% of subjects treated with ZILXI and more frequently than in subjects treated with vehicle was diarrhea (1% vs. 0%), respectively.

- During the two Phase 3 trials, local tolerability evaluations were conducted at each study visit by assessment of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness, itching, peeling and hyper-pigmentation. Subjects treated with ZILXI had improved local tolerability signs and symptoms at Week 12 when compared with corresponding baseline values. These occurred at a similar frequency and severity as subjects treated with the vehicle component of ZILXI. The local tolerance assessments in ZILXI patients (N = 1,008, of which 897 had local tolerability assessments at week 12) by incidence rate (%) and severity grade were as follows (mild, moderate, severe): erythema (36.2%, 18.3%, 0.7%), Telangiectasia (61.0%, 18.8%, 0%), burning/stinging (13.3%, 2.8%, 0%), flushing/blushing (39.0%, 9.6%, 0.9%), dryness (23.9%, 4.0%, 0.1%), itching (20.0%, 3.3%, 0%), skin peeling (16.1%, 1.9%, 0.1%), and hyperpigmentation (22.5%, 2.8%, 0%). Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with inflammatory lesions of rosacea. In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment) [NCT03276936], frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Risk Summary: Available data with ZILXI use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of ZILXI in humans is low following once daily topical administration of ZILXI under maximal clinical use conditions. Because of low systemic exposure, it is not expected that maternal use of ZILXI will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with ZILXI. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during organogenesis induced skeletal malformations in fetuses at systemic exposures of 2,000 and 1,300 times, respectively, the maximum recommended human dose (MRHD based on AUC comparison) of ZILXI *(see Data).* The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
- Data: *Animal Data:* Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (2,000 and 1,300 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (680 times the systemic exposure at the MRHD based on AUC comparison).
- Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (1,700 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).
- **Lactation:** Risk Summary: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with ZILXI.
- **Pediatric Use:** The safety and effectiveness of ZILXI for the treatment of inflammatory lesions of rosacea have not been evaluated in pediatric patients.
- **Geriatric Use:** There were 278 subjects aged 65 or older in the clinical trials of ZILXI (16.6% of 1,678 subjects). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY

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

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

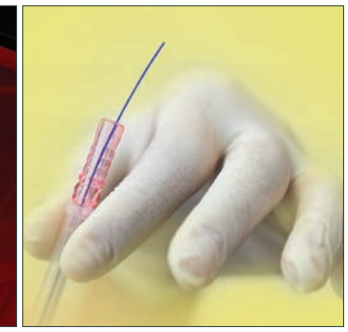
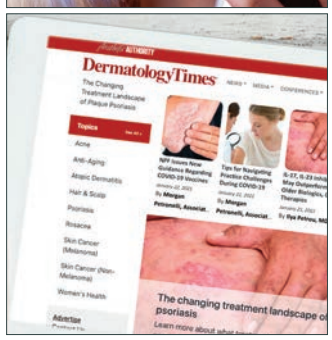
- **WARNING:** Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).

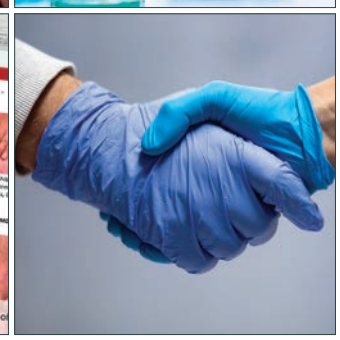
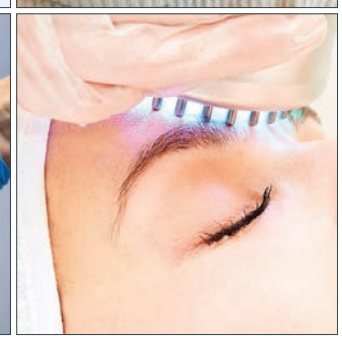
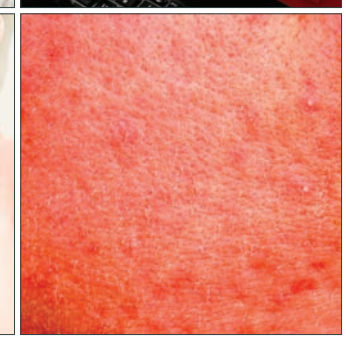
For more information, including the FDA-approved Prescribing Information, go to www.ZILXI.com or call 1-844-375-3673.

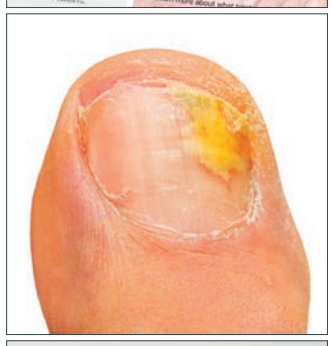
VYNE™ THERAPEUTICS

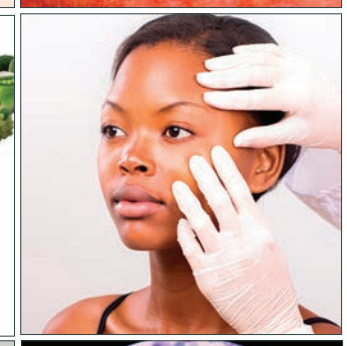
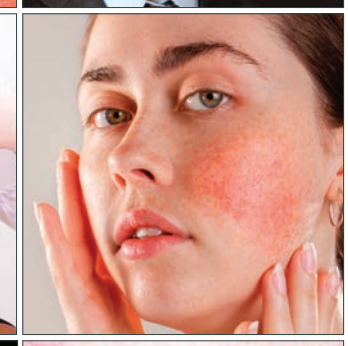
DermatologyTimes®

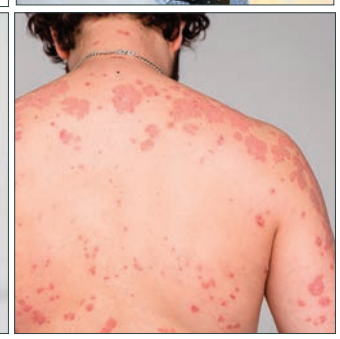


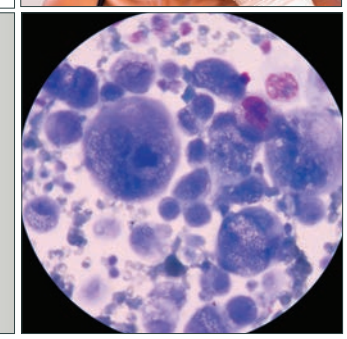
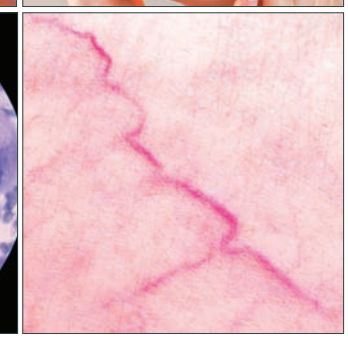




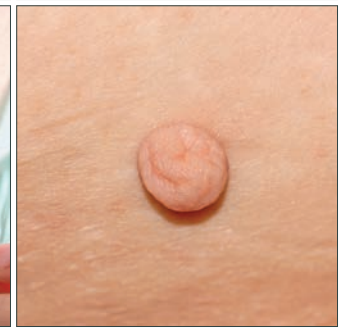
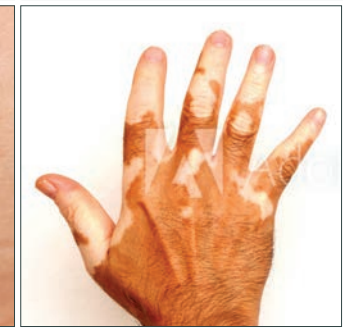
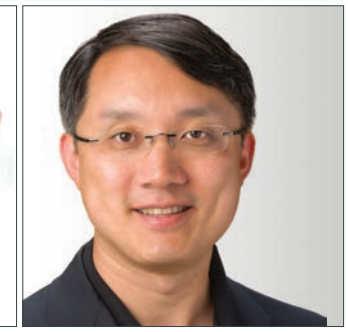


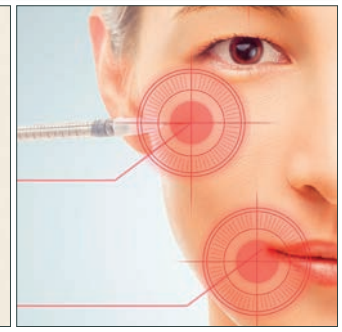
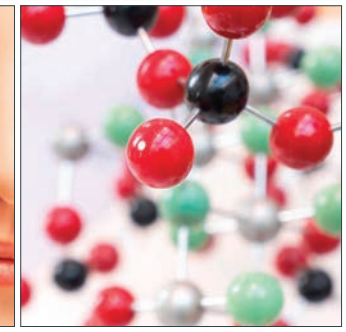






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What's next for COVID-19, coding, customized medicine

by **MIKE HENNESSY SR**

KEY OPINION LEADERS speaking at more than a half-dozed dermatology-related conferences during January and February predicted that 2021 will be a year of innovation. It's only March, and they're already being proven right.

That starts with coronavirus disease 2019 (COVID-19). Although vaccines are being rolled out worldwide, research continues on the mechanisms of this novel virus.

Not surprisingly, virologists, infectious disease specialists, and medical research experts have dominated the headlines covering the frontline fight to stop COVID-19. Now, the field of dermatology may be poised to make a powerful contribution to their efforts, according to Richard Gallo, MD, PhD, chair of the department of dermatology at the University of California San Diego (UCSD).

In his presentation[1] at the Maui Derm Live and Maui Derm Connect conferences, and in this issue's followup story "Update tracks advances in rosacea therapy" on page 28, Gallo noted that research on rosacea's mechanism of action could have important implications for understanding—and eventually halting—COVID-19.

Gallo and other study teams identified a possible structure in the cathelicidin peptide LL-37 that could be responsible for promoting inflammation. That conclusion alone is a breakthrough, but it takes on even more importance in the context of COVID-19.

Gallo pointed out that a functional screen confirmed that SARS-CoV-2 peptides amplify IL-6 in a manner similar to LL-37. Lessons learned about LL-37 may help explain metainflammation in COVID-19, he said.

Precision medicine is opening up new avenues of tailoring diagnosis, treatment and management of skin diseases to the individual patient's genetic, medical and lifestyle profiles. As *Dermatology Times*® reports in this month's cover story, "Tap Potential Medicine's Potential," the full benefits of patient care tailored to an individual's needs won't be felt for some time. However, clinicians and researchers are exploring near-term solutions for leveraging its potential.

One example would be topical platelet-rich plasma (PRP), says Zoe Diana Draelos, MD, founder and investigator, Dermatology Consulting Services, PLLC, High Point, North Carolina, and *Dermatology Times*® chief medical editor. If approved by the FDA, this novel topical would "personalize" treatments for improving facial appearance by harvesting the patient's own body-made materials to create a cosmetic vehicle specific to the individual. For more, see page 34, "Positive outcomes the way for topical PRP" in the January 2021 issue of *Dermatology Times*®

Like the rosacea research, PRP has potential beyond dermatology. Draelos said that personalized medical techniques such as PRP and cell-derived materials are being used for applications as diverse as stimulating bone growth in elite athletes.

Practice management is also changing dramatically this year—and none too soon. In late 2020, *Dermatology Times*® sister publication, *Medical Economics*® surveyed physician audiences about what they saw as the most challenging issues for 2021. Administrative burdens and paperwork topped the list. Other concerns are outlined in the story, "2021's Top Challenges Facing Physicians" in its January 2021 issue.

Fortunately for dermatologists, the American Medical Association (AMA) was well aware of those concerns. In January, the association issued the results of its first major overhaul to the codes and guidelines for office and outpatient evaluation and management in 25 years. The story on page 49, "AMA streamlines CPT codes," maps the highlights.

Just think what Q2, Q3, and 4 could bring. ◄

Reference

1 Webster G. Eichenfield E, Layton J, et al. Update 2021: acne and rosacea. Presented at: Maui Derm For Dermatologists 2021; January 25-29, 2021; Maui, Hawaii.

MIKE HENNESSY SR IS CHAIRMAN AND FOUNDER OF DERMATOLOGY TIMES' PARENT COMPANY, MJH LIFE SCIENCES™.

more **ONLINE**

Scan for MJH Life Sciences™' COVID-19 Coalition's webinar, *Emerging Sars-CoV-2 variants: What you need to know*

Chief MEDICAL EDITOR

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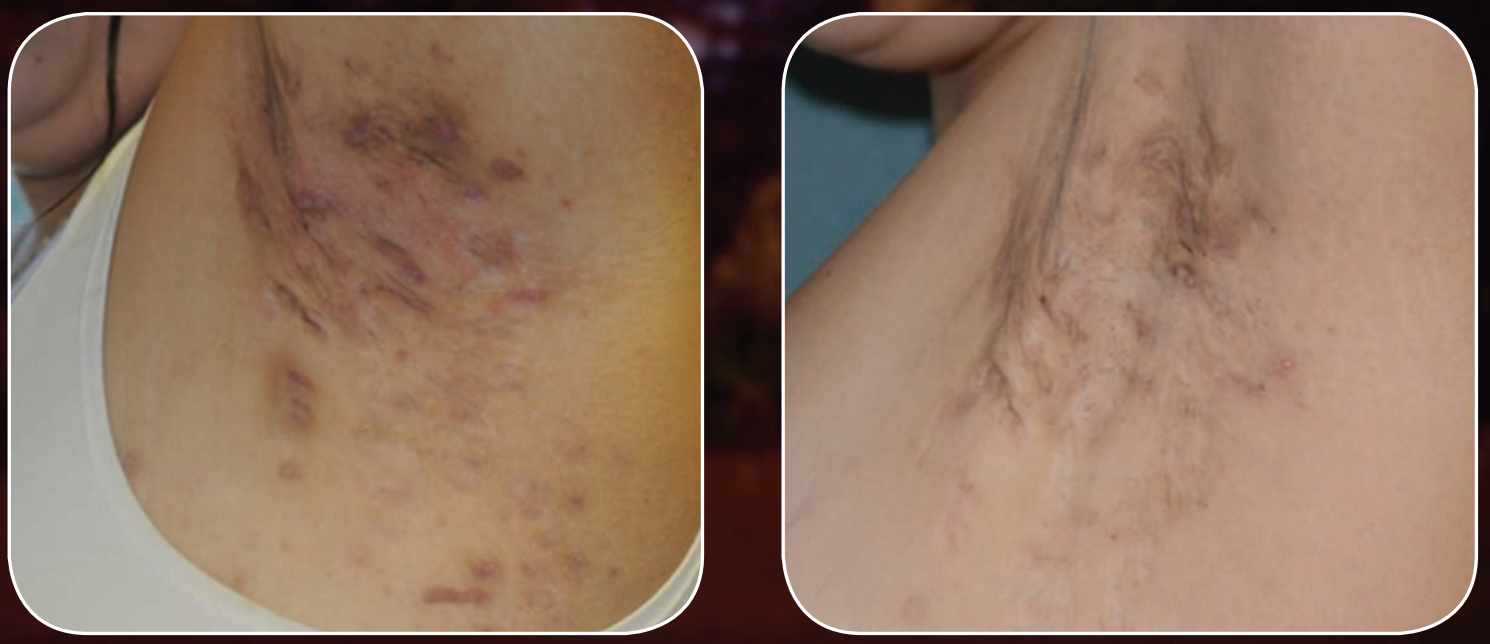
For the treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older

HUMIRA is the only FDA-approved treatment for your HS patients[1-3]

Results Your HS Patients Can See

MODERATE/STAGE II

Actual HUMIRA-treated patient achieving HiSCR



Before | After

Photos courtesy of Dr. Marc Bourcier

HiSCR is at least a 50% reduction in total abscess and inflammatory nodule count, with no increase in abscesses and draining fistulas relative to baseline[1]

Indication[1]

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

Safety Considerations[1]

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.

Clinically Meaningful Improvement (HiSCR) at Week 12

- In the PIONEER clinical trials, **42%** (PIONEER I) and **59%** (PIONEER II) of HUMIRA-treated adult patients achieved HiSCR at Week 12 **(primary endpoint)**, vs **26%** and **28%** on placebo, respectively[4]

HUMIRA also has flare data available for HS

OCCURRENCE OF FLARE THROUGH 3 MONTHS[5]
Pre-specified Other Secondary Endpoint in Period A

HUMIRA-treated patients
n=316 for HUMIRA EW

Control patients
n=317 for control

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

22% (of 100) patients who were withdrawn from HUMIRA after 12 weeks experienced flare.[1,4]

PIONEER I control=placebo.
PIONEER II control=placebo +/- antibiotic.

Integrated analysis of PIONEER I and PIONEER II through 12 weeks

Flare: ≥25% increase in AN count and an absolute increase of ≥2 relative to baseline[1,5]

DATA LIMITATIONS

- **Since PIONEER I did not reach statistical significance at the first key secondary endpoint, all endpoints in this integrated analysis cannot be regarded as statistically significant**[4,5]

Safety Considerations[1] (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.

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To learn more, please go to
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HUMIRA®
adalimumab

IMPORTANT SAFETY INFORMATION for HUMIRA® (adalimumab)[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue HUMIRA if a patient develops a serious infection or sepsis. Reported infections include:

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

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

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with 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 immunosuppressant 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 leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic 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: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc. **2.** US Food and Drug Administration. HUMIRA approval letter for hidradenitis suppurativa. September 2015. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125057Orig1s393ltr.pdf. Published September 9, 2015. Accessed January 31, 2020. **3.** AbbVie's HUMIRA® (adalimumab) receives first and only U.S. Food and Drug Administration approval for moderate to severe hidradenitis suppurativa [press release]. North Chicago, IL: AbbVie Inc.; September 10, 2015. https://news.abbvie.com/news/abbvies-humira-adalimumab-receives-first-and-only-us-food-and-drug-administration-approval-for-moderate-to-severe-hidradenitis-suppurativa.htm. Accessed January 30, 2020. **4.** Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375(5):422-434. **5.** van der Zee HH, Longcore M, Geng Z, Garg A. Weekly adalimumab treatment decreased disease flare in hidradenitis suppurativa over 36 weeks: integrated results from the phase 3 PIONEER trials. *J Eur Acad Dermatol Venereol.* 2019 Oct 20.doi: 10.1111/jdv.16023.

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

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HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. 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 with chronic or recurrent 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 *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing 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 these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) 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 *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

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

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

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 *[see Boxed Warning]*. 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 the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) 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. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

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 of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating 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.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

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 *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[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.

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in adult patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

Anti-adalimumab antibodies were measured in clinical trials of subjects with moderate to severe HS with two assays (an original assay capable of detecting antibodies when serum adalimumab concentrations declined to < 2 mcg/mL and a new assay that is capable of detecting anti-adalimumab antibody titers in all subjects, independent of adalimumab concentration). Using the original assay, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%. Using the new titer-based assay, anti-adalimumab antibody titers were measurable in 61% of HS subjects treated with HUMIRA. Antibodies

to adalimumab were associated with reduced serum adalimumab concentrations. In general, the extent of reduction in serum adalimumab concentrations is greater with increasing titers of antibodies to adalimumab. No apparent association between antibody development and safety was observed.

In adult patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis adult patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials
** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions, Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4-week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 adult patients with uveitis (UV) in placebo-controlled and open-label extension studies and in 90 pediatric patients with uveitis (Study PUV-I). The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia, lichenoid skin reaction

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available studies with use of adalimumab during pregnancy do not reliably establish an association between adalimumab and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby HUMIRA Pregnancy Registry in pregnant women with rheumatoid arthritis (RA) or Crohn's disease (CD). Registry results showed a rate of 10% for major birth defects with first trimester use of adalimumab in pregnant women with RA or CD and a rate of 7.5% for major birth defects in the disease-matched comparison cohort. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects *(see Data)*.

Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *(see Clinical Considerations)*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *(see Data)*.

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

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with RA or inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *(see Data)*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

A prospective cohort pregnancy exposure registry conducted by OTIS/MotherToBaby in the U.S. and Canada between 2004 and 2016 compared the risk of major birth defects in live-born infants of 221 women (69 RA, 152 CD) treated with adalimumab during the first trimester and 106 women (74 RA, 32 CD) not treated with adalimumab.

The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects. This study cannot reliably establish whether there is an association between adalimumab and major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

In an independent clinical study conducted in ten pregnant women with IBD treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA), pediatric Crohn's disease and pediatric uveitis have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Pediatric Uveitis

The safety and effectiveness of HUMIRA for the treatment of non-infectious uveitis have been established in pediatric patients 2 years of age and older. The use of HUMIRA is supported by evidence from adequate and well-controlled studies of HUMIRA in adults and a 2:1 randomized, controlled clinical study in 90 pediatric patients. The safety and effectiveness of HUMIRA has not been established in pediatric patients with uveitis less than 2 years of age.

Hidradenitis Suppurativa

Use of HUMIRA in pediatric patients 12 years of age and older for HS is supported by evidence from adequate and well-controlled studies of HUMIRA in adult HS patients. Additional population pharmacokinetic modeling and simulation predicted that weight-based dosing of HUMIRA in pediatric patients 12 years of age and older can provide generally similar exposure to adult HS patients. The course of HS is sufficiently similar in adult and adolescent patients to allow extrapolation of data from adult to adolescent patients. The recommended dose in pediatric patients 12 years of age or older is based on body weight.

The use of HUMIRA has not been established in patients less than 12 years of age with HS.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the HUMIRA 40 mg/0.8 mL Pen and 40 mg/0.8 mL, 20 mg/0.4 mL and 10 mg/0.2 mL prefilled syringe may contain natural rubber latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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Precision Medicine's Potential

Still in its infancy, personalized approach tailors treatment to each patient.

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cosmetic conundrums

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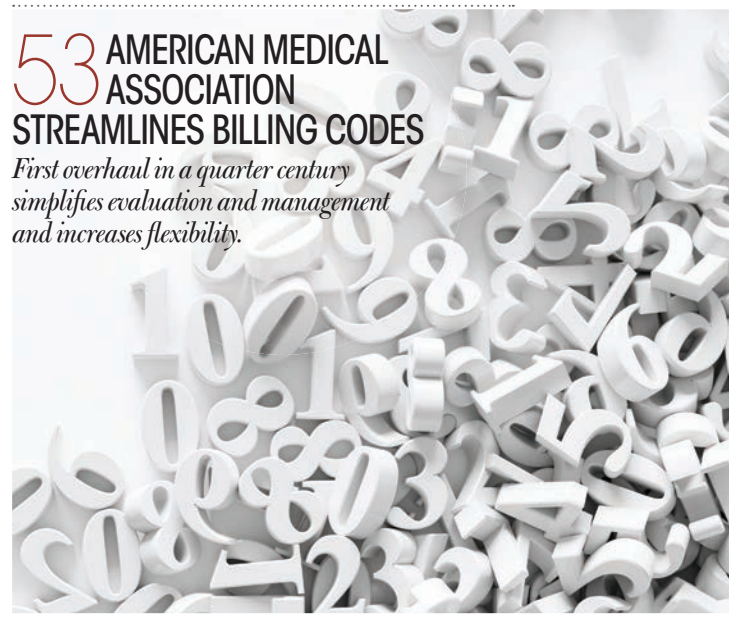

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Medical World News®

FROM OUR SISTER PUBLICATION, *MEDICAL ECONOMICS®*

2021's Top Challenges Facing Physicians

…and What to Do About Them

BY *MEDICAL ECONOMICS®* STAFF

In late 2020, *Medical Economics®* conducted a Physicians Report asking physician audiences what they thought would be the most challenging issues they will face this year. Here is what the respondents said.

Administrative burdens and paperwork

If doctors had to chart their feelings about practicing medicine, many would list "paperwork" as their chief complaint.

In countless surveys and studies, and across specialties, physicians consistently cite the time and energy they must devote to filling out forms and other administrative tasks near or at the top of their list of grievances. The mantra repeatedly heard throughout the profession is, "This isn't why I went into medicine."

The problem is worsened by electronic health records (EHR), now used by close to 90% of office-based physicians. Once seen as a way to streamline data documentation sharing, EHRs have become enormous time-sucks. A December 2016 study in *Annals of Internal Medicine* found that physicians in outpatient settings spent about 27% of their day on direct clinical face time with patients, but 49% on EHRs and desk work. Many also worked up to 2 hours every evening on EHR-related tasks.

More recently, the proliferation of quality metrics physicians must document, although well-intentioned, has resulted in another layer of time-consuming administrative tasks for them and their staffs.

"Payers and the Centers for Medicare & Medicaid (CMS) with their reporting requirements are trying to do the right thing and reward quality care, but the process and metrics we have today are adding to the burden with little evidence it is helping quality," David Gans, MHA, senior fellow of industry affairs for the Medical Group Management Association, told *Medical Economics®*.

86%

of respondents described the administrative burden of prior authorizations as "high or extremely high."

The growing number of treatments and medications requiring prior authorizations from payers is yet another source of administrative frustration for physicians and their staff. In a 2020 American Medical Association (AMA) survey, 86% of respondents described the administrative burden of prior authorizations as "high or extremely high."

Similarly, respondents to the *Medical Economics®* Physician Report said prior authorizations consumed, on average, more than 16 hours per week of practice time, including 11.6 hours for staff members and 4.6 hours for themselves.

Paperwork and administrative requirements are also linked to the alarming increase in physician burnout rates, especially among primary care doctors. When *Medical Economics®* asked doctors what contributed to their feelings of burnout, 31% cited "paperwork"—more than twice the percentage of the second-leading cause, a poor work-life balance.

"The data show that the things that cause burnout are the things that get in the way of why you went into medicine in the first place, such as being able to provide the kind of care you want to provide to your patients," Jack Resneck, MD, immediate past chairman of the AMA board of trustees told *Medical Economics*® in an interview this year.

Fortunately, there are steps physicians can take to reduce their administrative burden, starting with EHRs. Gans suggested that doctors and practices work with their EHR vendor on ways to automate data reporting, such as tailoring prompts according to patients' specific requirements. For example, in patients with diabetes, the EHR might be programmed to provide reminders of the need for foot and eye exams and report to payers that the patient received the reminder. In addition, some EHRs now offer the option of automatically reporting some quality data to CMS.

Employing scribes can also help to reduce paperwork and other administrative burdens. A 2018 study in *JAMA Internal Medicine* concluded that their use was associated with significant reductions in EHR documentation time and "significant improvements in productivity and job satisfaction."

Ultimately, doctors probably need to accept that paperwork and administrative tasks will be an inescapable part of practicing medicine—particularly with the spread of value-based care models, which usually require detailed tracking and reporting of quality metrics.

"In the long run, value-based reporting is going to be a requirement from all payers," Gans predicts.

Reforming the prior authorization process
When it comes to top physician frustrations, prior authorizations rank near the top of the list, right next to poorly designed EHRs.
Scan to read full article.

Getting paid and seeing enough patients

Generating enough revenue to keep a practice open requires knowing the intricacies of medical coding to ensure reimbursement is maximized, and also recognizing trends that keep patients coming back.

Getting paid is regularly listed as a top challenge facing physicians, according to the 2020 *Medical Economics*® Physician Report.

The good news for physicians who primarily deliver office and outpatient services is that the Centers for Medicare & Medicaid (CMS) has made significant changes to evaluation and management (E/M) coding and documentation to make the process simpler.

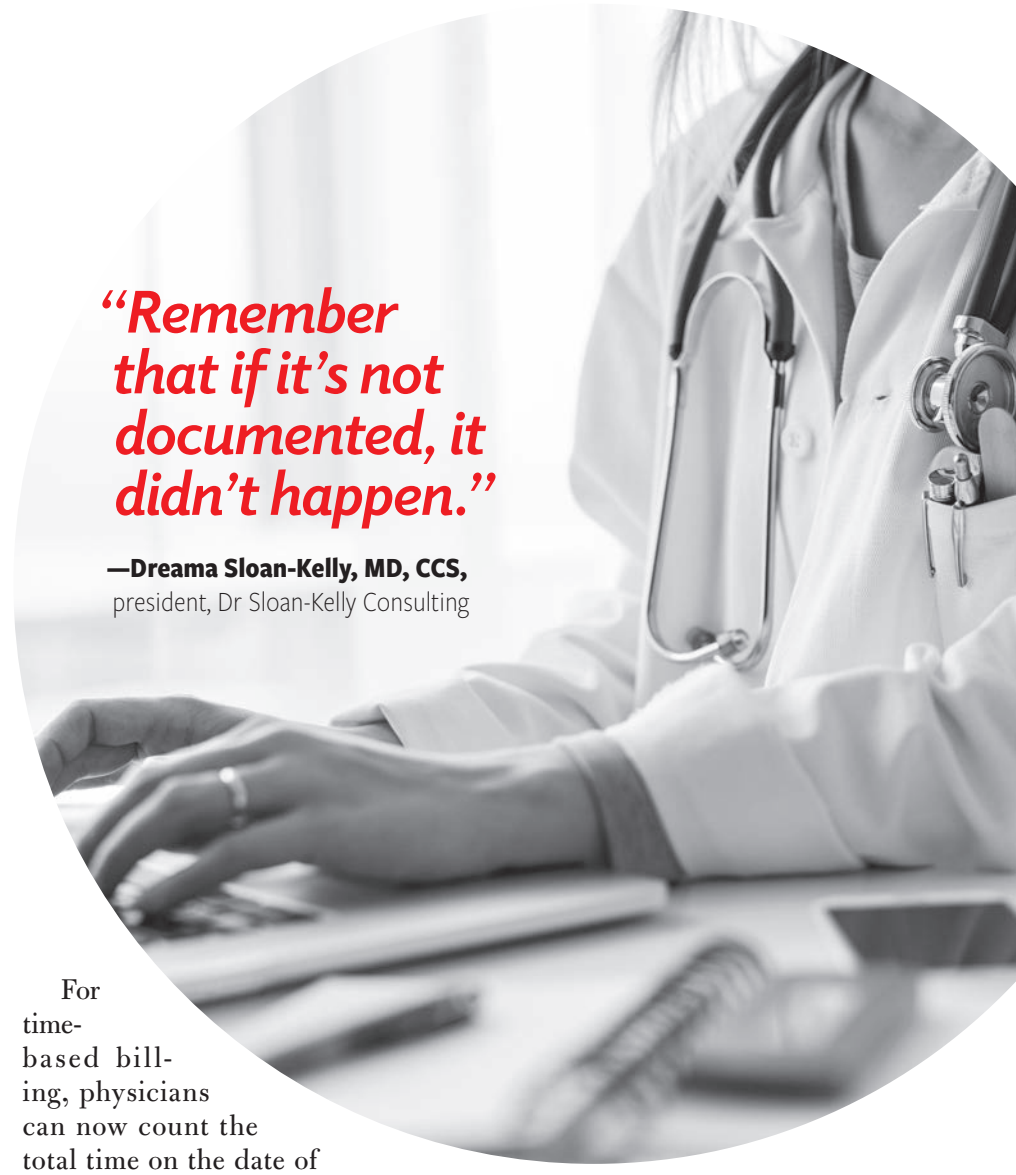
For 2021, there are 3 areas physicians need to focus on to make sure they get paid.

UNDERSTAND E/M CHANGES

According to coding experts, E/M codes are now much simpler Physicians will not select an E/M code based on total time spent during the encounter or medical decision making, whichever one pays more.

For medical decision-making (MDM), gone is the complicated points system derived from the number of treatment options, the complexity of data, and morbidity risks. The new MDM table includes easy-to-understand requirements and compensates them for complex cases, regardless of time spent, as long as documentation supports medically necessary services.

In addition, physicians now get credit for many tasks, including reviewing and interpreting test results, speaking with family members if a patient cannot provide their own history, and discussing patient treatments with another health provider or other professional involved in their care.



For time-based billing, physicians can now count the total time on the date of the encounter that may or may not include counseling and care coordination. Doctors may also count, among other tasks, documenting clinical information in the electronic health record (EHR), ordering medications or tests, preparing to see the patient, and referring the patient to and communicating with other health care professionals.

Physicians should contact their payers to verify whether they will adopt the CMS changes. Some payers may continue to require code selection based on history, exam, and MDM. They may also have requirements for individual codes.

The most important thing is to ensure that services performed match the documentation.

"Remember that if it's not documented, it didn't happen," says Dreama Sloan-Kelly, MD, CCS, president of Dr Sloan-Kelly Consulting, a medical coding consulting company.

MASTER TELEHEALTH PAYMENTS

The coronavirus disease 2019 (COVID-19) pandemic closed many primary care offices throughout the country, forcing physicians to quickly adopt telehealth as the only way to see patients and keep revenue up.

To say telehealth was a lifeline for practices during the pandemic is an understatement. According to the *Medical Economics*® 2020 Technology Survey, more than 93% of physicians used telehealth to see patients during 2020, and 77% of them were using telehealth for the first time.

CMS and private payers made many emergency exceptions to laws making telehealth more accessible for both patients and physicians and added or increased reimbursement for virtual visits to match payment rates for in-office visits.

TOP CHALLENGES CONTINUES ON PAGE 18 ▶

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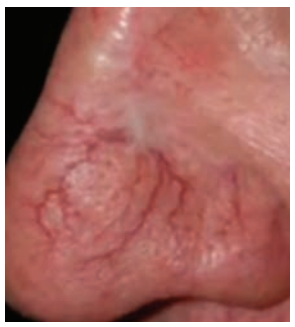
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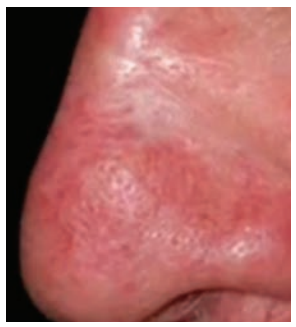
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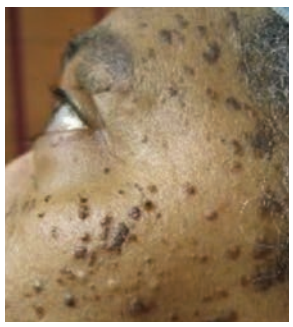
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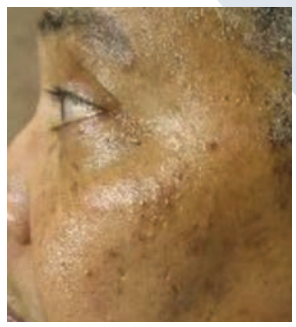
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Top challenges FROM PAGE 16

But the CMS changes were made as part of the federal government's public health emergency declaration that will end whenever the pandemic passes. Although no one knows for sure when that will happen, doctors need to be ready for a sudden s telehealth reimbursement shift. Some private payers have already rescinded reimbursement for certain telehealth visits as public confidence for in-office visits has increased.

Experts say physicians must balance keeping telehealth available for patients who are not comfortable coming into the office to capture as much revenue as possible, knowing that at some point in 2021, it's likely that reimbursement for it may dry up.

Before the pandemic, telehealth reimbursement was extremely limited. Even if reimbursement remains for some services, it may not be at the same level as for an in-office visit, so doctors need to understand their telehealth investment return both now and when the public health emergency ends.

EMBRACE THE DATA

Experts say fee for service (FFS) isn't going to vanish in 2021, but more contracts will focus on value-based care, and the lifeblood of any value-based care contract is data. Payers want data to evaluate the most effective physicians, and the top performers get the best bonuses.

Participating in the most lucrative forms of value-based care requires that physicians have plenty of data on their outcomes and show improvement in the ability to keep patients out of the hospital. An investment in software and equipment may be necessary to fully master all the data points within a practice. Without it, doctors will be at a disadvantage to both participate in and excel at value-based care.

"The key is for us to break the fallacy that FFS is a good way to pay for primary care," says Farzad Mostashari, MD, the former director of the Office of the National Coordinator for Health Information Technology and current CEO of Aledade, a company that assists small practices with transitioning to value-based care models. "We shouldn't be basing primary care payments on that—it should be on the value created, and we need to move towards more person-based rather than transactional."

How should primary care physicians be paid?
COVID-19 may have permanently changed the reimbursement landscape. **Scan to read full article.**

Physician burnout and autonomy

The perennial issue of physician burnout has only been intensified by the equipment shortages and shutdowns of the coronavirus disease 2019 (COVID-19) pandemic. Despite increased awareness in the health care system, the same problem persists.

The 2020 *Medical Economics*® Physician Burnout Survey found that burnout is pervasive among physicians, with 91% of doctors saying they have felt burned out from practicing medicine at some point in their career. A further 71% of physicians reported feeling burned out at the time of the survey.

When asked what caused their burnout, 31% of physicians said too much paperwork and government/payer regulations, 15% cited poor work-life balance, and 12% said the COVID-19 pandemic.

Although little can be done on the ground concerning increased stressors from the pandemic, there are ways health care leaders can reduce the underlying issues.

TIPS

Howard Baumgarten, LPC, has extensive experience working with physicians who feel burned out. He says there are 3 categories of burnout physicians may experience: physiological, which can take the form of physical symptoms like headaches and high blood pressure; mental/emotional, which can take the form of anxiety and depression; and behavioral, which can take the form of increased alcohol use or smoking, overspending, and not sleeping.

Baumgarten says that once a physician starts feeling burnout symptoms, they should take steps to fight it. He gave some helpful tips for physicians to prevent feeling the heat of the health care system.

The first strategy is to aim for 7 to 8 hours of sleep, starting at the same time every night, and avoiding both drinking alcohol and screen time before bed. The next is to get 30 minutes of aerobic exercise 4 or 5 times a week mixed with some muscle-building exercises. Physicians should also avoid sugary and fried foods and do something that makes them feel good, such as a hobby.

The National Academy of Medicine released a report early in 2020 saying personal stress management strategies are insufficient to tackle the burnout problem facing health care. Although some of the academy's suggestions relate to structural issues, independent practice leaders can adopt them.

Also, according to the same burnout survey, 11% of physicians experience burnout due to a lack of autonomy or career control.

Wendy Dean, MD, a psychiatrist, and president and cofounder of Moral Injury of Healthcare, says that following the long period of rigorous training, focusing on independent, critical thinking with strict adherence to algorithms based on reimbursement policies can be grating.

Beyond the big systemic hurdles that must be crossed to get this issue under control, Dean recommends that physicians learn how the incentives are aligned at their health care institution.

Stress Management Strategies

- ☐ Creating positive work environments
- ☐ Addressing burnout in training and at early career stages
- ☐ Reducing tasks that do not improve patient care
- ☐ Improving usability and relevance of health IT
- ☐ Reducing stigma and improve burnout recovery services
- ☐ Autonomy

"Understand how reimbursement happens, what the incentives are at their entity, and whether they can negotiate to build bridges with the administration, build bridges with other licensees so that everyone can work together to start fixing things at the local level," Dean says.

According to Dean, by talking to fellow physicians, they can see what the patterns are and where the stumbling blocks may be.

"As you start to look into that more and more, you can quickly

become an expert and can have the tools available to you to change what that problem is," Dean says.

RESOURCES

Susan T. Hingle, MD, professor of medicine at Southern Illinois University School of Medicine, says there are burnout resources available on the websites of most major physician organizations, such as the American College of Physicians for internists. She says many hospital systems also offer support phone lines to help deal with the increased stress from the COVID-19 pandemic.

"I want people to know that those [resources] are available and know that there's no shame in asking for help," Hingle says. "That's how we're all going to get through this: by helping each other and getting through it together.

HIRING AND RETAINING CLINICAL STAFF

A practice is only as good as the individuals who work there but finding and keeping the right them can seem like an insurmountable task. This task can be compounded with the uncertainty and increased scrutiny introduced by the coronavirus disease 2019 (COVID-19) pandemic.

In a recent entry in weekly studies performed by the Larry A. Green Center and the Primary Care Collaborative on how COVID-19 has affected primary care practices, 35% of physicians say hiring new staff is a significant obstacle to their practice.

With this perennial problem only getting worse, the question remains for physician leaders on how to hire, motivate, and retain clinical staff.

TIPS

Target the talent by looking for candidates from areas similar to those in the practice. This familiarity can smooth over some of the wrinkles the new staff member may feel starting at a practice.

Another suggestion is to adjust the payment system to reward hard work or to boost the total compensation package. Packages can take the form of creating bonuses for staff members who meet productivity goals, giving employees a sense of how to earn more without leaving the practice.

The practice leader can also consider offering staff members growth opportunities, such as enabling them to pursue more education through training. Sometimes the cost of training and giving the employee a raise can be a lower cost compared to hiring another employee for new duties.

Personalized benefits, such as flexible hours or more vacation time, can be a useful recruitment tool and a motivator for current staff members. Allowing newly hired physicians to hire their own care teams or set their office hours can increase their motivation.

All these changes should be documented and formalized so that, even if employment packages are individualized, they do not appear to be capricious.

MILLENNIALS

An often overlooked source for clinical staff is the newest batch of medical school graduates. Millennials can be a key part of a health care team.

Andrew Hajde, CMPE, assistant director of association content at Medical Group Management Association in Englewood, Colorado, says the health care system is reaching a point where millennial physicians are becoming the only ones left to pick up the slack of retiring boomers and Gen Xers before Generation Z comes of age.

When hiring millennials, it is important to remember that the cohort tends to put a premium on work-life balance and the feeling that their work has a purpose.

Natasha Bhuyan, MD, is a family physician and regional medical director with One Medical in Phoenix, Arizona, and is also a millennial. She says the members of her cohort no longer base their success on the hours they spend in the office or the number of patients seen.

"They measure success based on fulfillment of purpose, developing meaningful relationships with patients, having time to connect with patients and improve their behaviors, and see health results and outcomes change," she says.

Millennial physicians are also aware that they need feedback and mentoring and can see the value in picking a senior employee's brain to help them in their work.

Bhuyan says this new emphasis on mentorship is closer to coaching than in years past.

"How do we coach physicians to reach the top of their potential and beyond?" Bhuyan asks. "How do we push people beyond what they think is their best?" ◀

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"Physicians have an obligation to keep the workplace free from serious hazards."

Will OSHA Regulations Require Significant Changes in Running an Office?

by **DAVID J. GOLDBERG, MD, JD**

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 Mount Sinai; and adjunct professor of law at Fordham University School of Law, New York, New York.

Sarah Doe is a secretary at Dr Yes' practice. As 1 of 5 secretaries who work on the practice's computers, she is the most proficient in electronic medical records and works on the computer incessantly. Recently, she developed increasing pain in her wrist. After a medical examination, she received a diagnosis of carpal tunnel syndrome.

Yes explains to her that, as head of a small practice, he cannot afford to make such wholesale changes in the office. She responds by threatening to sue him for not complying with Occupational Safety and Health Administration (OSHA) regulations. He asks her, in the economically difficult times of the pandemic, if she can be "reasonable". She refuses to change her stance.

OSHA published "ergonomic suggestions" some 20 years ago. The aim was to reduce musculoskeletal disorders (MSD) in the workplace. These requirements state that all employers must determine whether work-related injuries meet the specific criteria for MSD. If an MSD injury occurs, OSHA requires employers to implement immediate remedies depending on the level of risk factors on the job as determined by specific screening tools.

The significant relevant regulations:

- apply to all general industry employers, including physician offices;
- provide a short minimum period during which full pay and benefits must be continued after an injury;
- provide a 2-page checklist for determining whether a work-related MSD required action by the employer; and
- require that covered employers distribute information to employees and receive and respond to reports of injuries.

These regulations were consistent with findings reported by the National Research Council and the Institute of Medicine. Although not directly supporting OSHA's approach with its ergonomic rules, the report did state that some elements of the regulations would likely alleviate musculoskeletal pain. According to the study, scientific approaches were effective when properly implemented.[1]

However, the report concluded that work-related exposures directly contributed to musculoskeletal disorders such as carpal tunnel syndrome.

However, it is unclear whether OSHA rules would mandate such stringent ordinances for small employers such as Yes. Rather than issuing general guidelines, OSHA developed industry-specific standards to help employees and employers minimize injuries. However, every industry, including medical offices, has its own guidelines.

Will OSHA come after Yes under the General Duty Clause? Even if no guidelines apply specifically to his office, as an employer, Yes still has an obligation under the General Duty Clause, Section 5(a)(1), to keep the workplace free from recognized serious hazards, including ergonomic hazards. OSHA also encourages employers to implement effective programs or other measures to reduce ergonomic risks.

The administration will cite for ergonomic hazards under the General Duty Clause or issue ergonomic hazard alert letters as part of its overall enforcement program. However, the central issue is what exactly poses as an ergonomic hazard.

Although one would hope that Yes could provide workplace accommodations that will suit Doe's needs, he may have no legal obligation to do so. Yes' contention that the pandemic's economic impact on his office precludes him from complying with OSHA regulations will have no validity. He could try to address these issues with various Paycheck Protection Program policies and Small Business Administration loans. ◀

Reference

1 National Research Council (US) and Institute of Medicine (US) Panel on Musculoskeletal Disorders and the Workplace. *Musculoskeletal Disorders and the Workplace: Low Back and Upper Extremities*. Washington, DC: The National Academies Press; 2001.

"The additional cost of full nonclinical testing... can be as much as $25 million."

Cosmetic Moisturizers, Topical Drug Vehicles

by **ZOE DIANA DRAELOS, MD**

Draelos is a consulting professor of dermatology at Duke University School of Medicine in Durham, North Carolina.

Q Why are cosmetic moisturizers and topical drug vehicles so different in texture? Is it the ingredients?

That is an excellent question. Dermatologists might think a pharmaceutical company could take a moisturizer and simply add any ingredient to make a new topical drug, [thereby improving texture]. Regrettably, this is not possible. The number of FDA-approved ingredients used in drug vehicles is much smaller than the unlimited ingredient list available to cosmetic formulators. The FDA requires new vehicle ingredients to undergo full nonclinical testing, including reproduction and fertility testing and 2-year carcinogenicity studies in 2 species. Also, the additional cost of completing this testing can be $25 million. Most pharmaceutical companies do not use ingredients that are not on the FDA Inactive Ingredients Database in their products. Thus, innovation in the topical treatment of skin occurs almost exclusively within the field of cosmetics rather than medical dermatology.

Q How does the limitation of ingredients in pharmaceutical vehicles affect dermatologic drugs?

One key area where FDA limitations on drug vehicle ingredient selection presents challenges is in the realm of emulsifiers. Emulsifiers are very important in topical drugs to allow the hydrophobic (water-hating) emollients suspended in moisturizing creams and lotions not to separate a few days after manufacture. However, emulsifiers are basically detergents, such as sodium alkyl sulfates, and can efficiently extract important epidermal intercellular lipids, compromising the skin barrier.

In 1957, topical pharmaceutical creams were emulsified with beeswax, polyoxyl esters, or sodium alkyl sulfates. Forty years later, 81 FDA-approved prescription topical creams were formulated with 1 of these 3 classes of emulsifiers. A search of the FDA Inactive Ingredient Database confirmed that the emulsifiers used in over-the-counter dermatologist-recommended cleansers and moisturizers (Cetaphil, Galderma Laboratories and CeraVe, L'Oréal) are not used as emulsifiers in FDA-approved prescription creams. Thus, modern ultra-gentle moisturizing cream vehicles are not used in pharmaceuticals presently.

Q How do penetration enhancers used in most topical pharmaceuticals affect the skin?

Many topical drugs contain alcohol, propylene glycol, dimethyl sulfoxide, sodium lauryl sulfate, or other skin penetration enhancers to overcome barrier properties of the skin and deliver higher therapeutic concentrations of drugs. This damage to the skin barrier is counterproductive, especially in conditions such as atopic dermatitis, where cumulative barrier damage from continued exposure to penetration enhancers may inhibit disease resolution.

Many topical medications are emollient formulations containing hydrophilic occlusive agents such as petrolatum, waxes, oils, or silicones that coat the skin surface and trap water in the stratum corneum. The most aesthetically pleasing emollient formulations are creams and lotions, which also contain significant amounts of water. These formulations require emulsifiers, such as sodium cetostearyl sulfate, the emulsifier used in pimecrolimus cream that also functions as a detergent mixing and disorganizing the stratum corneum lipids. The defective skin barrier of patients with atopic dermatitis makes them more vulnerable to the detergency effects of emulsifiers introduced into the stratum corneum. The defective skin barrier is the challenge formulators face when designing penetration-enhanced topical pharmaceuticals.

Q What is the best way to conquer irritation from topical pharmaceutical emulsifiers?

Until more modern dermatologic topical formulations are available, irritation from topical pharmaceutical emulsifiers can be overcome somewhat by using a modern cosmetic moisturizer, such as Cetaphil and CeraVe cream. The topical drug should be rubbed in thoroughly until it creates a thin film and is dried down on the skin surface. This process usually takes 10 to 15 minutes, depending on the drug formulation. The moisturizing cream can then be applied on top to mitigate damage induced by emulsifiers. In the future, hopefully, newer, more cosmetically elegant topical formulation may achieve this in 1 step. ◀

“Research on topical probiotics in skincare and dermatological therapy is still in the initial stages and is certainly a promising topic to be explored.”

Katlein França, MD, PhD, assistant professor in the Dr Phillip Frost Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine in *Miami, Florida*.

Probiotics FROM PAGE 1

versity of Miami Miller School of Medicine in Miami, Florida. “Emerging evidence points out the positive effect of some bacterial strains in the treatment of skin disorders.”

Quick TAKES

- Topical probiotics show promise, especially in treating acne and atopic dermatitis.
- Antimicrobial, anti-inflammatory effects may help combat *P acnes*.
- Probiotics modify several pathophysiological factors without irritating skin.

Meanwhile, new topical dermatologic products containing probiotics are quickly becoming available. “Patients continuously ask about their efficacy,” França added. “This [review] will help dermatologists understand the current scientific evidence on this emerging topic.”

To date, most studies in dermatology have examined oral probiotics. “New studies try to clarify if the application of exogenous probiotics could have the same benefit as oral probiotics in promoting positive bacterial balance to treat dermatologic conditions,” she said.

Topical probiotics have been shown to have antimicrobial and anti-inflammatory activity against *Propionibacterium acnes (P acnes)*. The first report suggesting that topical bacteriotherapy could combat acne appeared in 1912. More recently, results from a study showed that *Streptococcus thermophilus*, found in yogurt, could increase ceramide production when applied topically for 7 days by patients with acne.[2] Some skin ceramides, such as phytosphingosine, provide both antimicrobial and anti-inflammatory activity, and topical phytosphingosine has been shown to reduce acne papule and pustule counts. Similarly, *Streptococcus salivarius* possesses both antimicrobial activity and the ability to inhibit inflammatory pathways through immunomodulation.

In another study, a lotion containing *Enterococcus faecalis* SL-5 significantly reduced pustules compared with placebo, prompting study authors to suggest that this could provide an alternative to topical antibiotics.[3] Unlike many currently available topical acne treatments, probiotics modify several pathophysiological factors and, because they do not irritate the skin, may improve patient adherence, according to França.

In a 30-day, prospective, double-blinded, placebo-controlled study involving 75 volunteers with AD, a cream containing *Vitreoscilla* filiformis reduced *Staphylococcus aureus (S aureus)* colonization and had a direct immunomodulatory effect on skin-associated immune responses.[4] Additional bacteria that have shown efficacy in reducing *S aureus* burden and clinical AD symptoms include *Lactobacillus johnsonii* NCC 533 and *Roseomonas mucosa*. *S aureus* is known to display a dose-dependent predominance in the skin microbiota of patients with AD.

According to França, for skin aging, probiotic skincare products are being launched faster than research can catch up with them. These products can slow the intrinsic and extrinsic aging processes by mechanisms, including restoring acidic skin pH, alleviating oxidative stress, attenuating photodamage, improving skin barrier function, and enhancing hair quality.

In an in vitro study involving UV–B-exposed human dermal fibroblasts and keratinocytes, pretreatment with plant extracts fermented with *Lactobacillus buchneri* reduced elastase and collagenase activity, increased type I collagen expression, and promoted expression of moisture factor and antioxidant enzymes.[5] In a separate trial, the use of a high topical concentration of *Nitrosomonas eutropha* achieved significant improvement in wrinkle depth severity and hyperpigmentation of the forehead and glabella.[6]

In psoriasis, reductions of bacteria such as *S epidermidis* and *P acnes* in the skin microbiome may lead to higher *S aureus* colonization, causing cutaneous inflammation.[7] Patients with psoriasis also exhibit higher levels of Firmicutes, Proteobacteria, Acidobacteria, Schlegelella, Rhodobacteraceae, Campylobacteraceae, and Moraxellaceae species, as well as lower levels of Actinobacteria. So far, França said data regarding probiotics in psoriasis are limited largely to oral supplementation, but promising outcomes suggest exploration of topical probiotics is warranted.

For wound healing, França says, topical probiotics have demonstrated efficacy in a handful of studies involving human and animal models. However, França cautioned that significant variability among the studies precludes drawing firm conclusions. *Lactobacillus plantarum* (*L plantarum*) in particular has shown positive results for the topical treatment of burn infections and skin ulcers. In 1 skin ulcer trial, researchers found that *L plantarum* reduced bacterial load, neutrophil counts, and apoptotic and necrotic cells while modifying IL-8 production and inducing wound healing.

“Research on topical probiotics in skincare and dermatological therapy is still in the initial stages and is certainly a promising topic to be explored,” said França. ◀

Disclosures

França is an advisory board member for Dr Brandt Skincare and receives book royalties from Springer, Wiley-Blackwell, Nova Science Publishers.

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INDICATIONS AND USAGE

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

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated.

IMPORTANT SAFETY INFORMATION

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

Warnings and Precautions

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

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

IMPORTANT SAFETY INFORMATION (cont.)

- ***Teratogenic effects, inhibition of bone growth & permanent tooth discoloration:*** Use during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth.
- ***Clostridium difficile associated diarrhea (CDAD):*** If CDAD occurs, discontinue AMZEEQ.
- ***Hepatotoxicity & metabolic effects:*** If renal impairment exists or if liver injury suspected, discontinue AMZEEQ.
- ***Central nervous system effects:*** Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.
- ***Intracranial hypertension:*** Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue AMZEEQ immediately if symptoms occur.
- ***Autoimmune syndromes:*** Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue AMZEEQ immediately if symptoms occur.

Quick **TAKES**

- Factors from skin type to ethnicity and disease severity play a role in effective pediatric acne treatment regimens.
- Oral therapies, biologics, and less irritating retinoids expand treatment options.
- Quality of life and personal preferences are essential in treatment plans for pediatric patients with acne.

Customization Drives Pediatric Treatment Plans

Factors from age to lifestyle impact therapy choices.

JONATHAN LAI, MS2 | *Correspondent*

Acne regimens for pediatric patients should consider skin type, ethnic background, acne severity, lifestyle, and personal preferences as essential components in a treatment plan, according to Manasi Kadam Ladrigan, MD, pediatric dermatologist at Comprehensive Dermatology of Rochester PLLC, Pittsfield, New York. In the course of skin lesions, along with need and safety, agents used for treatment should also be tailored to age in neonatal, infantile, early childhood, preadolescent and adolescent acne.

Ladrigan outlined new approaches for treating pediatric acne as part of her presentation, "What's New in Pediatric Dermatology" at the 2020 Virtual American Academy of Pediatrics National Conference & Exhibition held in October 2020.

THERAPY CUSTOMIZATION

Ladrigan recommended gels and lotions for oily skin and creams for drier skin. Regular retinoids should be avoided for these patients with skin sensitivities, however, special new retinoids that are less irritating may be indicated.

In addition to gold standards such as topical retinoids, benzoyl peroxide, and oral antibiotics, Ladrigan noted the efficacy of hormonal therapies such as oral contraceptives, especially for acne on the temples, jawline, or neck. Recently approved treatments for acne include clascoterone (Winlevi; Cassiopea), a topical androgen receptor inhibitor; trifarotene (Aklief; Galderma), a new topical retinoid; sarecycline, (Seysara; Almirall), a narrow-spectrum tetracycline; and topical minocycline foam (Amzeeq; Foamix Pharmaceuticals).

Ladrigan added that oral retinoids often show efficacy in patients with inflammatory conditions with scarring acne that does not respond to oral antibiotics and topical agents within 6 to 8 weeks.

6-8 weeks

Time frame in which scarring acne generally responds to oral antibiotics and topical agents.

PEDIATRIC DERMATOLOGY UPDATE

Ladrigan also provided updates on other skin diseases impacting the pediatric population, like hidradenitis suppurativa. Often considered an autoinflammatory condition, its etiologies include increased friction on the skin, abnormal microbiomes, and follicular occlusions.

Among the initial treatments, Ladrigan recommended wearing loose-fitting clothing, using oral anticholinergics to reduce sweat, reducing weight in obese patients, and smoking cessation.

Oral tetracyclines, trimethoprim and sulfamethoxazole, and antiandrogenic agents such as spironolactone (Aldactone, Pfizer) can be effective systemic therapies. For patients with persistent and resistant disease, Ladrigan noted extensive clinical support for the use of adalimumab (Humira; AbbVie Inc), an immunomodulator, as a second- or third-line agent.

Ladrigan also discussed hemangiomas, which, she said, "can be devasting for patients" who spend years looking for therapies to try to resolve the scars. Because hemangiomas exhibit rapid growth between 1 and 3 months, she emphasized the need for early treatment with propranolol, preferably by 1 month of age, ceasing at 12 months.

In addition to propranolol, Ladrigan mentioned topical timolol as an alternative treatment for uncomplicated, thin, and small hemangiomas referred early in their course.

Ladrigan concluded the session with a description of other recent advances in pediatric dermatology. JAK inhibitors have recently been shown to improve hair growth in patients with alopecia areata after 6 to 12 months, although FDA approval is still needed for this indication.

Overall, Ladrigan covered a wide variety of pediatric dermatological disorders, discussing both established regimens, recent innovations, and future therapies.◀

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IMPORTANT SAFETY INFORMATION (cont.)

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

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

* Coprimary endpoints at Week 12 were: Absolute change from baseline in inflammatory lesion count and IGA endpoint success. IGA success was defined as an IGA score of 0 or 1 (clear or almost clear), and at least a 2-grade improvement (decrease). IGA = Investigator's Global Assessment. 2418 patients were included if they had 20-50 inflammatory lesions (papules, pustules, nodules) and 25-100 noninflammatory lesions (open, closed comedones) and an IGA score on a 6-point scale of moderate or severe (grade 3 or 4).

† Amzeeq 4% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol, and propellants (butane + isobutane + propane).

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION. PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATION

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

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Flammability:** The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).
- **Teratogenic Effects:** Minocycline, like other tetracycline-class drugs, may inhibit bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.
- **Tooth Discoloration:** The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline drugs. Use of tetracycline drugs is not recommended during tooth development. The safety and effectiveness of AMZEEQ have not been established in pediatric patients less than 9 years of age.
- **Inhibition of Bone Growth:** All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. The safety and effectiveness of AMZEEQ have not been established in patients less than 9 years of age. Results of animal studies indicate that oral tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated orally early in pregnancy.
- ***Clostridium difficile* Associated Diarrhea:** *Clostridium difficile* associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
- **Hepatotoxicity:** Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use in the treatment of acne.
- **Metabolic Effects:** The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.
- **Central Nervous System Effects:** Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
- **Intracranial Hypertension:** Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concomitant use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Because intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.
- **Autoimmune Syndromes:** Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have presented shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including AMZEEQ.
- **Photosensitivity:** Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although AMZEEQ did not induce phototoxicity or photoallergic responses in human dermal safety studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using minocycline. If patients need to be outdoors while using AMZEEQ, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with AMZEEQ at the first evidence of sunburn.
- **Serious Skin/Hypersensitivity Reaction:** Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with oral minocycline use in patients with acne. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue AMZEEQ immediately.
- **Tissue Hyperpigmentation:** Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.
- **Development of Drug-Resistant Bacteria:** AMZEEQ has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using AMZEEQ, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of AMZEEQ, it should be used only as indicated.
- **Superinfection/Potential for Microbial Overgrowth:** Use of AMZEEQ may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

ADVERSE REACTIONS

- **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In 3 randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied AMZEEQ or vehicle once daily for 12 weeks. A total of 1,356 subjects were treated with AMZEEQ and 1,058 with vehicle. The majority of subjects were White (74%) and female (60%). Approximately 34% were Hispanic/Latino and 49% were younger than 18 years of age.
- The most common adverse reaction reported by ≥1% of subjects treated with AMZEEQ and more frequently than in subjects treated with vehicle was

Quick **TAKES**

- Recently approved treatment focuses on decreasing activity within the sebaceous gland.
- New topical retinoid treatments aim to be effective with less skin irritation.
- More research is needed for the link between dairy intake and acne.

Sebaceous Gland Is Target for Acne Treatments

LISETTE HILTON | *Staff Correspondent*

Dermatologists are starting 2021 with an array of new acne treatments focused on a particular area that may change the way they treat patients: the sebaceous gland.

"Looking forward, the focus in 2021 will be more on the activity of the sebaceous gland, itself," said Joshua Zeichner, MD, director of Cosmetic & Clinical Research in Dermatology at Mount Sinai Hospital in New York City, New York.

The FDA recently approved clascoterone cream 1% (Winlevi; Cassiopea), which inhibits sebaceous gland activity and decreases sebum production. Clascoterone is the first topical to specifically address oil production in acne.[1] According to Zeichner, topical acne medications up until now have addressed the other key pathogenic factors for acne, including acne-causing bacteria, hyperkeratinization, and inflammation.

"The only medication we have that addresses all 4 of the main acne pathogenic factors is oral isotretinoin, commonly referred to as Accutane," said Zeichner. "This new topical is a great addition to the armamentarium of drugs that we have for our patients by working to decrease sebum production. In clinical trials, the drug was very well tolerated, and this is a topical medication that can be used for a wide variety of patients with acne."

According to Emmy Graber, MD, MBA, president and founder of The Dermatology Institute of Boston and affiliate clinical instructor of Dermatology at Northeastern University, both in Massachusetts, there has been a shift away from the broad-spectrum antibiotics and more focus on using narrow-spectrum antibiotics, such as hormonal agents, like spironolactone or oral contraceptives for female acne. These may also be prescribed for patients with a lower threshold for oral isotretinoin.

"We have taken a more critical look at some of the broad-spectrum antibiotics that we typically use, like tetracycline, doxycycline, minocycline, and have started to call into question if these are the type of antibiotics that we should be using," said Graber. "In the past 3 to 5 years, we have really taken a close look at how we might be affecting not only patients' acne but also their gastrointestinal tract and gut health when using broad-spectrum antibiotics."

Graber says that sarecycline (Seysara, Almirall), a novel tetracycline derivative, shows more specificity for microorganisms on the skin and fewer microorganisms in the gut.

"It is specifically approved only for acne treatment and not for treating infections. The drug is extremely well tolerated and does not exert the same type of photosensitivity, vestibular, or GI adverse effects that some of the other tetracycline antibiotics have," Graber added.

Some of the new topical alternatives help prevent adverse effects known to occur with similar oral agents. According to Graber, clascoterone is one example.

"Topical clascoterone acts similarly to oral spironolactone but in a topical version…there is almost no systemic absorption, and clascoterone bypasses some of the traditional adverse effects of oral spironolactone," she said.

It has been more than a year since the FDA approved topical minocycline foam 4% (Amzeeq; Vyne Therapeutics).[2] The topical formulation results in little systemic absorption. With regard to topical minocycline, Zeichner said there is a big positive to its use.

"We are able to deliver a high concentration of the active ingredient directly to the site of pathology without unnecessarily exposing the rest of the body to the drug," he said.

New options in topical retinoids are also making headlines in acne treatment. According to Zeichner, tazarotene lotion, 0.045% (Arazlo; Ortho Dermatologics), uses a novel formulation to deliver the drug to the skin. This retinoid has long been used in acne, and while effective, its use is limited by potential skin sensitivity.

"Arazlo delivers tazarotene to the skin in a specialized formula that helps reduce potential irritation," he said. "The vehicle itself uses a honeycomb mesh technology that allows for even distribution of the micronized tazarotene throughout the entire formula to enhance skin penetration and minimize potential skin irritation."

Trifarotene cream 0.005% (Aklief; Galderma), approved for acne in 2020, is a novel topical retinoid that specifically binds to RARγ, the most common retinoid receptor in the skin.[3] Because of its specificity for the RARγ, trifarotene is thought to exert less potential irritation to the skin, according to Zeichner.

"This topical is unique in that it is approved not only for facial acne, but also truncal acne," he said. "There are data from the phase 3 clinical trials showing efficacy for treating acne on the chest and back."

DIET AND ACNE

According to Zeichner, mounting data suggest what individuals eat does impact their skin. Foods with a high glycemic index are associated with acne breakouts, likely because the high sugar load promotes inflammation and oil production in the skin.

The literature suggests cow's milk, particularly skim milk, is associated with acne breakouts.[4] Whey protein and vitamin B12 supplements also appear to be culprits for some individuals with acne.[5]

Graber said the jury is still out on diet and acne.

"It is difficult to ascertain which patients may be affected by dairy," she said. ◀

more **ONLINE**

Scan for disclosures and references.

headache, which was reported in 3% of subjects treated with AMZEEQ and 2% of subjects treated with vehicle. Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, dryness, hyperpigmentation, skin peeling and itching. The active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with AMZEEQ were as follows (mild, moderate, severe): erythema (14.2%, 1.5%, 0%), dryness (6.8%, 0.6%, 0%), hyperpigmentation (12.4%, 2.8%, 0.1%), skin peeling (3.2%, 0.2%, 0%), and itching (5.1%, 0.8%, 0.1%). Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with acne. Local tolerability signs and symptoms occurred in similar frequency and severity as subjects treated with the vehicle component of AMZEEQ. In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment), frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Risk Summary: Available data with AMZEEQ use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of AMZEEQ in humans is low following once daily topical administration of AMZEEQ for 21 days . Because of low systemic exposure, it is not expected that maternal use of AMZEEQ will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with AMZEEQ. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during the period of organogenesis induced skeletal malformations in fetuses at systemic exposures of 750 and 500 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of AMZEEQ (*see Data*). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
- Data: *Animal Data:* Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (750 and 500 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (250 times the systemic exposure at the MRHD based on AUC comparison).
- Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (650 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).
- **Lactation:** Risk Summary: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with AMZEEQ.
- **Pediatric Use:** The safety and effectiveness of AMZEEQ have been established in pediatric patients 9 years of age and older for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. Use of AMZEEQ for this indication is supported by three adequate and well controlled 12-week trials in patients 9 years of age and older; two of the trials included a 40-week open-label extension. Additional data was obtained from a 7-day open-label safety and pharmacokinetics study conducted in 20 patients 10 years to less than 17 years of age with acne vulgaris. A total of 686 subjects 9 years of age and older received AMZEEQ in these clinical trials. Safety and effectiveness for this indication have not been established in pediatric patients less than 9 years of age. The use of oral tetracycline drugs during tooth development below the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and inhibition of bone growth.
- **Geriatric Use:** Clinical studies of AMZEEQ did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

NONCLINICAL TOXICOLOGY

- **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride was associated in both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females. Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.
- Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (10,000 times the systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (3,800 or 10,000 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis. Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

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Quick **TAKES**

- Rosacea studies on LL-37 may help explain metainflammation in COVID-19.
- Sun exposure is the number 1 trigger of rosacea.
- Cardiovascular, neurological and gastrointestinal comorbidity risks continue to grow.

New Research Addresses Rosacea Challenges

Update tracks trending factors changing the treatment landscape.

GABRIELLE IENTILE | *Assistant Editor,* Drug Topics®

Recent research on the importance of phenotype classification, comorbidities, triggers, and mechanism of action—including possible implications for metainflammation in coronavirus disease 2019 (COVID-19)—can expand the understanding of rosacea and suggests new directions for diagnosis and prognosis of this widespread skin disease.

Richard Gallo, MD, PhD, chair of the department of dermatology at the University of California San Diego (UCSD), provided an overview of current trends advancing rosacea therapy in his presentation at Maui Derm Live. The in-person dermatology continuing medical education (CME) conference in Hawaii was held concurrently with Maui Derm Connect, a virtual CME conference, from January 25 to January 29, 2021.[1]

His remarks were featured in the session, "Update 2021: Acne and Rosacea", which highlighted new drugs, research, and expert insights into the management of rosacea and acne. Guy Webster, MD, PhD, clinical professor of Dermatology at Thomas Jefferson University, Philadelphia, Pennsylvania, moderated the panel which included speakers Lawrence Eichenfield, MD, vice chair of Dermatology and chief of Pediatric and Adolescent Dermatology at UCSD, and James Leyden, MD, emeritus professor CE of Dermatology at University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Gallo outlined 4 key areas driving change in addressing the challenges of rosacea.

PHENOTYPES MATTER

"Rosacea is now understood by phenotypes," Gallo said. These phenotypes are (1) diagnostic: fixed centrofacial erythema in a characteristic pattern that may intensify periodically or phymatous changes; (2) major: flushing, papules and pustules, telangiectasia, and ocular manifestations; and (3) secondary: burning sensation; stinging sensation; edema; dryness and ocular manifestations.[2]

> "Perhaps what we learned about LL-37 can explain metainflammation in COVID-19."
>
> 
>
> Richard Gallo, MD, PhD, chair of the department of dermatology at the University of California San Diego

Gallo stressed the importance of using the phenotype-based classification system for rosacea rather than the subset-based method. Gallo noted limitations in describing a patient's rosacea through subsets. Often, patients experience many subtypes simultaneously. Categorizing by phenotype allows health care professionals to track patient progress.

COMORBIDITY RISK EXPANDS

"Studies from 2020 confirmed a growing number of rosacea comorbidities including those related to cardiovascular, neurologic, and gastrointestinal risks," said Gallo. Two meta-analyses found that patients with rosacea have a higher risk of hypertension, CRP, high LDL, epicardial fat, and insulin resistance, Gallo pointed out. According to 8 recent studies that evaluated a total of 200,000 patients, individuals who have rosacea also have an increased risk of migraine, Parkinson disease, and depression. Several studies pointed to higher risks of inflammatory bowel disease.

That is not all. "Innate immune dysfunction drives rosacea's comorbidities," said Gallo.

SUN EXPOSURE TOPS TRIGGER LIST

Ultraviolet (UV) light releases potential trigger molecules such a nucleic acids and other damage-associated molecular patterns. Although these endogenous danger molecules released from damaged or dying cells activate the innate immune system by interacting with pattern recognition receptors, they may also promote pathological inflammatory responses.

The cathelicidin peptide LL-37 is another

ROSACEA CHALLENGES CONTINUES ON PAGE 32 ▶

New E-BPO Improves Rosacea

Formulation could be first FDA-approved single-agent E-BPO prescription drug to treat rosacea.

ILYA PETROU, MD | *Staff Correspondent*

In a recent extension study of 2 phase 3 clinical trials, a novel 5% encapsulated benzoyl peroxide (E-BPO) cream (Epsolay, Sol-Gel Technologies Ltd) demonstrated significant superiority over vehicle in achieving clear or almost clear skin and reducing the number of lesions in patients with papulopustular rosacea. Data also showed improvement in facial erythema and telangiectasia.[1]

According to study authors, the primary objective of the extension study was safety evaluation. Findings showed the cream was well tolerated with adverse events (AEs) and cutaneous safety and tolerability comparable to the vehicle group.[1] Results supported other research that found microencapsulation not only extends drug delivery time but improves efficacy and potently reduces the potential for skin irritation.[2]

"Epsolay uses a patented microencapsulation technology that effectively reduces the risk of skin irritation by encapsulating the BPO inside porous silica microcapsules," said Neal Bhatia, MD, director of clinical dermatology, Therapeutics Clinical Research, San Diego, California, and lead author of the study. "The capsules form a barrier between the skin and the BPO crystals or other ingredients, allowing for the active drug to be released in a timely fashion, resulting in less skin irritation and a much higher tolerability and amenability of the medication in patients."

The study results addressed a key challenge; the idea that BPO causes more skin issues. "The phase 3 trials were actually surprising in their outcome because the historical opinion was that BPO was too irritating for rosacea skin, which in the nonencapsulated form is true," said Wm. Philip Werschler, MD,FAAD, FAACS, assistant clinical professor of medicine/dermatology, University of Washington School of Medicine in Seattle, founding member of Spokane Dermatology Clinic, in Spokane, Washington, and coauthor of the study. "The Sol-Gel technology found in Epsolay was very well tolerated and very effective."

Bhatia and Werschler presented a poster on the study findings at Maui Derm Live. The in-person dermatology continuing medical education (CME) conference in Hawaii was held concurrently with Maui Derm Connect, a virtual CME conference, from January 25 to January 29, 2021.[1]

Quick TAKES

- A novel microencapsulated benzoyl peroxide (E-BPO) cream proves superior to vehicle in achieving clear or almost clear skin.
- This encapsulation reduces the potential for skin irritation that has been a challenge for BPO in rosacea treatment.
- The cream is also reported to aid rapid skin clearance.

DATA REVEAL FASTER OUTCOMES

Patients were followed for up to 40 additional weeks in the extension and for up to a total of 52 weeks, including the 12 weeks in the phase 3 trial.[1]

At each follow-up visit in the extension study occurring at baseline and at 4-week intervals out to week 40, patients were assessed using a 5-point IGA scale of rosacea severity and completed a Rosacea-specific Quality of Life index (RosaQoL) questionnaire. Outcome measures included an Investigator's Global Assessment (IGA) status of "clear or almost clear", number and timing of retreatments, and tolerability at 40 weeks. IGA success was defined as achievement of clear or almost clear at the 40-week follow-up visit.

These phase 3 trials (SGT 54-01 and SGT 54-02) evaluated the efficacy, safety, and tolerability of Epsolay in a total of 547 patients, 363 previously treated with Epsolay cream and 184 patients previously treated with vehicle. The study included male and female patients aged at least 18 years with moderate to severe rosacea with a baseline IGA score of 3 (moderate severity) or 4 (severe) on a severity scale of 0-4, between at least 15 and 70 total inflammatory lesions with 2 or fewer nodules present.[1]

Results showed a progressive improvement of rosacea symptoms over the total 52-week study period. At the 40-week follow-up, 67.2% of patients (66.5% in the vehicle group; 67% in the E-BPO group) achieved IGA success. In the extension study, there was an average of 1.4 retreatments with an average of 58 treatment-free days. The investigators also noted that facial erythema generally improved during the study. In addition, results from the RosaQoL questionnaire showed improvements from baseline to week 40 in the total score, symptom subscale score, functional subscale score, and emotional subscale score.[1]

For each of the cutaneous safety and tolerability parameters, data showed small increases in the percentages of patients with no or mild signs and symptoms over 52 weeks. At least 1 treatment-related AE was reported by 185

BENZOYL PEROXIDE CONTINUES ON PAGE 32 ▶

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The production of this *Dermatology Times*® educational video was supported by Galderma Laboratories, L.P.
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Rosacea is a common, chronic, inflammatory skin disease that can substantially impact patient's physical, mental, and emotional wellbeing.[1,2] Despite the availability of treatment options, more than 80% of patients feel that their rosacea is not properly controlled.[3] When selecting among rosacea treatment options, dermatologists have the opportunity to consider factors such as the patient-specific burden of rosacea, setting a treatment goal of clear skin, and limiting the risk of antibiotic resistance.

Join **Hilary E. Baldwin, MD, FAAD,** and **Jeffrey S. Fromowitz, MD, FAAD,** in this educational video to learn more about a patient-focused approach to the treatment of papulopustular rosacea with ORACEA® (doxycycline, USP) 40 mg* Capsules, the only FDA-approved oral formulation for inflammatory lesions of rosacea. ORACEA Capsules are precisely formulated to provide an immediate and consistent anti-inflammatory response without crossing the antibiotic threshold.[4,5]

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Clinical Associate Professor
Rutgers Robert Wood Johnson
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In this program, Dr Hilary E. Baldwin and Dr Jeffrey S. Fromowitz will:

- **Appreciate** the unmet needs and opportunities to address the physical, emotional, and psychological burden of rosacea
- **Review** treatment goals and clinical rationale for the management of rosacea, including increased awareness of selection considerations regarding antimicrobial dosages
- **Explore** the unique formulation and clinical results of ORACEA Capsules
- **Discover** ORACEA Capsules' safety, efficacy, tolerability, and considerations for selection in the management of papulopustular rosacea
- **Highlight** a patient-focused approach to care, including best practices in how to communicate effectively with patients about concerns, understanding the nature of the condition and emotional burden of disease

Important Safety Information

Indication: ORACEA® (doxycycline, USP) 40 mg* Capsules are indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. ORACEA Capsules do not lessen the facial redness caused by rosacea. **Adverse Events:** In controlled clinical studies, the most commonly reported adverse events (>2%) in patients treated with ORACEA Capsules were nasopharyngitis, sinusitis, diarrhea, hypertension and aspartate aminotransferase increase. **Warnings/Precautions:** ORACEA Capsules should not be used to treat or prevent infections. ORACEA Capsules should not be taken by patients who have a known hypersensitivity to doxycycline or other tetracyclines. ORACEA Capsules should not be taken during pregnancy, by nursing mothers, or during tooth development (up to the age of 8 years). Although photosensitivity was not observed in clinical trials, ORACEA Capsules patients should minimize or avoid exposure to natural or artificial sunlight. The efficacy of ORACEA Capsules treatment beyond 16 weeks and safety beyond 9 months have not been established.

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

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Please see brief summary of ORACEA Capsules on the following page.

USMP/ORA/0037/0820b

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This summary contains important information about ORACEA (Or-RAY-sha) Capsules. It is not meant to take the place of your doctor's instructions. Read this information carefully before you start taking ORACEA Capsules. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about ORACEA Capsules. For full Prescribing Information and Patient Information please see the package insert.

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ORACEA Capsules are a tetracycline class medicine. ORACEA Capsules are a prescription medicine to treat only the pimples or bumps (papules and pustules) caused by a condition called rosacea. ORACEA Capsules do not lessen redness caused by rosacea. ORACEA Capsules should not be used for the treatment or prevention of infections. It is not known if ORACEA Capsules are effective for use for longer than 16 weeks, safe for use longer than 9 months, or safe and effective in children. ORACEA Capsules should not be used in infants and children less than 8 years of age because it may cause stained teeth in infants and children.

WHO SHOULD NOT TAKE ORACEA CAPSULES?
Do not take ORACEA Capsules if you are allergic to doxycycline or other medicines in the tetracycline class. Ask your doctor or pharmacist for a list of these medicines if you are not sure.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING ORACEA CAPSULES?
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- have liver problems.
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- have vision problems.
- have had surgery on your stomach (gastric surgery).
- have or had a yeast or fungal infection in your mouth or vagina.
- have any other medical condition.
- are pregnant or planning to become pregnant. ORACEA Capsules may harm your unborn baby. Taking ORACEA Capsules while you are pregnant may cause serious side effects on the growth of bone and teeth of your baby. Stop taking ORACEA Capsules and call your doctor right away if you become pregnant while taking ORACEA Capsules.
- are breastfeeding or plan to breastfeed. ORACEA Capsules can pass into your breast milk and may harm your baby. Talk to your doctor about the best way to feed your baby if you take ORACEA Capsules. You and your doctor should decide if you will take ORACEA Capsules or breastfeed. You should not do both.

You should not take ORACEA Capsules if you are male with a female sexual partner who plans to become pregnant at any time while you are being treated with ORACEA Capsules.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ORACEA Capsules and other medicines can affect each other causing serious side effects.

Especially tell your doctor if you take:
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- products containing iron or bismuth subsalicylate.
- a medicine taken by mouth that contains isotretinoin or acitretin.
- a medicine to treat seizures, such as carbamazepine or phenytoin.

Ask your doctor or pharmacist for a full list of your medicines, if you are not sure. Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ORACEA CAPSULES?
ORACEA Capsules may cause serious side effects, including:
- **Harm to an unborn baby**. **See "What should I tell my doctor before taking ORACEA Capsules?"**
- **Permanent teeth discoloration.** ORACEA Capsules may permanently turn a baby or child's teeth yellow-grey-brown during tooth development. ORACEA Capsules should not be used during tooth development. Tooth development happens in the last half of pregnancy, and from birth to 8 years of age. See "What should I tell my doctor before taking ORACEA Capsules?"
- **Intestine infection (pseudomembranous colitis).** Pseudomembranous colitis can happen with most antibiotics, including ORACEA Capsules. Call your doctor right away if you get diarrhea or bloody stools.
- **Immune system reactions including a lupus-like syndrome, hepatitis, and inflammation of blood or lymph vessels (vasculitis).** Stop taking ORACEA Capsules and tell your doctor right away if you get joint pain, fever, rash or body weakness.
- **Discoloration (hyperpigmentation).** ORACEA Capsules can cause darkening of your skin, scars, teeth, gums, nails, and whites of your eyes.
- **Benign intracranial hypertension, also called pseudotumor cerebri.** This is a condition where there is high pressure in the fluid around the brain. The swelling may lead to vision changes and permanent vision loss. Stop taking ORACEA Capsules and tell your doctor right away if you have blurred vision, vision loss, or unusual headaches.

The most common side effects of ORACEA Capsules include: soreness in the nose and throat, diarrhea, sinus infection, stomach (abdominal) bloating or pain, fungus infection, high blood pressure (hypertension), flu-like symptoms, and change in certain blood tests.

Tell your doctor if you have any side effect that bothers you or does not go away. These are not all the possible side effects of ORACEA Capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to GALDERMA LABORATORIES, L.P. at 1-866-735-4137.

HOW SHOULD I TAKE ORACEA CAPSULES?
- Take ORACEA Capsules exactly as prescribed by your doctor. Taking more than your prescribed dose may increase your chance of side effects, including the chance that bacteria will become resistant to ORACEA Capsules.
- Take ORACEA Capsules 1 time a day in the morning on an empty stomach.
- You should take ORACEA Capsules at least one hour before or two hours after a meal.
- Take ORACEA Capsules with enough fluid to completely swallow the capsule and to lower your risk of getting irritation or ulcer in your esophagus. Your esophagus is the tube that connects your mouth to your stomach.
- If you took too much ORACEA Capsules, call your doctor right away.
- Your doctor may do blood tests during treatment with ORACEA Capsules to check for side effects.

WHAT SHOULD I AVOID WHILE TAKING ORACEA CAPSULES?
- Avoid sunlight or artificial sunlight, such as a tanning booth or sunlamp. You could get severe sunburn. Use sunscreen and wear clothes that cover your skin while out in sunlight.

HOW SHOULD I STORE ORACEA CAPSULES?
- Store ORACEA Capsules at room temperature between 59ºF to 86ºF (15ºC to 30ºC).
- Keep ORACEA Capsules in a tightly closed container.
- Keep ORACEA Capsules inside container and out of light.

Keep ORACEA Capsules and all medicine out of the reach of children.

GENERAL INFORMATION ABOUT ORACEA CAPSULES
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take ORACEA Capsules for a condition for which it was not prescribed. Do not give ORACEA Capsules to other people, even if they have the same symptoms you have. It may harm them.

This Brief Summary summarizes the most important information about ORACEA Capsules. If you would like more information, talk with your doctor. You can also ask your doctor or pharmacist for information that is written for health professionals.

WHAT ARE THE INGREDIENTS IN ORACEA CAPSULES?

Active ingredient: doxycycline. Inactive ingredients: hypromellose, iron oxide red, iron oxide yellow, methacrylic acid copolymer, polyethylene glycol, Polysorbate 80, sugar spheres, talc, titanium dioxide, and triethyl citrate.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT ORACEA CAPSULES?
- Talk to your doctor or pharmacist
- Go to **www.oracea.com** or call **1-866-735-4137**

GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA
Revised: August 2013

GALDERMA
Once-daily 40 mg* Capsules
Oracea®
(doxycycline, USP) *30 mg immediate release & 10 mg delayed release beads

> **“Epsolay uses a patented microencapsulation technology that effectively reduces the risk of skin irritation by encapsulating the BPO inside porous silica microcapsules.”**

Neal Bhatia, MD, director of clinical dermatology, Therapeutics Clinical Research, *San Diego, California*

Benzoyl Peroxide FROM PAGE 29

patients (34.6%), which were mild to moderate in severity and were not considered to be related to the study treatment. Ten patients experienced serious AEs, none of which were considered to be related to the study treatment.

“I think for those patients who have not had a good chance of recovery and good maintenance, Epsolay cream could do well for them because the activity of BPO in the study led to a quicker clearance in patients who applied the product,” Bhatia said.

BY THE NUMBERS

N=547

NUMBER OF PATIENTS ENROLLED IN EXTENSION STUDY

THE FUTURE OF EPSOLAY

The FDA is currently evaluating Epsolay, but according to a press release, if approval is passed this spring, Sol-Gel Technologies Ltd projects that the novel formulation has the potential to be the first single-agent BPO prescription drug product.[3]

“This innovative formulation is coming out at a great time because many patients with rosacea have gotten frustrated with their existing therapies that often do not adequately address their symptoms,” Bhatia said. “I think Epsolay cream might be better for patients, particularly because it’s also cream based which might be more amenable to patients.” ◀

Disclosures

Bhatia and **Werschler** report no relevant or financial disclosures.

References

1 Bhatia N, Werschler W, Baldwin H, et al. Long-term efficacy and safety of benzoyl peroxide cream, 5%, prepared with microencapsulation in papulopustular rosacea: results from an extension of two phase 3, vehicle-controlled trials. Poster presented at: Maui Derm Live In-Person Dermatology CME Conference and Maui Derm Connect Virtual Dermatology CME Conference; January 25-29, 2021; Maui, Hawaii; Virtual.

▼ *more* **ONLINE**

Scan for full reference list.

Rosacea Challenges FROM PAGE 28

factor. “LL-37 facilitates DNA recognition but does that explain UV sensitivity in patients with rosacea?” asked Gallo. In a study published last year, Gallo and his fellow authors saw results showing that LL-37 amplifies the response to UV products and predicts vascular cell adhesion molecule response in rosacea.[3]

MECHANISM OF ACTION

According to Gallo, research on rosacea’s mechanism of action could hold promise for better understanding COVID-19. Mutation scanning identified a possible structure necessary for inflammatory activity relating to LL-37. Results from more than a half-dozen studies from 2016 through 2020 enabled a machine learning classifier (a support vector machine) “to recognize structures in LL-37 responsible for promoting inflammation,” he added.

Lessons learned from that research may help in the fight against coronavirus because preliminary results suggest some SARS-CoV-2 peptides mimic the structure of LL-37, Gallo noted. “A functional screen confirmed that SARS-CoV-2 peptides amplify IL-6 in a manner similar to LL-37,” he said. “Perhaps what we learned about LL-37 can explain metainflammation in COVID-19.” ◀

Disclosure

Gallo is a co-founder and holds equity interest in MatriSys Bioscience and is a consultant for Sente Inc.

References

1 Webster G. Eichenfield E, Layton J, et al. Update 2021: acne and rosacea. Presented at: Maui Derm For Dermatologists 2021; January 25-29, 2021; Maui, Hawaii.

2 Gallo R, Granstein R, Kang et al. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol.* 2018;1(78):148-155. doi:10.1016/j.jaad.2017.08.037

3 Kulkarni NN, Takahashi T, Sanford JA, et al. Innate immune dysfunction in rosacea promotes photosensitivity and vascular adhesion molecule expression. *J Invest Dermatol.* 2020;40(3):645-655.e6. doi:10.1016/j.jid.2019.08.436

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we are committed to the relentless pursuit of science that can improve the lives of patients and make a difference in healthcare.

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 MAT-INC-01018 11/20

Quick TAKES

- Systemic therapy has a critical role in managing atopic dermatitis and has entered a new era with the approval of dupilumab.
- Selection of a particular agent considers disease and patient characteristics but does not depend on AD phenotype.
- Forthcoming systemic therapies are expected to include a new biologic and 3 oral JAK inhibitors, which may prove to be "game changers" for managing moderate to severe AD.

Systemic Therapy Advances for Atopic Dermatitis

New treatments offer more options with favorable safety and efficacy.

CHERYL GUTTMAN KRADER , BS PHARM | *Staff Correspondent*

Adequate control of atopic dermatitis (AD) gives patients and their families a new life. A discussion of systemic therapies is definitely warranted for anyone whose disease is not well controlled using topical therapies, said Eric L. Simpson, MD, MCR, professor of dermatology, Oregon Health & Science University, Portland, Oregon, during Maui Derm Live. Maui Live was an in-person dermatology continuing medical education (CME) conference in Hawaii held concurrently with Maui Derm Connect, a virtual CME conference, from January 25 to January 29, 2021.

Simpson discussed his decision-making process for choosing and using systemic treatments for AD and provided an update on dupilumab (Dupixent, Sanofi Genzyme/Regeneron Pharmaceuticals) and forthcoming systemic agents.

"Because of dupilumab's remarkable efficacy and favorable safety, its approval for the treatment of moderate to severe AD introduced an exciting era for patients needing systemic therapy, and new options are coming, including oral JAK inhibitors that may be just as effective albeit associated with very rare severe adverse events," he said.

According to Simpson, communication is key when it comes to AD therapy.

"Clinicians should be developing their skills for shared decision-making because patients of all ages whose AD is not adequately controlled by topical therapy deserve a discussion of the pros and cons of systemic therapies," he said.

DETAILS FOR DEFINING CANDIDACY

Simpson said the answer to the question of when to use systemic therapy can be distilled down to 1 concept—if aggressive topical therapy is infeasible or has failed to achieve adequate control of the disease.

"A role for systemic therapy is not determined by an AD or itch severity score," Simpson said. "Rather, it is something to consider and offer patients if moderate- to high-potency topical corticosteroids were used in a safe manner along with topical calcineurin inhibitors or crisaborole and the AD was still not controlled. Also, systemic therapy may be considered as the initial choice for patients whose disease is so severe or so extensive that it requires more than topical therapy."

Qualifying his remarks, Simpson pointed out the need to first take a careful patient history to identify any modifiable factors that explain the insufficient response to topical therapy. Additional issues to explore include if patients lack an understanding of the chronic nature of their disease and the need for maintenance therapy, if they are following instructions on adjunctive measures such as bathing and moisturization, and if they are using their topical agents properly.

Similarly, once systemic therapy is started, clinicians should carefully review the idea that a particular treatment is not effective or intolerable before it is abandoned, according to Simpson.

"Currently, we do not have many options for systemic treatment, so we don't want to waste what we have without first making sure that perhaps a longer trial or dose adjustment could improve the therapeutic response or mitigate an adverse event," he explained.

WHAT'S NEW: REPORT FROM MAUI DERM LIVE AND MAUI DERM CONNECT

Simpson also suggested accessing a downloadable, brief patient-reported outcome tool to quickly learn how AD is impacting an individual as this information can help with the decision to start aggressive therapy (adcontroltool.com).[1] Then, the consultation conversation should identify the patient's outcome goals and provide information about the risks and benefits of the available options to support shared decision-making.

SYSTEMIC CHOICES

According to Simpson, there is no need to consider any particular biomarker or AD phenotype when deciding among systemic agents.

"Because the Th2 cytokine axis is involved in the pathogenesis of AD regardless of phenotype, Th2 blockade is likely to help almost all patients with AD," Simpson said. Results from an Italian study, which included 221 patients representing 6 phenotypes of AD, found significant improvements from baseline to week 16 in all outcomes measured and persistent benefit to week 52.[2]

THERAPY ADVANCES CONTINUES ON PAGE 39 ▶

#1 PRESCRIBED BIOLOGIC IN NEW AND SWITCHING PLAQUE PSORIASIS PATIENTS

As of 7/2020. New patients defined as bio-naïve; switch patients defined as bio-experienced switching biologics. Source: Integrated Symphony Health (PatientSource) and IQVIA (NSP) through proprietary method on diagnosis classification.[1]

Skyrizi®
risankizumab-rzaa
75mg/0.83mL Injection

An IL-23 inhibitor for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy[2]

NOTHING IS EVERYTHING

Nothing less than the opportunity for durable skin clearance.[2]

For your patients, that's **everything.**

DURABLE
Most patients achieved PASI 90 at Week 16 and maintained it at Week 52[2,3]

RAPID
Co-primary endpoints of PASI 90 and sPGA 0/1 at Week 16,[1,2] including response 4 weeks after first dose[3,4]

CLEAR
The majority of patients achieved PASI 100 at Week 52[2,3]

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

TURN THE PAGE TO **VIEW THE LONG-TERM DATA**

SAFETY CONSIDERATIONS[2]

SKYRIZI may increase the risk of infection. Instruct patients to report signs or symptoms of clinically important infection during treatment. Should such an infection occur, discontinue SKYRIZI until infection resolves. Evaluate patients for tuberculosis infection prior to initiating treatment with SKYRIZI. Avoid use of live vaccines in SKYRIZI patients.

Please see additional Important Safety Information on the inside spread.

Please see the Brief Summary of the full Prescribing Information on the last page of this ad.

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AN IL-23 INHIBITOR FOR ADULTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS[2]

ACHIEVEMENTS AT WEEK 16 IN ULTIMMA-1 & ULTIMMA-2 (NRI)[3]

CO-PRIMARY ENDPOINTS (*P*<0.0001) | SECONDARY ENDPOINT (*P*<0.001)

	PASI 90 at Week 16		sPGA 0/1 at Week 16		PASI 100 at Week 16	
	ULTIMMA-1	ULTIMMA-2	ULTIMMA-1	ULTIMMA-2	ULTIMMA-1	ULTIMMA-2
SKYRIZI	75% (229/304)	75% (220/294)	88% (267/304)	84% (246/294)	36% (109/304)	51% (149/294)
PLACEBO	5% (5/102)	2% (2/98)	8% (8/102)	5% (5/98)	0% (0/102)	2% (2/98)

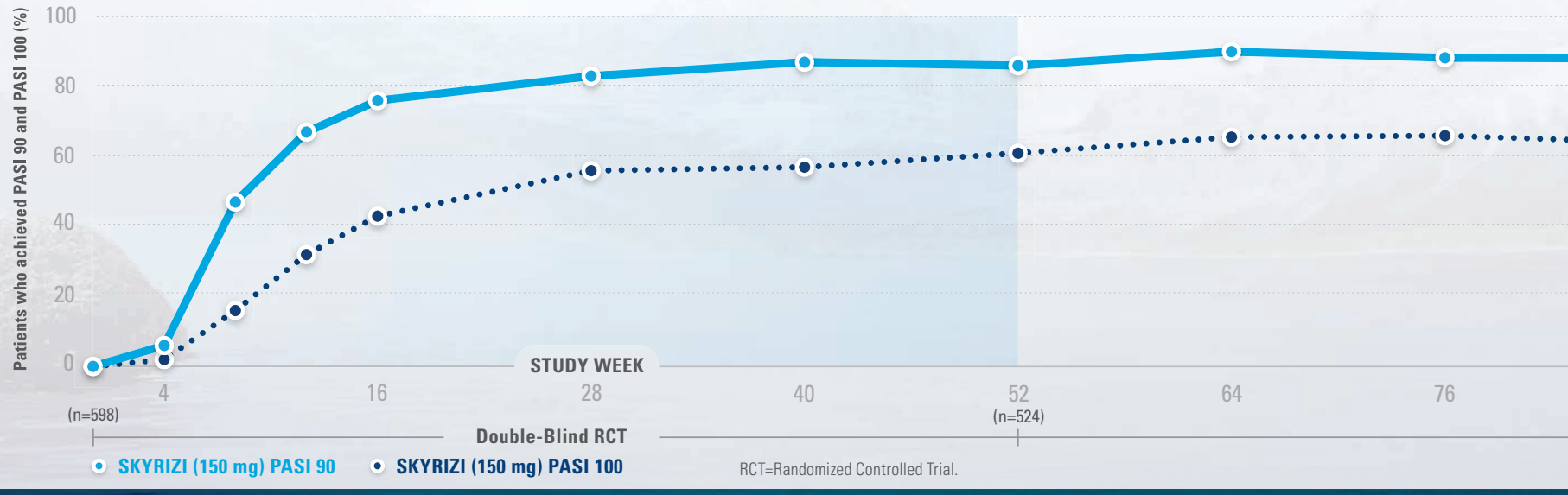
NRI=Non-Responder Imputation.

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 over 16 weeks and biologic active control over 52 weeks in adult patients with moderate to severe plaque psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous injections at Weeks 0, 4, and every 12 weeks thereafter.[3]

CONSISTENT PASI 90/100 RATES AT 2.5 YEARS IN OPEN-LABEL EXTENSION[5,6]

INTEGRATED RESULTS FROM ULTIMMA-1 AND 2—ALL DATA ARE AS OBSERVED

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



RCT=Randomized Controlled Trial.

INDICATION[2]

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

IMPORTANT SAFETY INFORMATION[2]

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, closely monitor and discontinue SKYRIZI until the infection resolves.

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.

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EXPLORE LONG-TERM DATA AT **VIEWTHEDATA.COM**

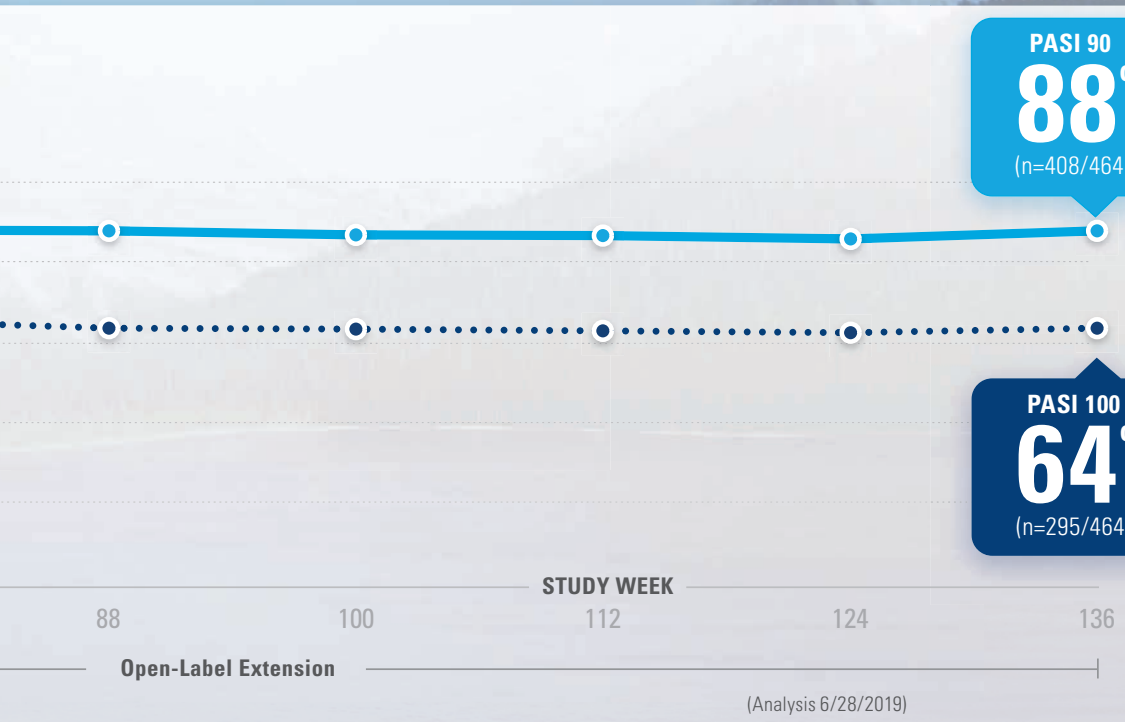
MAINTENANCE OF RESPONSE

AT WEEK 52

In the randomized controlled trials, among patients who achieved PASI 90 and PASI 100 at Week 16, level of response was maintained at Week 52 by 88% (n=398/450) and 80% (n=206/258), respectively.[2]

AT WEEK 136

In an observed analysis, among patients who achieved PASI 90 and PASI 100 at Week 52 and had available data at Week 136 in the open-label extension, level of response was maintained at Week 136 by 94% (n=375/398) and 82% (n=232/282), respectively.[5,6]



KEY VARIABLES (AS MEASURED EVERY 12 WEEKS) OF OLE

sPGA 0/1, sPGA 0, PASI 75, PASI 90, and PASI 100

OLE LIMITATIONS: In an open-label extension, there is potential for enrichment of the long-term data in the remaining patient populations since patients who are unable to tolerate or do not respond to the drug often drop out.

STUDY DESIGN: The data presented here are a sub-analysis of LIMMitless (OLE) and include only patients from ultIMMa-1 and 2 who were originally randomized to SKYRIZI, completed the RCT, and enrolled in the OLE. LIMMitless is an open-label extension for which patients who completed either ultIMMa trial, IMMhance, or IMMvent were eligible to participate.

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: 1. Data on file, AbbVie Inc. In-play patient share. 2020. **2.** SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **3.** Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661. **4.** Lebwohl M, Bachelez H, Valdecantos WC, Wu T, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis: an integrated analysis of UltIMMa-1 and UltIMMa-2. Poster presented at: American Academy of Dermatology Annual Meeting; March 1-5, 2019; Washington, DC. **5.** Data on file, ABVRRTI69209. **6.** Leonardi C, Lebwohl M, Bachelez H, et al. Maintenance of response through 136 weeks of long-term continuous risankizumab treatment: an analysis of patients from UltIMMa-1 and UltIMMa-2. Poster presented at: Virtual Annual Meeting of the American Academy of Dermatology; June 12-14, 2020.

Skyrizi®
risankizumab-rzaa
75mg/0.83mL Injection

SKYRIZI® (sky-RIZZ-ee) (risankizumab-rzaa) injection, for subcutaneous use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infections

SKYRIZI may increase the risk of infections. In clinical studies, infections occurred in 22.1% of the SKYRIZI group compared to 14.7% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections and tinea infections occurred more frequently in the SKYRIZI group than in the placebo group. Subjects with known chronic or acute infections were not enrolled in clinical studies *[see Adverse Reactions]*.

The rate of serious infections for the SKYRIZI group and the placebo group was ≤ 0.4%. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection 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, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the IMMHANCE study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in 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 therapy with SKYRIZI, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with SKYRIZI. No data are available on the response to live or inactive vaccines.

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 drug 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 2234 subjects were treated with SKYRIZI in clinical development studies in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled studies were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

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 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

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared to 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis and herpes zoster. In ULTIMMA-1 and ULTIMMA-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety through Week 52

Through Week 52, no new adverse reactions were identified and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

Immunogenicity

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

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI) had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

DRUG INTERACTIONS

Live Vaccinations

Avoid use of live vaccines in patients treated with SKYRIZI *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Limited available data with SKYRIZI use in pregnant women are insufficient to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Human IgG is known to cross the placental barrier; therefore, SKYRIZI may be transmitted from the mother to the developing fetus.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 and 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. At the 50 mg/kg dose [20 times the maximum recommended human dose (MRHD); 2.5 mg/kg based on administration of a 150 mg dose to a 60 kg individual], increased fetal/infant loss was noted in pregnant monkeys *(see Data)*. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

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

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared to the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg (20 times the MRHD, based on mg/kg comparison) and the NOAEL for developmental toxicity was identified as 5 mg/kg (2 times the MRHD, based on mg/kg comparison). In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Lactation

Risk Summary

There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of SKYRIZI in pediatric patients less than 18 years of age have not yet been established.

Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in risankizumab-rzaa exposure, safety or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

OVERDOSAGE

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with SKYRIZI.

No effects on male fertility parameters were observed in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg risankizumab-rzaa (at 20 times the clinical exposure at the MRHD, based on mg/kg comparison) once weekly for 26 weeks.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) before starting SKYRIZI therapy and to reread the Medication Guide each time the prescription is renewed. Advise patients of the potential benefits and risks of SKYRIZI.

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions]*.

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique.

Instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the 150 mg dose of SKYRIZI.

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

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA

US License Number 1889

Ref: 20063596-R1 Revised March, 2020

LAB-3553 **MASTER**

US-SKZ-210029

abbvie

Therapy advances FROM PAGE 34

"The same holds true in my experience," Simpson said when referring to the study results.

He considers cyclosporine if patients need rapid relief or to get off an "oral steroid roller coaster", if they have failed dupilumab or if the biologic is not covered by insurance, as well as in children aged more than 6 years for whom nothing else is approved when deciding whether or not to use specific systemic therapy. He avoids cyclosporine in older patients on multiple medications and in patients with hypertension or a history of cancer.

"Cyclosporine can be used safely for about 1 year," Simpson said. "I use it at a starting dose of 5 mg/kg with tapering over 4 to 12 months while transitioning with overlap to alternative therapy, usually to phototherapy or methotrexate."

There is another systemic therapy to consider in certain patient populations. According to Simpson, methotrexate is considered for systemic treatment in patients with more moderate AD or for older patients with chronic AD, if dupilumab is not covered, as an add-on to dupilumab, or if he is unsure about the diagnosis. He also uses it in children at a dose of 0.2 to 0.6 mg/kg. Patients with liver disease, women of childbearing potential not using adequate contraception, and anyone who drinks alcohol heavily are not candidates for methotrexate.

Simpson discussed the ease of use of dupilumab compared with the other systemic therapies. According to him, it can be used without laboratory monitoring and is suitable for a long-term approach, including a patient population with viruses.

"I would not use dupilumab during pregnancy, but I see few contraindications for treatment with dupilumab based on medical comorbidities," he said. "It appears safe to use in HIV-positive patients, and I do not hesitate to use in patients with hepatitis B or C who are on antiviral therapy. Underinsurance is a barrier to its use, as is needle phobia, but there are patient assistance programs for dupilumab, and patients can get over their fear of needles."

COVID-19 CONSIDERATIONS

Although there was concern about potential safety issues with the use of biologics and non-targeted immunosuppressive agents at the onset of the coronavirus disease 2019 (COVID-19) pandemic, accumulating experience indicates that these medications do not put patients at risk for a worse outcome and may even have a favorable impact on the disease course.

For example, reports show better outcomes in hospitalized patients receiving cyclosporine compared with patients not on cyclosporine and in kidney transplant patients maintained on a full dose of cyclosporine versus those whose dose was reduced. In vitro evidence that cyclosporine inhibits COVID-19 replication provides a biological basis for these findings.

According to Simpson, regarding dupilumab, dermatology and allergy guidelines state its use should be continued during the pandemic. However, the American Academy of Dermatology recommends stopping biologic treatment if a patient becomes infected with COVID-19. Nevertheless, early evidence from registries show that patients may do better if they are on the biologic, which makes sense because it reduces the cytokine storm.

DUPILUMAB RESEARCH UPDATES

The latest research results on dupilumab shows that it improves the skin barrier and reduces Th1- and Th2-mediated inflammation and *Staphylococcus aureus* colonization. As another advantage, it is effective in treating allergic comorbidities, including asthma and chronic rhinosinusitis with nasal polyposis.

New data from an open-label extension study of adults treated with dupilumab for moderate to severe AD show responses are sustained and increase overall during ongoing use to 3 years. In addition, the long-term benefit occurs without any new safety signals. In fact, rates of new skin infections and conjunctivitis decreased over time.

The same efficacy and safety patterns are seen during 52 weeks of available follow-up in adolescent patients (aged 12-17) treated with dupilumab. Impressive efficacy was also observed in a 16-week study of school-aged children (6-11 years) whose AD characteristics at baseline were consistent with severe disease. Notably, in the latter trial, the incidence of skin infections was lower in dupilumab-treated groups than in the placebo-treated controls, and the rate of conjunctivitis was lower than what was reported in adults and lower in the study group treated with dupilumab every 4 weeks compared with the group treated every 2 weeks.

Simpson recommends checking the information on the drug's website when prescribing dupilumab as the dosage regimen for dupilumab in pediatric patients varies depending on weight.

EXPANDING OPTIONS

New systemic agents for the treatment of AD are anticipated in 2021, including 1 biologic and 3 oral JAK inhibitors. Based on results achieved in completed phase 3 trials, the oral JAK inhibitors hold promise to be "real game changers" for the treatment of moderate to severe AD, Simpson said.

Overall, the 3 JAK inhibitors investigated in AD pivotal trials provided rapid improvement in overall AD and itch severity ratings, albeit with some distinctions among them in their efficacy and safety profiles.

Of the 3, upadacitinib (Rinvoq, AbbVie Inc) seemed to be the most potent, with 62% of patients treated achieving clear or almost clear status per the Investigators Global Assessment (IGA) score. However, acne was common (17%) at higher doses of upadacitinib. The efficacy of abrocitinib was comparable, if not slightly better, than dupilumab, and abrocitinib relieves itch faster. Baricitinib had more modest efficacy but seemed to be the best tolerated of the 3 JAK inhibitors. Compared with abrocitinib, baricitinib was associated with lower rates of headache and nausea.

Simpson has a little apprehension about the 3 therapies.

"My biggest concern with these drugs was a risk of pulmonary embolism that have occurred as rare events with JAK inhibitors," he said.

"Thus far in the AD clinical trials, single cases have been reported with baricitinib and abrocitinib," he added. "Nevertheless, all patients on a JAK inhibitor will need risk mitigation for venous thrombosis along with some monitoring of the complete blood count and for herpes zoster virus and herpes simplex virus."

more **ONLINE**

Scan for full article, disclosures, and references.

> "A role for systemic therapy... is something to consider and offer patients if moderate- to high-potency topical corticosteroids used safely with topical calcineurin inhibitors or crisaborole did not control their AD."
>
> **Eric L. Simpson, MD, MCR, professor of dermatology, Oregon Health and Science University,** *Portland, Oregon*

INDICATION

KLISYRI is a microtubule inhibitor indicated for the topical treatment of actinic keratosis of the face or scalp.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Ophthalmic Adverse Reactions

KLISYRI may cause eye irritation. Avoid transfer of the drug into the eyes and to the periocular area during and after application. Wash hands immediately after application. If accidental exposure occurs, instruct patient to flush eyes with water and seek medical care as soon as possible.

almirall

KLISYRI™
tirbanibulin ointment

KLISYRI® is a microtubule inhibitor indicated for the topical treatment of actinic keratosis (AK) of the face or scalp.

THE ONLY 5-DAY, FDA-APPROVED TOPICAL TREATMENT FOR AK

A NOVEL APPROACH TO TOPICAL AK TREATMENT

POWER WITHOUT OVERPOWERING

- **5x MORE PATIENTS** vs vehicle **DEMONSTRATED COMPLETE (100%) CLEARANCE of AK** at day 57 in two Phase 3 studies[1,2*]
  - **44%** (n/N=77/175) KLISYRI® vs 5% (n/N=8/176) vehicle in study 1, and **54%** (n/N=97/178) vs 13% (n/N=22/173) vehicle in study 2[1]
- **SAFETY PROFILE OF KLISYRI®** demonstrated in the **LARGEST PIVOTAL CLINICAL TRIAL PROGRAM** of an AK topical Rx treatment[1,3]
  - The most common adverse reactions (incidence ≥2%) were local skin reactions, application site pruritus, and application site pain[1]

Visit www.klisyrihcp.com to learn more.

*Calculation based on pooled analysis of 702 patients from two Phase 3 studies evaluating all treatment locations (face or scalp): 49% KLISYRI® and 9% vehicle.[2]

Local Skin Reactions

Local skin reactions, including severe reactions (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) in the treated area can occur after topical application of KLISYRI. Avoid use until skin is healed from any previous drug, procedure, or surgical treatment. Occlusion after topical application of KLISYRI is more likely to result in irritation.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥2%) were local skin reactions, application site pruritus, and application site pain.

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

References: 1. KLISYRI [package insert]. Exton, PA: Almirall, LLC, 2020. **2.** Blauvelt A, Kempers S, Forman S, et al; Tirbanibulin Phase III Study Group. Tirbanibulin ointment 1%, a novel inhibitor of tubulin polymerization and Src kinase signaling, for the treatment of actinic keratosis (AK): results from two pivotal phase III studies. *J Skin*. 2020;4(5):s63. https://doi.org/10.25251/skin.4.supp.62. **3.** Data on file. 2021. Pivotal Clinical Trials.

Brief Summary of Full Prescribing Information for KLISYRI® (tirbanibulin) ointment

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KLISYRI safely and effectively. See full Prescribing Information for KLISYRI.

WARNINGS AND PRECAUTIONS

Ophthalmic Adverse Reactions

KLISYRI may cause eye irritation.

Avoid transfer of the drug into the eyes and to the periocular area during and after application. Wash hands immediately after application. If accidental exposure occurs, instruct patient to flush eyes with water and seek medical care as soon as possible.

Local Skin Reactions

Local skin reactions, including severe reactions (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration) in the treated area can occur after topical application of KLISYRI [see Adverse Reactions (6.1)]. Avoid use until skin is healed from any previous drug, procedure, or surgical treatment. Occlusion after topical application of KLISYRI is more likely to result in irritation.

ADVERSE REACTIONS

Clinical Trials Experience

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

Two double-blind, vehicle-controlled clinical trials were conducted in 702 adult subjects with actinic keratosis on the face or scalp. Subjects were randomized 1:1 to KLISYRI or vehicle. Subjects enrolled in the trials had 4 to 8 clinically typical, visible, and discrete AK lesions in a contiguous area of 25 cm^2 on the face or scalp. Subjects had an average age of 70 years (range 45 to 96 years) and were predominantly Caucasian (99%), male (87%), with Fitzpatrick skin types I or II (72%) and actinic keratosis on the face (68%) or scalp (32%). Treatment groups were comparable across all demographics and baseline characteristics, including AK lesion count and distribution on the face or scalp.

In the controlled trials, local skin reactions (LSRs) were collected independent of adverse events. Local skin reactions, including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosions/ulcerations were assessed by the investigators using a grading scale of 0 = absent, 1 = mild (slightly, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense).

The percentages of subjects with the maximal post-baseline grades for each local skin reaction greater than baseline by treatment group are provided in Table 1. LSRs were mostly mild to moderate in degree (Table 1).

Table 1. Investigator Assessment of Maximal Post-Baseline Local Skin Reactions Greater Than Baseline in the Treatment Area (face or scalp) - Pooled Data from 2 Controlled Clinical Phase 3 Trials

	KLISYRI N = 353			Vehicle N = 349		
Local Skin Reactions	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Erythema	76 (22%)	223 (63%)	22 (6%)	98 (28%)	20 (6%)	0
Flaking/ Scaling	92 (26%)	166 (47%)	31 (9%)	86 (25%)	33 (9%)	1 (<1%)
Crusting	107 (30%)	50 (14%)	7 (2%)	31 (9%)	8 (2%)	0
Swelling	102 (29%)	32 (9%)	2 (<1%)	15 (4%)	1 (<1%)	0
Vesiculation/ Pustulation	25 (7%)	2 (<1%)	2 (<1%)	3 (<1%)	0	0
Erosion/ Ulceration	32 (9%)	9 (3%)	0	10 (3%)	0	0

Table 2 presents the adverse reactions experienced in ≥2% of subjects participating in the controlled clinical trials with KLISYRI. No subject withdrew from the trials due to adverse reactions.

Table 2. Adverse Reactions Occurring in ≥2% of Subjects in 2 Controlled Clinical Trials– Pooled Safety Population

Adverse Reaction System Organ Class	KLISYRI N = 353	Vehicle N = 349
Number of Subjects (%) with any adverse reaction (possibly related to treatment)	56 (16%)	35 (10%)
Application site pruritus	32 (9%)	21 (6%)
Application site pain[a]	35 (10%)	11 (3%)

[a]Application site pain includes pain, tenderness, stinging, and burning sensation at the application site.

For the 51 subjects (45 KLISYRI, 6 vehicle) who maintained complete clearance through the 12-month follow-up period, no additional local adverse reactions were reported.

Dermal Safety Studies

Clinical studies in healthy subjects demonstrated KLISYRI did not cause contact sensitization (261 subjects), phototoxic skin reactions (31 subjects), or photoallergic skin reactions (64 subjects).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data with KLISYRI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of tirbanibulin to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal deaths and malformations at a systemic exposure that was at least 74 times the exposure associated with the maximum recommended human dose (MRHD). Oral administration of tirbanibulin to pregnant rabbits during the period of organogenesis resulted in reduced mean fetal weight and size at a systemic exposure that was 159 times the exposure associated with the MRHD (see Data).

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

Data

Animal Data

Tirbanibulin induced fetal deaths and external, visceral, and skeletal malformations when administered orally to pregnant rats during the period of organogenesis at doses greater than or equal to 1.25 mg/kg/day, which resulted in systemic exposures at least 74 times the exposure associated with the MRHD on an Area Under the Curve (AUC) comparison basis. Tirbanibulin had no apparent effects on fetal development in rats at a dose of 0.5 mg/kg/day, which resulted in systemic exposures 18 times the exposure associated with the MRHD.

Tirbanibulin reduced mean fetal weight and size (crown-rump length) when administered orally to pregnant rabbits during the period of organogenesis at a dose of 3 mg/kg/day, which resulted in a systemic exposure 159 times the exposure associated with the MRHD on an AUC comparison basis. Tirbanibulin had no apparent effects on fetal development in rabbits at a dose of 1 mg/kg/day, which resulted in systemic exposures 53 times the exposure associated with the MRHD.

Tirbanibulin was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation at dosages up to 1.25 mg/kg/day. These dosages resulted in systemic exposures up to 74 times the exposure associated with the MRHD on an AUC comparison basis. No adverse effects on maternal function or developmental, neurobehavioral, or reproductive performance of offspring were observed.

Lactation

Risk Summary

There are no data on lactational transfer of KLISYRI to human or animal milk. The effects of KLISYRI on the breastfed infant, or its effects on milk production, are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KLISYRI and any potential adverse effects on the breastfed child from tirbanibulin or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of KLISYRI for actinic keratosis in subjects less than 18 years of age have not been established. Actinic keratosis is not a condition generally seen within the pediatric population.

Geriatric Use

Of the 353 subjects with AK treated with KLISYRI in the 2 controlled Phase 3 trials, 246 (70%) were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Overdose of KLISYRI could cause an increase in incidence and severity of local skin reactions.

CLINICAL PHARMACOLOGY

Drug Interactions

Clinical Studies

No clinical studies evaluating the drug interaction potential of KLISYRI have been conducted.

In Vitro Studies

CYP Enzymes: Tirbanibulin and the metabolite KX2-5036 directly or time-dependently inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 with an IC50 value of >17 µM. Tirbanibulin up to 1 µM (431.5 ng/mL) and the metabolite KX2-5036 up to 3 µM (1024 ng/mL) did not induce CYP 1A2, 2B6, or 3A4. These findings suggest that KLISYRI has no clinically meaningful effect on the PK of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4.

Drug Transporters: Neither tirbanibulin nor the metabolite KX2-5036 was a substrate of MDR1, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2. Tirbanibulin and the metabolite KX2-5036 inhibited MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and/or OCT2 with an IC50 value of >1 µM. The results suggest that KLISYRI has no clinically meaningful effect on the PK of drugs mediated by MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and OCT2.

Manufactured for: Almirall, LLC. Exton, PA 19341 USA. Revised: December 2020

Quick TAKES

It can be challenging trying to prescribe dupilumab for pediatric atopic dermatitis patients from the beginning.

Documentation of disease severity and failure with other therapies will help with prior authorization of dupilumab.

Cyclosporine can be a helpful bridge for patients having trouble obtaining dupilumab.

Strategies for managing pediatric atopic dermatitis

MORGAN PETRONELLI | *Associate Editor*

Biologics and a range of inhibitors in the pipeline may expand the menu of safe, effective treatment options for pediatric patients with atopic dermatitis (AD). However, according to a recent presentation at the 2021 ODAC Dermatology, Aesthetic and Surgical Conference, held virtually January 14 through 17, 2021, getting the right medication to each may continue to be a hurdle.[1]

Yasmine Kirkorian, MD, interim chief, dermatology, Children's National Hospital and associate professor of dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC, provided tips on how to start pediatric patients on systemic medications for AD and navigate cost and availability problems in her presentation "Challenging Cases in Pediatric Dermatology".

"Pediatric AD is the bread and butter for all dermatologists, but I wanted to touch on the pragmatic aspects on how to start systemic medications now that we have drugs that are FDA-approved in children," said Kirkorian.

Currently, the only biologic approved by the FDA to treat AD in patients 6 years and older is dupilumab (Dupixent, Sanofi Genzyme and Regeneron Pharmaceuticals).[2] Kirkorian noted that this monoclonal antibody inhibits the signaling of IL-4 and IL-13. Adverse effects (AEs) of the biologic, including injection site reactions, facial rash, and ocular surface diseases such as keratitis and conjunctivitis, are well-tolerated in children.

Dupilumab is now being studied in clinical trials for patients as young as 6 months. Other medications being studied for treating pediatric patients age 12 to 17 years include abrocitinib (Pfizer), a JAK1 inhibitor; lebrikizumab (Eli Lilly and Company), an IL-13 inhibitor; tralokinumab (Leo Pharma), an IL-13 inhibitor; and nemolizumab (Galderma), an IL-31 receptor α inhibitor.

"We have this huge armamentarium hopefully coming for us, so we have to think practically about how we are going to get these drugs to our patients," she added.

Kirkorian said most of her patients are enrolled in insurance plans that will not approve dupilumab without prior failure of another immunosuppressant.

Her tips for helping pediatric AD patients get on dupilumab include:

- documenting Investigator's Global Assessment or Eczema Area and Severity Index score;
- documenting prior failure of topical corticosteroids, topical calcineurin, inhibitors, and topical crisaborole; and
- prescribing cyclosporine prior to prescribing dupilumab when requiring systemic medication for severe disease.

USING CYCLOSPORINE

Kirkorian's rationale in prescribing cyclosporine prior to dupilumab for patients with severe AD is that it's inexpensive, effective, has a fast onset, and is safe for short-term use that will provide sufficient relief to patients' symptoms.

She recommended starting pediatric patients with severe disease on 5 mg/kg of cyclosporine. For monitoring patients, she suggested collecting baseline laboratory values and vitals and repeating them at 1 month and then monthly for 3 months. At the 3-month visit, she added, make sure to document improvement and AEs from long-term cyclosporine use. Following this, she said physicians should be able to prescribe and initiate prior authorization for dupilumab.

Additionally, Kirkorian mentioned the importance of communicating the AEs of using cyclosporine with patients and their families and pointing out any combinations of therapeutics that increase the drug's concentration.

"Doctors need to discuss that with their patients," she said. "There are also drugs that decrease concentrate of cyclosporine, but this is really more important in organ transplant rejection. However, in our case, it might decrease efficacy, but not as much of a risk as dose increase."

A pragmatic strategy that she recommends when prescribing cyclosporine is creating a thorough patient handout that outlines all AEs, pregnancy precautions, dosing, and vaccination information. Additionally, Kirkorian suggested physicians fully explain the dosing and AEs with their patients and have a nurse review the patient handout on cyclosporine.

She added that communication for the patient and parent on off-label usage and providing a means for contact, such as a patient portal or on-call number, is also important for when AEs occur.

Notably, Kirkorian said pediatric patients should not receive live vaccines during cyclosporine treatment, like the varicella vaccine, due to it being contraindicated with the systemic therapy.

WHAT ABOUT METHOTREXATE?

Kirkorian cautioned against the use of methotrexate for treating pediatric AD. "Methotrexate is still very important for treatment of other pediatric inflammatory diseases such as psoriasis and others, but I don't use it much for eczema anymore," she said. "It takes a long time to be effective, and its efficacy is quite poor even when you get to the dose that you intended to reach."

The risk of dosing errors in a weekly dose of medication is another concern. To prevent this, Kirkorian suggested creating a dosage calendar, having the parent sign a copy, and uploading it to the electronic medical records. ◀

Disclosure

Kirkorian reports no relevant conflicts of interest.

References

1 Kirkorian J. Challenging cases in pediatric dermatology. Presented at: ODAC Dermatology, Aesthetic & Surgical Conference; January 14-17, 2021; Virtual.

2 FDA approves Dupixent (dupilumab) for children aged 6 to 11 years with moderate-to-severe atopic dermatitis. Asthma and Allergy Foundation of America. June 1, 2020. Accessed February 4, 2021. https://community.aafa.org/blog/fda-approves-dupixent-dupilumab-for-children-aged-6-to-11-years-with-moderate-to-severe-atopic-dermatitis

Quick TAKES

Phase 3 trials show promise for novel biologic dual inhibitor of IL-17A and IL-17F as well as oral JAK inhibitor.

Completed study findings support expanding the secukinumab plaque psoriasis indication to include children and new dosing regimen for heavier patients.

Postmarketing safety data on rates of serious infections and malignancies associated with IL-17 and IL-23 inhibitors are similar to the background rates in the psoriasis patient population.

Novel Therapeutics Usher In Year of Innovation

WHAT'S NEW: REPORT FROM MAUI DERM LIVE AND MAUI DERM CONNECT

CHERYL GUTTMAN KRADER, BS PHARM | *Staff Correspondent*

With completed phase 3 trials of novel drugs showing impressive results, 2021 could bring major advances in treatment options for patients with moderate to severe plaque psoriasis, says Bruce E. Strober, MD, PhD, clinical professor of dermatology, Yale University, New Haven, Connecticut. He reviewed upcoming developments in psoriasis therapeutics and new safety data on IL-17A inhibitors at Maui Derm Live. The in-person dermatology continuing medical education (CME) conference in Hawaii was held concurrently with Maui Derm Connect, a virtual CME conference, January 25 to January 29, 2021.

FIRST-IN-CLASS BIOLOGIC

Investigators of bimekizumab, a dual-targeting monoclonal antibody that inhibits IL-17A and IL-17F, completed a series of phase 3 trials. These studies compared the investigational subcutaneous agent administered every 4 weeks with a placebo, as well as compared with adalimumab (Humira, AbbVie Inc), secukinumab (Cosentyx, Novartis), and ustekinumab (Stelara, Janssen Pharmaceuticals).

All phase 3 studies met their primary end points, demonstrating that bimekizumab-treated patients achieved superior skin clearance at week 16, compared with those who received placebo and adalimumab as measured by the Psoriasis Area and Severity Index 90 (PASI 90) and an Investigator Global Assessment (IGA) response of clear or almost clear skin with a score of 0/1.[1-3]

"The PASI 90 rate for patients treated with bimekizumab at the week 16 primary end point in all of the phase 3 trials was in the range of 85% to 90%," Strober says. "Results from ongoing phase 3 trials are likely to show that bimekizumab is also very effective for treating psoriatic arthritis."

According to Strober, the safety profile of bimekizumab appears similar to available IL-17A inhibitors except for a higher risk of *Candida* infections. Across the studies, *Candida* infections occurred in 10% to 20% of patients treated with bimekizumab, which is approximately 5-fold higher than the rate reported for other IL-17A inhibitors in the trials. As with the IL-17A blockers, the labeling for bimekizumab will likely include a warning about its use in patients with a history of inflammatory bowel disease (IBD).

NOVEL ORAL AGENT

Deucravacitinib (BMS-986165, Bristol Myers Squibb) is a JAK inhibitor that acts as a selective allosteric inhibitor of TYK2 to inhibit IL-12, IL-23, and interferon-α/β signaling pathways. The deucravacitinib phase 3 psoriasis clinical trial data have not yet been publicly released, but according to Strober, it's expected to show robust efficacy and a favorable safety profile.

Due to its novel mechanism of enzyme inactivation, deucravacitinib does not cause inhibition of multiple JAK signaling pathways that explain the potentially serious adverse effects and safety warnings associated with JAK inhibitors that act by binding the kinase domain of JAK family enzymes.

"The kinase domain of the JAK family enzymes are very similar so that a drug that binds to this active site of 1 JAK enzyme will promiscuously bind to some extent to other JAKs, which has implications for safety," Strober explains. "Deucravacitinib binds a domain on TYK2 that is not shared by the other JAKs and theoretically, would be less likely than other JAK inhibitors to cause hematologic changes and generalized immunosuppression. If deucravacitinib is approved, it remains to be seen if these differences are reflected in its label's warnings and recommendations for laboratory monitoring."

SECUKINUMAB LABEL CHANGES

Based on its phase 3 study results, secukinumab is expected to join ixekizumab (Taltz; Eli Lilly and Company) as an approved IL-17A inhibitor for the treatment of moderate to severe plaque psoriasis in children older than 6 years who are candidates for systemic or phototherapy.

"As with ixekizumab, it will be important to carefully screen children for a history of IBD before treating with secukinumab," Strober adds.

Results from a multicenter, randomized, double-blind study investigating secukinumab in patients weighing more than 90 kg are expected to lead to new dosing information for this subgroup of heavier patients with psoriasis with a recommendation to treat every 2 weeks. ◀

more ONLINE

Scan for full article, disclosures, and references.

We've only scratched the surface on understanding the **JAK/STAT pathway's role** in atopic dermatitis (AD)

Key cytokines, including IL-4, IL-13, IL-22, IL-31, and TSLP, contribute to this chronic, relapsing-remitting inflammatory skin disease. Many of these cytokines are also thought to contribute to itch, a symptom responsible for much of the disease burden.[1-5]

By inhibiting the JAK/STAT pathway, it may be possible to decrease signaling of key cytokines that drive AD inflammation, itch, and skin barrier disruption.[3,6]

IL=interleukin; JAK=Janus kinase; STAT=signal transducer and activator of transcription; TSLP=thymic stromal lymphopoietin.

Let's explore more about the JAK/STAT pathway at scratchingtheADsurface.com

Pfizer does not currently have any JAK inhibitors approved for the treatment of AD.

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Optimize Risk, Management of Pigmented Lesions

Melanoma presents differently in the pediatric population.

MIRANDA HESTER | *Editor,* Contemporary Pediatrics®

Diagnosis, risk assessment and treatment of congenital melanocytic nevi (CMN), as well as melanoma, require specific strategies for pediatric patients. Elena B. Hawryluk, MD, PhD, assistant professor of dermatology at Harvard Medical School in Boston, Massachusetts, discussed recommendations for understanding how melanoma presents in pediatric cases and how to optimize outcomes during her presentation at Maui Derm Live. Maui Live was an in-person dermatology continuing medical education (CME) conference in Hawaii held concurrently with Maui Derm Connect, a virtual CME conference, from January 25 to January 29, 2021.[1]

ASSESSING CMN RISKS

Hawryluk first addressed CMN, noting that they increase the risk of melanoma and that the likeliness increases with the papule's size. For small (<1.5 cm) and medium (1.5-20 cm) nevi, the risk increases by roughly 1%. For large (>20 cm) and giant (>40 cm) nevi, the risk is 2% for large nevi and 6% to 15% for giant nevi. In CMN-associated melanoma, the risk is highest for patients with giant congenital nevi (78%) with many satellite nevi (94%).

Hawryluk added that atypical or dysplastic nevi, which are not premelanoma, can indicate an increased risk of developing melanoma. Because of this, Hawryluk recommended a thorough examination with continual monitoring. According to Hawryluk, pediatric patients with large or giant nevi who develop melanoma tend to have high mortality (55%), and 14% have visceral melanoma."

Hawryluk also noted study results showing that patients with 2 or more nevi have an increased risk of central nervous system involvement, with 21% of patients having abnormal MRI findings.[1]

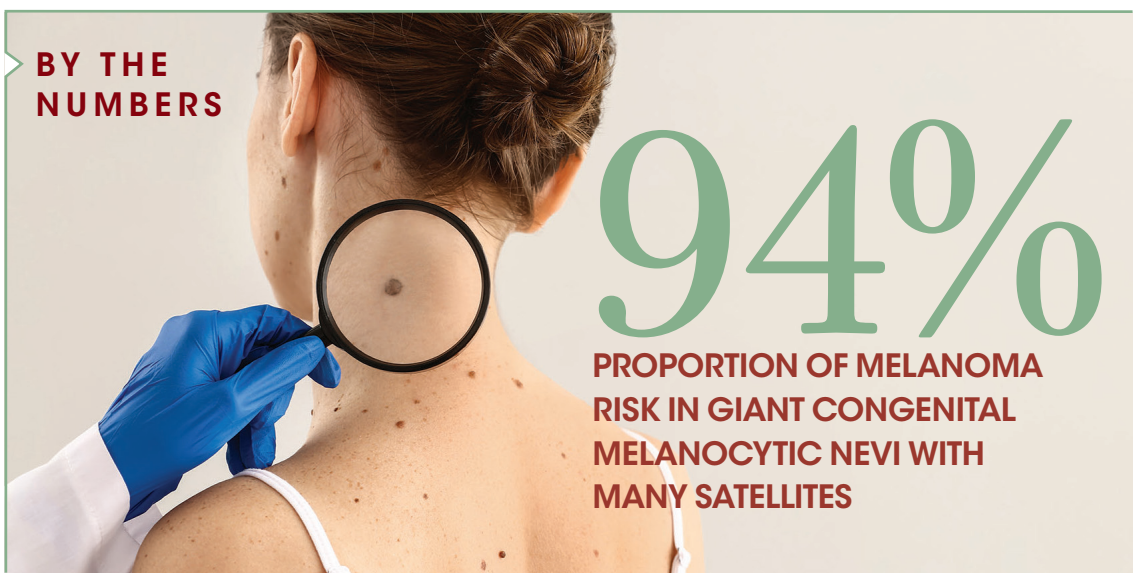
IS IT MELANOMA?

Hawryluk explained that various types of melanoma affect the pediatric population and gen-

PIGMENTED LESIONS CONTINUES ON PAGE 48 ▶

Quick TAKES

- Risk of melanoma increases with size of congenital melanocytic nevi.
- Melanoma presents differently in pediatric patients.
- The majority of pediatric melanoma cases are patients who receive a diagnosis at age 15 to 17.



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> “Early MRI of congenital melanocytic nevi is helpful as a baseline and to predict risk [of melanoma.]”

Elena B. Hawryluk, MD, PhD, assistant professor of dermatology at Harvard Medical School in *Boston, Massachusetts*

Pigmented lesions FROM PAGE 46

erally present differently than adult patients. A 2013 study advised assessing these lesion characteristics when diagnosing pediatric cases: amelanotic, bump, bleeding, color uniformity, de novo, at any diameter. **(See Table).**[2]

Physicians can often misdiagnose amelanotic melanoma as a benign lesion. Hawryluk cited 2016 study results from the *Journal of the American Academy of Dermatology* that found dermatologists, following a first impression, had identified an amelanotic melanoma as a Spitz nevus, hemangioma, and acneiform lesion. To illustrate this point, she shared a case from her practice involving a girl with a suspected wart that hadn't responded to all typical treatments.

Spitzoid melanoma can harbor kinase fusions in roughly 50% of lesions and can be challenging to diagnose and distinguish from atypical Spitz tumors, in part because nonmelanoma Spitz lesions can also harbor kinase fusions, Hawryluk added.

TABLE

DIFFERENCES IN PEDIATRIC MELANOMA VERSUS ADULT[2]

Tradtional MM	Pediatric MM (Cordoro et al 2013)
A symmetry	A melanotic
B order	B ump, bleeding
C olor variegation	C olor uniformity
D iameter > 6mm	D e novo, and diameter
E volution/change	

OPTIMIZE WORK-UPS AND MANAGEMENT OPTIONS

If there is no suspicion of melanoma, some parents prefer to simply keep the lesions under observation. According to Hawryluk, other choices include surgical excision, although no substantial evidence has been found that the treatment choices reduce the risk of melanoma; curettage; dermabrasion; chemical peels; cryotherapy; laser; and electrotherapy. These treatment options can remove CMN cells, but Hawryluk remarked that they carry the risk of scars or disfigurement and may make it more difficult to detect melanoma.

When considering whether a child needs an MRI, she recommended it for infants with 2 or more nevi, a large axial nevus, the presence of satellites, or older patients who exhibit neurologic changes. She also noted that having imaging from infancy to serve as a baseline can make it easier to discern changes.

For the work-up of patients with CMN and melanoma suspicion, she shared 2 algorithms dependent on whether the presentation was cutaneous or if it was a central nervous system manifestation.

For cutaneous presentations, a thorough clinical examination with photo documentation should occur with a review within 4 weeks. If the new mark is resolved or unchanged, the area should be monitored continually to ensure stability. If the mark progresses or has an abnormal presentation, an excision biopsy should occur, along with histopathology and hotspot genotyping.

If it's malignant and confirmed by another expert, baseline blood, histology, staging, and further excision should occur as dictated. For new neurological symptoms, imaging should occur. If it's normal or unchanged from the last imaging session, regular monitoring should continue. For abnormal results, a biopsy followed by histopathology and genotyping may help determine if the result is malignant or nonmalignant. ◀

Disclosure

Hawryluk reported no relevant or financial disclosure.

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> **“There are so many things that can be done to revise scars. We want happy patients. After all, it’s really your name on the patients’ skin.”**
>
> **Tim Flynn, MD, medical director of Cary Skin Center,** *Cary, North Carolina*

Modalities FROM PAGE 1

highlighted a number of patient cases that put these various modalities to use.

The panel included Tim Flynn, MD, medical director of Cary Skin Center, in Cary, North Carolina; Joel Cohen, MD, director at AboutSkin Dermatology and DermSurgery, in Denver, Colorado; and Jill Waibel, MD, of Miami Dermatology and Laser Institute, subsection chief of dermatology at Baptist Hospital, and medical director of Miami Cancer Institute Multidisciplinary Skin Cancer Clinic, in Miami, Florida.

Quick **TAKES**

- Lasers are first-line therapy in the management of scars.
- A combination of ablative fractional and nonablative lasers can help with treatment.
- Microneedling with radiofrequency is beneficial for the treatment of acne scars on all skin types.

Waibel stressed the importance of identifying the etiology and physical classification of a scar to treat it effectively.

“Look at that scar and diagnose it,” said Waibel. “As dermatologists, we’re used to making a physical exam diagnosis.”

SOLVING THE CHALLENGES OF DEPRESSED SCARS

Different scars benefit from different modalities. For example, according to Flynn, one method for treating a depressed scar is subcision using a noncoring needle or an 18-gauge regular needle, which is useful for scars depressed by a tether at the base of the dermis. Inserting the needle parallel under the skin surface and moving it back and forth to break these tethers helps release the depressed scar.

According to Flynn, some depressed scars need excision because they are too tightly bound down to the underlying fat. He suggested letting the scar mature until stable, usually around 9 months, and then excising the thick depressed scar or portions of the scar. He noted that often, the jawline and chin are prone to these scars.

However, not all depressed scars are bound down. Those that result from missing volume require a replacement to sufficiently treat the scar. In one case, Flynn used a filler to temporarily restore volume loss in a depressed scar on a patient’s nose.

Cohen added that he sometimes injects fillers to add volume to depressed scars but cautioned about using them in the distal nose. Instead, he recommended taking a dermal graft from behind the ear with a 3-mm punch biopsy. After taking off the epidermis, he makes a small incision at the tip of the nose to lift the scar using a subcision needle and employs a “windshield wiper motion.” He then positions the graft with Bishop-Harmon forceps and sutures it in place.

“I feel good about building this area up using something that has durability and avoiding filler in areas already scarred and where vessels may be compressed,” said Cohen.

EXPANDING TREATMENT CHOICES

According to Flynn, microneedling can be another modality for scar revision. He added that although it’s easy to perform, microneedling requires multiple treatment sessions to achieve desired results.

Cohen frequently uses radiofrequency (RF) microneedling for treating acne scars, particularly rolling scars because it can be used on any skin type.

What’s more, Flynn noted that performing a Z-plasty can be a viable option to treat scars with the need to reorient, release tension in a free margin, fix a postoperative web, or reposition an anatomical unit.

EFFECTIVE COMBINATION THERAPY

Waibel suggested using lasers as first-line therapy in the management of scars. She recommended implementing multiple lasers in 1 session to help progress the treatment of scars. In 1 patient burn case she presented, Waibel utilized 3 different lasers to help repair the scar: a pulsed dye laser to treat the red areas, a nonablative fractional to treat atrophic areas, and an ablative fractional to treat hypertrophic areas.

According to Cohen, lasers may also offer a solution to the challenges of treating acne scars on skin of color. He added that physicians now benefit from using ablative fractional erbium and nonablative lasers to help with the treatment of acne scars in darker skin types. “In some cases, I actually do a combination with a hybrid fractional called Halo, using 2940 ablative fractional erbium and then a1470 nonablative,” he said.

Cohen highlighted the importance of early intervention for scar therapy.

“Historically, people have often waited until a scar ‘declared itself’. I don’t think anybody has a great understanding of what that means, but we do know that it’s more difficult to treat scars that are older,” he said. “So, it would be optimal in many cases to start treating a scar, whether it’s a traumatic scar or a post-skin cancer removal scar, at about 2 or 3 months.”

Cohen added that research on pulsed dye and fractional carbon dioxide lasers showed a synergy for early intervention scar therapy.

“We need to rethink how we approach scars and how we can make scars look better earlier [during which] the wound is still remodeling, and the area is still repairing by using these modalities like fractional ablative lasers,” Cohen said. ◀

Disclosures

Flynn is a consultant with Canfield Scientific.

Cohen reports no relevant conflict of interest or financial disclosures.

Waibel reports working with AbbVie, Cytrellis Biosystems, Dominion Aesthetic Technologies, Eli Lilly and Company, L’Oréal, Lumenis, Lutronic, Michelson Diagnostics, Novartis, ReGenX, Pfizer, Sciton, Sebacia, Strata Skin Sciences, and Syneron Candela.

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Quick TAKES

- Data is key to analyzing effectiveness of therapies for hair loss, and simple tools make that possible.
- It is important to understand how to evaluate efficacy because many different types of treatment exist for scarring alopecias.
- Upcoming treatments under development include autologous dermal sheath cup, dermal papilla cell injections into the scalp, and hair farming/cloning.

Data Key to Treatment

ROBERT KRONEMYER | *Staff Correspondent*

Simply observing symptoms can often help a patient receive a hair loss disorder diagnosis. However, observation alone is less helpful in evaluating treatment methods.

"It is important for a dermatologist to be able to quantify how much hair has been lost or gained," said Jerry Shapiro, MD, professor of dermatology at the NYU Grossman School of Medicine, New York, New York, who spoke on managing hair loss disorders at Maui Derm Live.[1] The in-person dermatology continuing medical education (CME) conference in Hawaii was held concurrently with Maui Derm Connect, a virtual CME conference, January 25 to 29, 2021.

"Because of the tools now available to quantify, we now have a more scientific approach to determine how much [hair] gain or loss the patient has had from their treatment protocol."

Trichometrics/numerics are key to measuring the efficacy of treatment modalities for hair growth. The 3 devices most effective to confirm success or failure in the office setting, according to Shapiro, are the Folliscope (LeadM Corporation), FotoFinder (FotoFinder Systems), and artificial intelligence with Vectra (Canfield Scientific Inc).

"These are easy and accurate devices to use," Shapiro told *Dermatology Times*®. "Patients also appreciate them because they like to know their numbers and whether those numbers have gone up or down or are the same."

ALOPECIA PHENOTYPES AND TREATMENT

Scarring alopecias are a group of disorders characterized by a final common pathway of replacement of follicular structure by fibrous tissue. One of these conditions is primary cicatricial alopecia, which involves preferential destruction of follicular epithelium with sparing of interfollicular dermis.

Discoid lupus erythematosus, another type of scarring alopecia, presents with lesions often localized to the scalp and can be treated based on the extent of disease.

> "Because of the tools now available to quantify, we now have a more scientific approach to determine how much [hair] gain or loss the patient has had from their treatment protocol."
>
> Jerry Shapiro, MD, a professor of dermatology at the NYU Grossman School of Medicine, **New York, New York**

An increasingly common hair-loss condition is frontal fibrosing alopecia (FFA), which is irreversible and a trichologic emergency that requires immediate attention. "We do not know why we are seeing so many more cases," Shapiro said. "Fortunately, there are treatments that can halt FFA by creating follicular rescue, so that no more hairs are lost."

Aggressive management of FFA is necessary, including cortisone injections, topical tacrolimus, cortisone lotions, topical minoxidil, doxycycline, hydroxychloroquine, pioglitazone (Actos; Takeda Pharmaceuticals), and low-dose naltrexone. Finasteride or dutasteride, types of 5-alpha-reductase inhibitors, may also be used.

"Patients can start seeing a positive effect usually in 3 months," Shapiro said. "There is also a low likelihood of [adverse] effects."

Platelet rich plasma (PRP) is an adjunctive modality for treating androgenetic hair loss or alopecia areata. "Patients usually need 3 treatment sessions, spaced 1 month apart, followed by a hair count to determine if they have improved," Shapiro said. "Photographs may not be sufficient to quantify the amount of improvement, so meticulous quantification is key to PRP treatments."

JAK INHIBITORS

A game changer for managing alopecia areata is the use of oral Janus kinase (JAK) inhibitors, according to Shapiro. "They can also be used to treat certain forms of scarring hair loss," he said. "Overall, JAK inhibitors have the highest chance of success for alopecia totalis or universalis."

Shapiro favors the JAK inhibitor tofacitinib at a dose of 5 mg, twice a day. Newer JAK inhibitors, such as baricitinib (Olumiant; Eli Lilly and Company), have also proven to be effective.

"Patients, though, need to be monitored for [adverse] effects; namely the immune system through a complete metabolic panel, a complete blood count, and testing of triglyceride and cholesterol levels," Shapiro said.◀

Disclosure

Shapiro is a consultant/investigator for the following companies: Samumed, Incyte, Applied Biology, Eirion Therapeutics, RepliCel Life Sciences, Regen Lab SA, Keeps.com, Cassiopea, Pfizer, and Almirall. He also is an investigator for the non-approved uses of the medications naltrexone and pioglitazone.

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Quick TAKES

- A goal of personalized medicine it to predict early on if a given therapy will work in an individual patient.
- An individual patient's genetic profile, microbiome, medical history, lifestyle and diet help determine the treatment plan.
- Patients with melanoma, psoriasis, psoriatic arthritis, and AD could benefit near-term.

Precision Medicine FROM PAGE 1

Despite the futuristic genetics involved in personalized medicine, the basic tenet is hardly novel. It's a matter of degree. "Physicians are already practicing precision or personalized medicine every day as they try to determine the best therapy for each patient that results in quick recovery time with little or no adverse events," said Julie C. Harper, MD, of the Dermatology and Skin Care Center of Birmingham in Alabama. "Although it is early days, we are trying to take this concept a step further by using the patient's genetic profile, medical history, microbiome, lifestyle, diet and other environmental factors to create the most effective treatment plan for that individual."

PERSONALIZED BENEFITS

As precision medicine becomes increasingly influential in both dermatology and broader clinical practice, clinicians are looking for ways to implement this approach. "It would save the medical system and patients a lot of money and time if we could predict which biologic works best for each person…however, there still isn't any way to predict outcomes," said Zoe Diana Draelos, MD, of Dermatology Consulting Services, PLLC, in High Point, North Carolina and *Dermatology Times*® chief medical editor.

IMPROVING PSORIASIS, PSORIATIC ARTHRITIS OUTCOMES

Although there have been exciting developments in personalized medicine in dermatology, including experimental gene expression profiling tests treating and managing melanoma, the general consensus is that there is still a long way to go before patients benefit from the full impact of precision medicine's capabilities for other skin diseases. Psoriasis and psoriatic arthritis are two areas where personalized medicine could play a major role.

"It is not uncommon that patients go through 1 or 2 different biologic drug therapies, spending three months on each just to find out that they are suboptimal or ineffective while costing tens of thousands of dollars in medical bills," said Draelos.

> "There are many very specific comorbidities or other conditions and patient parameters affecting our psoriasis patients that determine which drug we are going to use for them. That is the essence of personalized medicine."
>
> 
>
> Mark Lebwohl, MD, dean for Clinical Therapeutics, and Chairman Emeritus, Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai, **New York, New York**

Precision medicine could also provide alternatives for patients with contraindications that could limit therapy choice. For example, clinicians can choose from an ever-increasing number of innovative biologics to treat patients with moderate to severe psoriasis. As effective as these agents are in quelling and managing symptoms, they may be contraindicated for patients with arthritis, obesity, personal or family history of heart attack, diabetes, high blood pressure, smoking, cancer history, multiple sclerosis, lupus, Crohn disease or ulcerative colitis, hepatitis B or C, positive test for tuberculosis or HIV, positive pregnancy test or a woman of childbearing potential, among others.[1,2]

Some medications can prove to be better suited than others for individual patients, depending on their individual patient parameters.

"In psoriasis, there are many specific comorbidities or other conditions and patient parameters affecting patients with psoriasis that determine which drug we are going to use for them. That is the essence of personalized medicine," said Mark Lebwohl, MD, dean for Clinical Therapeutics, and Chairman Emeritus, Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York.

He added that insurance companies will often promote certain medications that will generate the most money for them. The companies call it a discount or rebate but, according to Lebwohl, many of those dollars end up in the coffers of insurance companies.

"We know, and we can determine based on other factors in our patients, what the best therapy would be for them, but the insurers get in the way," said Lebwohl. "They only care about one thing which is how much money they will earn when we prescribe certain drugs. In my view, this remains one of the main challenges going forward in personalized medicine."

The dilemma in personalized medicine is the abundance of therapeutic options that clinicians and their patients can choose from, he said. That's already true for psoriasis and acne treatments and will be the case for atopic dermatitis (AD) in a few short years.

BIOMARKERS MAY PLAY KEY ROLE

Whether used for discovery or for prognostic and theranostic approaches, biomarkers have become one of the main focuses of precision medicine. The push to research and find different biomarkers associated with dermatologic diseases such as AD has resulted in the discovery of useful biomarkers that could in the future lead to more targeted therapies specific to the individual genetic makeup and personal parameters of the patient in the future.

"I think the biomarkers, transcription work, and other approaches that are being used have been hypothesis-generating and have uncovered

> "Exploratory biomarkers have their purpose and are here to stay."
>
> **Jonathan Silverberg, MD, PHD, MPH, associate professor, director of Clinical Research, director of Patch Testing, George Washington University School of Medicine and Health Sciences,** *Washington, DC*

> **“Physicians already practice precision medicine every day as they try to determine the best therapy for each patient…this concept just takes that a step further.”**

Julie C. Harper, MD, *of the Dermatology and Skin Care Center of Birmingham in Alabama*

some interesting and important pathways to be probed with follow-up research,” said Jonathan Silverberg, MD, PHD, MPH, associate professor, director of Clinical Research, director of Patch Testing, George Washington University School of Medicine and Health Sciences, Washington, DC. “As such, I believe exploratory biomarkers have their purpose and are here to stay.”

Although research is advancing, there is still much to learn about biomarkers, including decision-based biomarkers and disease biomarkers. According to Silverberg, the discovery of markers that fit the definition of a true biomarker remains a challenge. The goal would be to have a marker that would perform in AD or in other chronic inflammatory skin diseases the way, for example, hemoglobin A1c performs in diabetes as what has become essentially a universal measure of disease control.

“I would argue that we are decades away from such high-level specific biomarkers for atopic dermatitis,” Silverberg said. “Unfortunately, at this point, we won’t have enough to go on to realize a precision medicine approach in our therapeutic decision making. But with ongoing research that could change rapidly.”

APPROACH SHOWS PROMISE F OR ANTI-AGING, COSMECEUTICALS

Personalized medicine in the classical sense is practiced regularly in the cosmeceutical field, Draelos said. One of the biggest breakthroughs center on platelet rich plasma (PRP) techniques being used for truly personalized treatments.

Clinicians harvest the patient’s platelets and process them such that they are rich in growth factors. These can then be reinjected into the patient’s scalp to encourage hair growth or into the face to encourage collagen growth. Topical PRP therapies can be applied in on the skin as a personalized pharmaceutical in a vehicle that contains an individual patient’s own platelet derived growth factors, epidermal growth factors, and fibroblast growth factors.

“This is a little different approach to personalized medicine,” said Draelos. “The doctor is not really making a decision about what drug to give someone based on their disease. Instead, the physician is harvesting the patient’s own unique body-made materials and repositioning them in different areas of the body to deliver results.”

> **“It would save the medical system and patients a lot of money and time if we could predict which biologic works best for each person…however, there still isn’t any way to predict outcomes.”**

Zoe Diana Draelos, MD, founder and investigator, Dermatology Consulting Services, PLLC, High Point, North Carolina and *Dermatology Times*® chief medical editor

Beyond cosmetic and procedural dermatology, Draelos said that personalized medical techniques such as PRP and cell-derived materials are being used in elite athletes to stimulate bone growth, in dental surgery to stimulate mandible and gingival growth, as well as to expedite healing for diabetic ulcers.

She predicted that, while the progressive understanding of human genes and the quest to identify which genes code for certain diseases including the advent of CRISPR-Cas and its ability to address genetic abnormalities and deliver gene therapy are all in their infancy, and interest in their use will increase.

“I think perhaps there is a little more media hype regarding personalized medicine than reality at this point,” Draelos said. “For the average person, personalized medicine is not a widespread reality to deliver therapeutic care. But people are hopeful that personalized medicine will actually come to fruition. I have no doubt that it will.” ◀

Disclosures

Draelos, Harper, Lebwohl and **Silverberg** reported no relevant disclosures or financial interests.

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BY THE NUMBERS

3 months

TYPICAL TRIAL PERIOD TO DETERMINE IF A BIOLOGIC DRUG IS OPTIMAL AND EFFECTIVE FOR AN INDIVIDUAL PATIENT WITH PSORIASIS OR PSORIATIC ARTHRITIS.

AMA Streamlines Billing CPT Codes

First overhaul in a quarter century simplifies evaluation and management and increases flexibility.

JOHN JESITUS | *Staff Correspondent*

Quick TAKES

- A history and physical exam are no longer elements for code selection.
- Physicians can base code level selection on medical decision-making or total time, enabling them to choose the best patient care.
- More details were added to *Current Procedural Terminology* code descriptors and guidelines to promote payer consistency.

A result of the first major overhaul in 25 years, the 2021 *Current Procedural Terminology* (*CPT*) code set published by the American Medical Association (AMA) incorporated foundational changes that ease evaluation and management (E/M).[1]

"Wholesale changes to CPT E/M coding that took effect January 1, 2021, streamline billing documentation for dermatologists," said Mark D. Kaufmann, MD, chief medical officer at Advanced Dermatology and Cosmetic Surgery in Maitland, Florida, in his presentation at Maui Derm Live. The in-person dermatology continuing medical education (CME) conference in Hawaii was held concurrently with Maui Derm Connect, a virtual CME conference, January 25 to January 29, 2021.

These changes would result in a shift in billing patterns for dermatologists, Kaufmann added. He likened the new 5-column grid[1] used for coding E/M services to the Bible stating that, "This is the guidance that the AMA has given us—a 1-page graphic with language that is broadly open to interpretation."[2] Kaufmann is also clinical associate professor of the Department of Dermatology at the Icahn School of Medicine at Mount Sinai New York and an advisor to the American Academy of Dermatology Relative Value Scale Update Committee.

Dermatologists must use information from 2 of the 3 medical decision-making (MDM) columns in the code set to support the codes they bill, Kaufmann said. For example, androgenetic alopecia automatically merits a moderate (level 4) degree of MDM because it is a chronic condition that progresses. Dermatologists can choose level 4 in the first MDM column, Number and Complexity of Problems Addressed.

According to Kaufmann, a dermatologist prescribing a medication such as finasteride for androgenic alopecia can document this activity in the third MDM column, Risk of Complications and/or Morbidity or Mortality of Patient Management. With this example of moderate MDM in column 3, the dermatologist should have "moderate" in columns 1 and 3. Accordingly, the dermatologist could code the visit at 99204 or 99214, he says.

If the physician recommends an OTC medication such as minoxidil, this qualifies for low-level MDM, making the visit level 3 instead of 4. Counseling a patient without recommending treatment represents a straightforward MDM, a level 2 visit.

According to Kaufmann, medical dermatologists will "live" primarily at the low and moderate levels. Among the MDM columns, there will be appropriate occasions for column 2, such as when Mohs surgeons undertake patient consultations known as Amount and/or Complexity of Data to be Reviewed and Analyzed. "But in general dermatology, I have found that if you're looking to get to a moderate level of MDM, a level 4

Image: Stock.Adobe.com/corund

visit in column 2, you're probably already there with columns 1 and 3," he noted.

Risk levels associated with specific treatments require interpretation, Kaufmann said. For example, prescription drug management (an intervention option in the third column) corresponds with a moderate risk level. "Prescription drug management is a very broad statement," he said. "In this regard, the AMA has said that even if a physician discusses a systemic drug with a patient and the patient refuses the drug, that's prescription drug management. You don't have to write the prescription. On the flip side, you have to decide where you sit when a patient says, 'I need the same triamcinolone prescription you gave me last year for my winter's itch.'"

Dermatologists must determine whether they are comfortable calling this interaction prescription drug management for billing purposes. "Everyone has to define the lines in their own minds," he said. "In my opinion, when patients come in for refills of systemic drugs, that's always prescription drug management because you're going to be talking about the drug with the patient."

In Kaufmann's view, financial implications of the E/M changes are likely to provoke payer anxiety. Initially, the Centers for Medicare & Medicaid Services (CMS) estimated that the changes' net impact would be neutral or even feature a 1% cost reduction. The stimulus package signed by President Donald Trump in December 2020 turned the expected impact into a 5% cost increase.

The boost is helpful for 2021, according to Kaufmann. "But that doesn't do anything for us in 2022 and beyond," he said. "I'm sure that many of us will go to Capitol Hill later this year with the American Academy of Dermatology and other groups to ask that this fix be extended. But there's no guarantee that it will be. And next year, we may be in the same position we were prior to the stimulus bill being signed."

CMS' cost estimates rested on the expectation that in 2021, the number of codes used at each level would remain the same as in 2020, but 99201 was eliminated. More importantly, Kaufmann expects 99202 usage to decline this year because many of these visits will shift to 99203. "I believe that many of the 99203s will shift to 99204, which was hardly perceptible up until January 2021," he noted.

According to Kaufmann, CMS did not consider those dynamics when formulating their predictions. "We are probably going to see more audits," he said, "which may lead to further deliberations on how to deal with these new realities." ◀

Disclosures

Kaufmann is adviser to the American Association of Dermatology RVS Update Committee. He also owns stock in Modernizing Medicine and stock options in Klara.

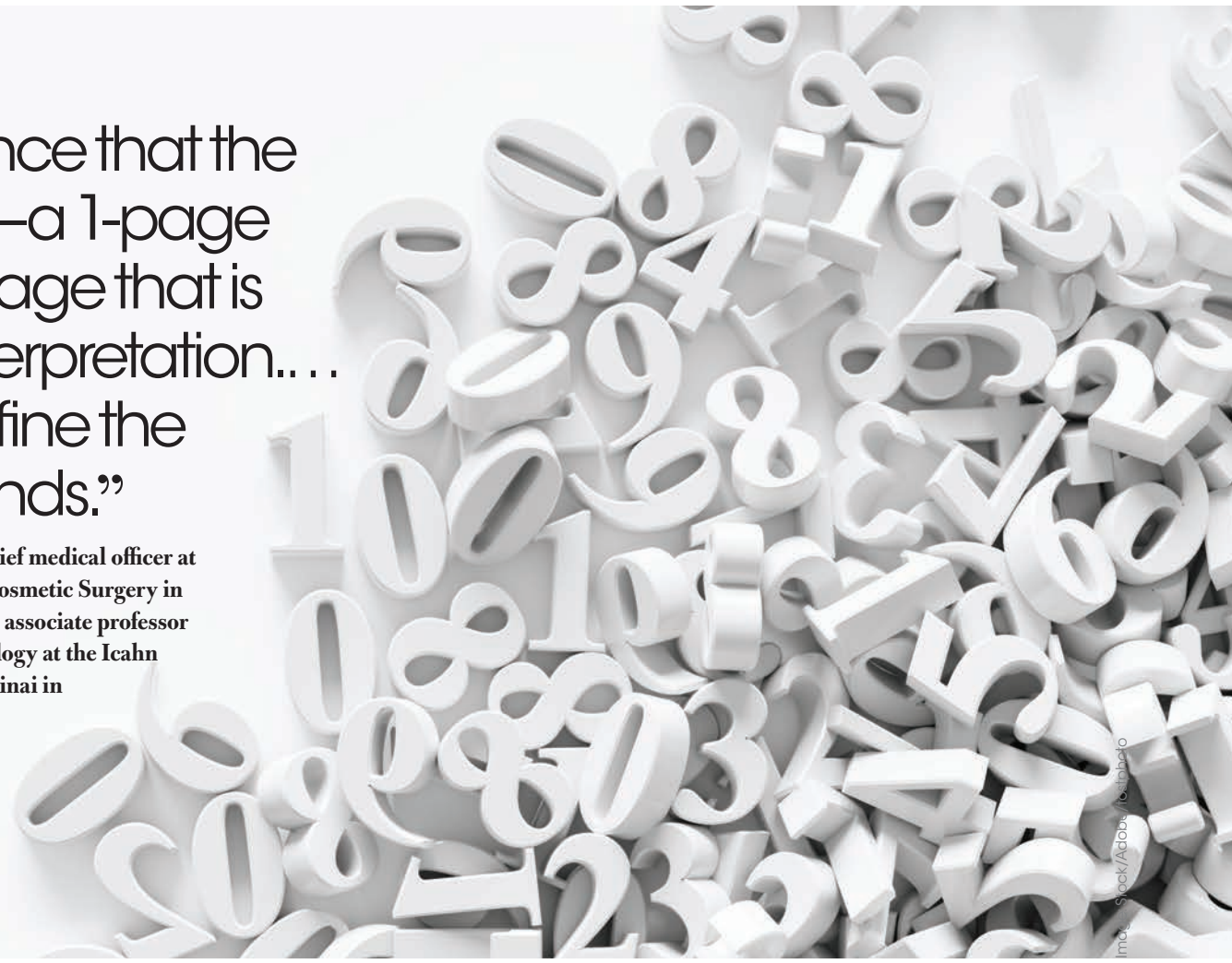
References

1 CPT evaluation and management (E/M) office or other outpatient (99202-99215) and prolonged services (99354, 99355, 99356, 99XXX) code and guideline changes. September 1, 2020. Accessed January 26, 2021. https://www.ama-assn.org/system/files/2019-06/cpt-office-prolonged-svs-code-changes.pdf

2 Kaufmann MD. How to maximize your billing effectiveness in the era of dwindling reimbursements and ICD-10. Presented at: Maui Derm For Dermatologists 2021; January 25-29, 2021; Maui, Hawaii.

"This is the guidance that the AMA has given us—a 1-page graphic with language that is broadly open to interpretation.... Everyone has to define the lines in their own minds."

Mark D. Kaufmann, MD, is chief medical officer at Advanced Dermatology and Cosmetic Surgery in Maitland, Florida, and clinical associate professor of the Department of Dermatology at the Icahn School of Medicine at Mount Sinai in *New York, New York*



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