DermatologyTimes®
CLINICAL INSIGHTS THAT EXPAND EXPERTISE AND ADVANCE PRACTICE
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Top 20 Stories of 2021

***Dermatology Times*® print and online versions were a must-read this year, from breaking news on sunscreens to new treatments coming to market. We visit the 20 stories of 2021 that made the greatest impact.**

LINDA STOCUM | *ASSISTANT EDITOR*

For many, the past 12-months may have felt less anxiety-inducing than 2020, but the COVID-19 pandemic continued to top headlines. The vaccine rollout prompted questions from both physicians and patients about reactions, including skin symptoms and guidelines. However, other news in the dermatology field also grabbed readers' attention.

Sunscreen and photoprotection is always a hot topic, so it is no surprise that reports about benzene and sunscreen products were at the forefront of coverage. *Dermatology Times*® broke the news about benzene contamination in 78 aerosol sunscreen and after-care products, which eventually led to voluntary recalls of some products. The issue continues into the new year, as people seek guidance regarding which sunscreens are safe.

It was also a mixed year for innovation, with many advances stalling in the dermatology pipeline. However, the aesthetic industry did see advances, such as the ellacor system by Cytrellis for the treatment of moderate to severe wrinkles. There was also a need to combat misinformation, so a *Pointers With Dr Portela* video on brown spots debunked a TikTok post spreading false information on how brown spots are produced.

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CLINICAL INSIGHTS

2022 Game Changers: Watch-worthy Drugs, Devices, and Technology

LISETTE HILTON | *Staff Correspondent*

EXCITING MEDICINES MIGHT FINALLY GET THEIR DEBUT

There are important drug approvals looming in 2022 that could change the landscape of options for people with atopic dermatitis (AD) and psoriasis, according to Christopher G. Bunick, MD, PhD, associate professor of dermatology at Yale University and member of *Dermatology Times*®' editorial advisory board.

The FDA's approval of the biologic bimekizumab (Bimzelx; UCB) was delayed in 2021. The interleukin (IL)-17 inhibitor for plaque psoriasis and psoriatic arthritis blocks IL-17 A and IL-17 F cytokines.

"Bimekizumab was off the charts in clinical trials in terms of patients that experienced and maintained a PASI [Psoriasis Area and Severity Index] 100 score," Bunick said. "It really redefines the ability to achieve PASI 100 in patients, and I think this medication is going to be well received in psoriasis. It works quickly, is very durable and powerful."

GAME CHANGERS CONTINUES ON PAGE 31 ▶

PIGMENTARY DISORDERS

Step Up Strategies for Patients with Vitiligo

MARY SCOVIAK | *Managing Editor*

THE RANGE OF TREATMENT MODALITIES for pigmentary disorders has been frustratingly limited, according to Seemal R. Desai, MD, FAAD. "In fact, the lack of choice has been horrible," said Desai, who is founder and medical director of Innovative Dermatology in Dallas, Texas.

The next 12 to 24 months could start resolving that problem. "We are truly on the cusp of some revolutionary changes, particularly as clinical trial results for topical and oral Janus kinase [JAK] inhibitors continue to evolve as possible treatments for vitiligo and other conditions," Desai noted.

The earliest beneficiaries of this wave of innovation could be patients with vitiligo. The National Clinical Trials registry reported that 47 vitiligo-related clinical trials were at some stage of

PIGMENTARY NEW DRUGS CONTINUES ON PAGE 26 ▶

For the treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older[1]

WITH HS, THE SURFACE DOESN'T ALWAYS SHOW

HUMIRA targets and blocks TNF-α to help address HS inflammation beneath the skin

The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown.

HUMIRA delivers clinically meaningful improvement (HiSCR) at week 12[1,3]

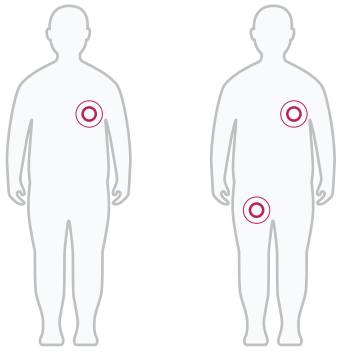
In the PIONEER clinical trials, **42%** (PIONEER I) and **59%** (PIONEER II) of HUMIRA-treated adult patients achieved HiSCR* at Week 12 **(primary endpoint)**, vs 26% and 28% on placebo, respectively.[3]

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.[3]**

*HiSCR=Hidradenitis Suppurativa Clinical Response.

LESION SPREAD:

Lesion observed in any anatomic region not seen at baseline[4]



Baseline | Example of lesion spread

◎ **Lesions=abscesses, inflammatory nodules, or draining fistulas[4]**

HUMIRA has data on lesion spread for HS

In a post-hoc analysis, **47%** of HUMIRA-treated adult patients (n=99, PIONEER I/II) did not experience lesion spread at week 36 vs **25%** in control group (n=151, PIONEER II)[4]

DATA LIMITATIONS:

- **Lesion spread was not a pre-specified endpoint and was not controlled for multiplicity. This data cannot be regarded as statistically or clinically significant, and therefore, no conclusions can be drawn.**
- **Placebo comparator data are only available from PIONEER II so differences should be interpreted with caution.**

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

PRIMARY ENDPOINT HiSCR at week 12 (Period A), defined as ≥50% reduction from baseline in abscess and inflammatory nodule count, with no increase in abscess and draining-fistula count.[1] In an integrated exploratory post-hoc analysis of PIONEER I and II, lesion spread was assessed through 36 weeks in patients randomized to HUMIRA 40 mg weekly or placebo in Period A and B.[3]

THE DISEASE YOU NEED TO TREAT BELOW[2]

Not an actual patient with HS.

To learn about dosing: HUMIRADERMPRO.COM/HS/dosing

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.

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.

HUMIRA®
adalimumab

IMPORTANT SAFETY INFORMATION[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.** Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol*. 2019;80(1):60-69.e2. doi:10.1016/j.jaad.2018.05.040 **3.** 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. doi: 10.1056/NEJMoa1504370 **4.** Data on file. ABVRRTI71291.

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

HUMIRA® adalimumab

HUMIRA® (adalimumab) Injection, for subcutaneous use

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.

Crohn's Disease

HUMIRA is indicated for the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

Ulcerative Colitis

HUMIRA is indicated for the treatment of moderately to severely active ulcerative colitis in adults and pediatric patients 5 years of age and older.

Limitations of Use

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 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. 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 65 years of age and older, 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).[1]

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).[1] 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. 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. 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, hypersensitivity reactions (e.g., 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.

Increased Risk of Infection when Used 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]*.

Increased Risk of Infection When Used 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 following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Hepatitis B Virus Reactivation *[see Warnings and Precautions]*
- Neurologic Reactions *[see Warnings and Precautions]*
- Hematological Reactions *[see Warnings and Precautions]*
- Heart Failure *[see Warnings and Precautions]*
- Autoimmunity *[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 Crohn's Disease 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 adult 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 the controlled Phase 3 trial of HUMIRA in patients with pediatric ulcerative colitis (N=93), which evaluated efficacy and safety of a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (N=31) and a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every week (N=32), following body weight based induction doses of 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=63), or an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=30), ALT elevations ≥ 3 X ULN occurred in 1.1% (1/93) of 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.

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%

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
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

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in HUMIRA-treated patients in RA studies were:

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

Cardiovascular System: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, polycythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder

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 concentrations 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.

Crohn's Disease Clinical Studies

Adults: The safety profile of HUMIRA in 1478 adult patients with Crohn's disease from four placebo-controlled and two open-label extension studies was similar to the safety profile seen in patients with RA.

Pediatric Patients 6 Years to 17 Years: The safety profile of HUMIRA in 192 pediatric patients from one double-blind study (Study PCD-I) and one open-label extension study 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

Adults: The safety profile of HUMIRA in 1010 adult patients with ulcerative colitis (UC) from two placebo-controlled studies and one open-label extension study was similar to the safety profile seen in patients with RA.

Pediatric Patients 5 Years to 17 Years: The safety profile of HUMIRA in 93 pediatric patients with ulcerative colitis from one double-blind study and one open-label extension study was similar to the safety profile seen in adult patients with ulcerative colitis.

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.

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 adalimumab products may be misleading.

There are two assays that have been used to measure anti-adalimumab antibodies. With the ELISA, antibodies to adalimumab could be detected only when serum adalimumab concentrations were < 2 mcg/mL. The ECL assay can detect anti-adalimumab antibody titers independent of adalimumab concentrations in the serum samples. The incidence of anti-adalimumab antibody (AAA) development in patients treated with HUMIRA are presented in Table 2.

Table 2: Anti-Adalimumab Antibody Development Determined by ELISA and ECL Assay in Patients Treated with HUMIRA

Indications		Study Duration	Anti-Adalimumab Antibody Incidence by ELISA (n/N)		Anti-Adalimumab Antibody Incidence by ECL Assay (n/N)
			In all patients who received adalimumab	In patients with serum adalimumab concentrations < 2 mcg/mL	
Rheumatoid Arthritis[a]		6 to 12 months	5% (58/1062)	NR	NA
Juvenile Idiopathic Arthritis (JIA)	4 to 17 years of age[b]	48 weeks	16% (27/171)	NR	NA
	2 to 4 years of age or ≥ 4 years of age and weighing < 15 kg	24 weeks	7% (1/15)[c]	NR	NA
Psoriatic Arthritis[d]		48 weeks[e]	13% (24/178)	NR	NA
Ankylosing Spondylitis		24 weeks	9% (16/185)	NR	NA
Adult Crohn's Disease		56 weeks	3% (7/269)	8% (7/86)	NA
Pediatric Crohn's Disease		52 weeks	3% (6/182)	10% (6/58)	NA
Adult Ulcerative Colitis		52 weeks	5% (19/360)	21% (19/92)	NA
Pediatric Ulcerative Colitis		52 weeks	3% (3/100)	13% (3/23)	33% (33/100)[i]
Plaque Psoriasis[f]		Up to 52 weeks[g]	8% (77/920)	21% (77/372)	NA
Hidradenitis Suppurativa		36 weeks	7% (30/461)	28% (58/207)[h]	61% (272/445)[j]
Non-infectious Uveitis		52 weeks	5% (12/249)	21% (12/57)	40% (99/249)[k]

n: number of patients with anti-adalimumab antibody; NR: not reported; NA: Not applicable (not performed)

[a] In patients receiving concomitant methotrexate (MTX), the incidence of anti-adalimumab antibody was 1% compared to 12% with HUMIRA monotherapy

[b] In patients receiving concomitant MTX, the incidence of anti-adalimumab antibody was 6% compared to 26% with HUMIRA monotherapy

[c] This patient received concomitant MTX

[d] In patients receiving concomitant MTX, the incidence of antibody development was 7% compared to 1% in RA

[e] Subjects enrolled after completing 2 previous studies of 24 weeks or 12 weeks of treatments.

[f] In plaque psoriasis 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

[g] One 12-week Phase 2 study and one 52-week Phase 3 study

[h] Among subjects in the 2 Phase 3 studies 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)

[i] No apparent association between antibody development and safety was observed. The association of antibody development and efficacy outcome was not assessed due to limited number of subjects in each treatment group stratified by anti-adalimumab antibody titer.

[j] No apparent association between antibody development and safety was observed

[k] No correlation of antibody development to safety or efficacy outcomes was observed

Rheumatoid Arthritis and Psoriatic Arthritis: Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab using the ELISA during the 6- to 12-month period. 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.

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 observed 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 concentrations 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 concentration of adalimumab was higher than the maternal serum concentration, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum concentrations 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 concentration. 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

The safety and effectiveness of HUMIRA have been established for:

- reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 2 years of age and older.
- the treatment of moderately to severely active Crohn's disease in pediatric patients 6 years of age and older.
- the treatment of moderately to severely active ulcerative colitis in pediatric patients 5 years of age and older.
- the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.
- the treatment of non-infectious intermediate, posterior, and panuveitis in pediatric patients 2 years of age and older.

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 concentrations 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 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]*.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with JIA less than 2 years of age.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for the treatment of moderately to severely active Crohn's disease have been established in pediatric patients 6 years of age and older. Use of HUMIRA for this indication is supported by evidence from adequate and well-controlled studies in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose concentrations of HUMIRA in 192 pediatric patients (6 years to 17 years of age) *[see Adverse Reactions]*. The adverse reaction profile in patients 6 years to 17 years of age was similar to adults.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with Crohn's disease less than 6 years of age.

Pediatric Ulcerative Colitis

The safety and effectiveness of HUMIRA for the treatment of moderately to severely active ulcerative colitis have been established in pediatric patients 5 years of age and older. Use of HUMIRA for this indication is supported by evidence from adequate and well-controlled studies in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose concentrations of HUMIRA in 93 pediatric patients (5 years to 17 years of age) *[see Adverse Reactions]*. The adverse reaction profile in patients 5 years to 17 years of age was similar to adults.

The effectiveness of HUMIRA has not been established in patients who have lost response or were intolerant to TNF blockers.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with ulcerative colitis less than 5 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 have 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 dosage in pediatric patients 12 years of age or older is based on body weight.

The safety and effectiveness of HUMIRA have 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 65 years of age and older was higher than for those less than 65 years of age. Consider the benefits and risks of HUMIRA in patients 65 years of age and older. In patients treated with HUMIRA, closely monitor for the development of infection or malignancy *[see Warnings and Precautions]*.

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

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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 *[see Warnings and Precautions]*.

Malignancies

Counsel patients about the risk of malignancies while receiving HUMIRA *[see Warnings and Precautions]*

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe hypersensitivity 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 *[see Warnings and Precautions]*.

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 *[see Warnings and Precautions]*.

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Remembering Michael J. Hennessy Sr

***DERMATOLOGY TIMES*® MOURNS THE** passing of Michael J. Hennessy Sr, chairman and CEO of MJH Life Sciences™.

Hennessy was committed to improving health care and patients' lives, as is seen throughout his career. Following his graduation from Rider University in 1982, he started his journey in medical publishing as a sales trainee, eventually advancing to the position of chief operating officer. In 1986, Hennessy became chief operating officer of Medical World Business Press. The company prospered and was eventually sold to a Boston-based venture capital firm.

Hennessy launched MultiMedia Healthcare, LLC, in 1993 and built a portfolio of award-winning clinical journals. In 2001, Freedom Communications, Inc, acquired MultiMedia HealthCare, about the time that Hennessy was pioneering a new approach to print and digital publishing with Intellisphere®, LLC (now part of MJH Life Sciences™). Guided by the principles of innovation and entrepreneurial spirit and reflecting its founder's dedication to improving quality-of-life through health care research and education, Intellisphere publishes a variety of integrated print and digital products on a range of topics in research and clinical medicine.

To build a comprehensive multimedia and education platform, Hennessy added other companies and capabilities to the MJH Life Sciences™ portfolio, including health care market research leader HRA®, respected journals *Pharmacy Times*® and *The American Journal of Managed Care*®, and the leading accredited continuing medical education company Physicians' Education Resource®, LLC (PER®).

In 2019, MJH Life Sciences™ made its largest acquisition to date with the Healthcare and Industry Sciences divisions of UBM Medica, nearly doubling the size of the organization and adding legacy titles such as *Dermatology Times*® to an already impressive portfolio. This acquisition made the organization the largest independently owned medical communications company in North America.

In late 2019, Hennessy elevated his role to Chairman while naming his son, Mike Hennessy Jr, to assume the leadership role of the organization and carry on the family legacy. Under Mike Jr's leadership, the company enhanced its global potential by entering into a long-term partnership with BDT Capital Partners, LLC, in November 2021.

Due to his broad business and educational experience, Hennessy's counsel and insight had been sought out by several organizations, including his alma mater Rider University, where he served on the Board of Trustees and was elected to the executive committee. He also had a long record of service at the local level, where he was a strong advocate for veterans and environmental issues.

Hennessy's true passion was his relationship with his wife, Patrice "Patti" Hennessy. After meeting her in college, Hennessy devoted his life to Patti and his family, raising 4 children. Hennessy was Patti's rock as she bravely battled cancer for almost 10 years until her death in January 2020. Hennessy recently honored Patti by making a donation to Rider University to expand the Science and Technology Center at their alma mater. The Mike and Patti Hennessy Science and Technology Center is set to be completed in 2022.

Hennessy's legacy and "family first" mantra will live on through his children, their spouses, and his 10 grandchildren. He will be greatly missed by his family, friends, and his MJH Life Sciences™ family. ◀

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HIPAA Violation, COVID-19 and the Lawsuit

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.

Dr Corona has a large dermatology practice. He also regularly performs studies on new treatments for a variety of dermatoses. Because he has been doing this research for more than 10 years, he has accumulated both demographic and physical data on thousands of patients. All these data are stored in his Health Insurance Portability and Accountability Act (HIPAA)–compliant electronic medical record (EMR) system.

A pharmaceutical company that wants to work with him on COVID-19–related dermatoses contacts his research nurse and asks for a copy of all this electronic data since the pandemic started in March 2020, which would allow them to develop better treatments for unusual dermatoses. Trying to be helpful, the nurse gives them the data.

One of Corona's other employees finds out about this transfer of data. She tells some friends, one of whom is a former research patient in Corona's office, about what has occurred. This patient is furious about the disclosure of her medical data and hires an attorney, who reaches out to Corona. He tells Corona that he will sue him for a HIPAA violation unless Corona settles with his client for $100,000. Should Corona settle this case and pay the $100,000?

EMR is clearly here to stay. Despite all the benefits, EMR use also has introduced a number of problems—most important, perhaps, potential privacy breaches associated with electronic record and data storage. As more personal information, such as school records, credit card information, and bank account data, goes online and is stored electronically, people seem to have become accustomed to accepting the associated risks, especially in view of the convenience and other benefits that these data offer.

Although breaches of other personal data are intrusive and potentially harmful, medical records contain possibly the most private and personal information and therefore are subject to unique privacy and security concerns. For example, a breach of a customer's banking records might cause temporary inconveniences, but credit cards can easily be cancelled and bank accounts can quickly be frozen. However, once private medical information is breached, it is nearly impossible to mitigate the potential harm.

In light of these concerns, Congress passed HIPAA more than 20 years ago. Under this act, the US Department of Health & Human Services (HHS) has the authority to adopt standards for HIPAA-specified entities to follow in protecting, using, and disclosing patients' medical information and records. There are specific obligations of medical practices regarding the safekeeping and privacy of protected health information. The Privacy Rule defines protected health information as medical information that is "individually identifiable" as pertaining to a specific patient. Individually identifiable information includes health information that (1) is maintained in any form or medium; (2) relates to, identifies, or could identify the person that the health information concerns; and (3) is transmitted or maintained by a covered entity.

The Privacy Rule covers, for example, what a patient's doctors, nurses, and other health care providers put in their medical record conversations a doctor has with nurses and others about a patient's care or treatment; information about a patient from a health insurer's computer system; billing information about a patient at his/her office; and most other health information about a patient that is held by covered entities.

If patients believe that their privacy was breached under HIPAA requirements, they have the right to file a complaint with their health care provider or health insurer or directly with the United States government. They cannot, however, sue covered entities that commit HIPAA privacy violations. Instead, HHS and the Department of Justice have enforcement authority for HIPAA privacy complaints. After receiving patient complaints, HHS may then investigate and initiate civil administrative proceedings, if warranted.

Notably, the penalties for breaches of the Privacy Rule are relatively light. If HHS investigates a complaint, the matter goes through full administrative proceedings, and violations are found, the violators may be assessed civil penalties of between $100 and $50,000 per violation.

Even if a violation is found, HHS has the authority to waive the civil penalty. However, HIPAA also contains a criminal liability provision that outlaws the knowing disclosure or acquisition of individually identifiable health information in violation of the statute and the Privacy Rule. In reality, the rule itself has gone largely unused since taking effect.

Corona's nurse has committed a HIPAA violation. He should have a risk management team review HIPAA privacy rules with his staff, and he should discuss with his attorney how to settle the case. ◀

> *"Once private medical information is breached, it is nearly impossible to mitigate the potential harm."*

Understanding Cosmetic Claims

by **ZOE DIANA DRAELOS, MD**

Draelos is an adjunct assistant professor of dermatology at Duke University School of Medicine in Durham, North Carolina, and chief medical editor of Dermatology Times®.

Q What does it mean when advertising says: "98% of users agreed product X reduced the appearance of wrinkles in 48 hours"?

Ninety-eight percent agreement that product X "reduced the appearance of wrinkles in 48 hours" is an amazing claim, given that 98% of people may not agree the sky is blue. How exactly are these extraordinary claims constructed and supported? Through a statistical manipulation known as the top box/bottom box analysis.

Top box/bottom box is a commonly used analytical technique when constructing agreement or disagreement claims. The technique involves crafting a number of statements that represent the desired claim. For example, in this case, the statement might read: "The product reduced the appearance of my wrinkles in 48 hours." The subjects are then presented with a 9-point scale over which to grade their agreement or disagreement with the statement, with 1 representing "strongly agree" and 9 representing "strongly disagree." The top box is defined as a rating of 1, 2, or 3 representing agreement. The middle box is defined as a rating of 4, 5, or 6 representing "neither agree or disagree," and the bottom box is defined as a rating of 7, 8, or 9 representing disagreement. The number of subjects who rated the statement a 1, 2, or 3 is determined as a percentage of all subjects who responded to the statement and the claim is supported. In this case, it was 98%.

Does this claim mean that the wrinkles were gone? No. The claim states that the appearance of wrinkles was reduced, not that the wrinkle was somehow physically modified. Basically, the subjects thought the wrinkles looked better. How much better? This is unknown. We only know that in their opinion, the wrinkles were reduced. What constitutes reduction? This is opinion only. Why does this refer to the appearance reduction at 48 hours? This is because the question was asked of the subjects 48 hours after product application.

In summary, what exactly does this claim mean from a dermatologic perspective? Nothing. We know that in the opinion of the subjects who participated in this consumer questionnaire, their wrinkles were reduced 48 hours after applying the product. We do not know how the participants were selected. We do not know what they were told or paid to take the questionnaire. We do not know how frequently they applied the product and for how long. We do not know what other variables might have influenced their evaluation. These claims are very powerful in the marketing world and grab my attention, even as a dermatologist. However, dermatologists must remove themselves from the consumer world and enter the medical world to understand the meaning of top box/bottom box substantiated claims.

> *"What does 'sensitive skin' mean? Nothing. Sensitive skin is a term that defies medical definition. It is purely marketing jargon that means something to consumers looking to purchase skin care products from a crowded shelf."*

Q What does the claim "appropriate for sensitive skin" imply medically?

"Sensitive skin" is an important claim for dermatologists, as most of the patients we treat in the office by definition have sensitive skin because they have skin disease. Most skin disease is characterized by barrier dysfunction to a greater or lesser degree, and restoring the skin to health requires improving the skin barrier. Can dermatologists therefore assume that products labeled "appropriate for sensitive skin" can be recommended to their patients without concern? No.

What does "sensitive skin" mean? Nothing. *Sensitive skin* is a term that defies medical definition. It is purely marketing jargon that means something to consumers looking to purchase skin care products from a crowded shelf. This becomes apparent when you understand how sensitive-skin testing panels are constructed.

Most companies perform human repeat insult patch testing (HRIPT) on their products prior to sale to be sure there are no contact dermatitis problems. This test is conducted by placing a patch containing the test product on the backs of volunteers, usually recruited from college campuses, who would like to earn some extra money. The patches are changed 3 times weekly for around 3 weeks, and any reaction to the product is recorded. The problem is that most of the volunteers are young and healthy, without skin disease. As you might imagine, over the time the people who have problems with the patches no longer volunteer, you select for HRIPT participants who have robust unreactive skin. Some companies use their HRIPT testing to substantiate sensitive skin claims. Although this type of testing is valuable to detect problems, you cannot necessarily say the product is appropriate for sensitive skin when it was not tested in sensitive skin.

Another way of substantiating sensitive-skin claims is to recruit subjects with self-perceived sensitive skin. What does this mean? This means you ask recruits if they have "sensitive skin," and if they say yes, you enroll them in your sensitive-skin panel and ask them to use your product and provide feedback. Although this type of questioning may produce a good panel for evaluating the marketing agreement/disagreement statements discussed previously, it will not produce a dermatologically relevant panel for true sensitive-skin testing. In my opinion, sensitive-skin products must be tested on subjects with eczema, atopic dermatitis, rosacea, psoriasis, and frequent irritant contact dermatitis. In other words, sensitive-skin testing should be performed on the population to whom the dermatologist will recommend these products.

Fortunately, there is now interest in this type of more rigorous testing, and many companies are stepping up to the challenge. In the future, the wording *appropriate for sensitive skin* may have more medical meaning. ◀

ITCH-SCRATCH-
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THE ONE-OF-A-KIND
TOPICAL JAK INHIBITOR

NEW for uncontrolled, mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥12 years[1]

> **Clear or almost clear skin** (IGA 0/1)* in >50% of patients at week 8 (53.8% vs 15.1% and 51.3% vs 7.6% vehicle†; *P*<0.0001)[1,2]

> **Meaningful itch relief** (Itch NRS4) in >50% of patients at week 8 (52.2% vs 15.4% and 50.7% vs 16.3% vehicle†; *P*<0.0001)[1,2‡]

– **Itch NRS4 response seen as early as day 3** (18.4% OPZELURA vs 4.2% vehicle and 13.2% OPZELURA vs 0% vehicle†)[3]

OPZELURA was studied in 1249 adult and adolescent patients ≥12 years of age in 2 identically designed double-blind, randomized, vehicle-controlled trials (TRuE-AD1 and TRuE-AD2). In both studies, patients had an affected BSA of 3%-20% and an IGA score of 2 or 3 on a severity scale of 0-4. Patients were randomized to monotherapy with OPZELURA or vehicle BID for 8 weeks.[1,2]

*With a ≥2-grade improvement from baseline.[1]

†In TRuE-AD1 and TRuE-AD2, respectively.[1,2]

‡≥4-point improvement in NRS among patients with a score of ≥4 at baseline.[1]

BID=twice daily; BSA=body surface area; IGA=Investigator's Global Assessment; JAK=Janus kinase; NRS=numeric rating scale.

Discover the difference at OpzeluraHCP.com

Incyte Dermatology

INDICATION

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use:

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections.

If a serious infection develops, interrupt OPZELURA until the infection is controlled. Carefully consider the benefits and risks of treatment prior to initiating OPZELURA in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA.

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Please see additional Important Safety Information on following page.

Please see Brief Summary of Full Prescribing Information on following pages.

Opzelura™
(ruxolitinib) cream 1.5%

IMPORTANT SAFETY INFORMATION for OPZELURA™ (ruxolitinib) cream 1.5% (continued)

SERIOUS INFECTIONS (continued)

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

MORTALITY

Higher rate of all-cause mortality, including sudden cardiovascular death, has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.

Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia

Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Adverse Reactions

The most common adverse reactions (≥1%) are nasopharyngitis (3%), diarrhea (1%), bronchitis (1%), ear infection (1%), eosinophil count increased (1%), urticaria (1%), folliculitis (1%), tonsillitis (1%), and rhinorrhea (1%).

Pregnancy

There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 855-4MEDINFO or 855-463-3463.

Lactation

Advise women not to breastfeed during treatment with OPZELURA and for four weeks after the last dose (approximately 5 elimination half-lives).

Please see Brief Summary of Full Prescribing Information on following pages.

References: 1. Opzelura. Prescribing Information. Incyte Corporation; 2021. **2.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol*. Published online May 3, 2021. doi:10.1016/j.jaad.2021.04.085. **3.** Data on file. Incyte Corporation. 2021.

Opzelura™
(ruxolitinib) cream 1.5%

OPZELURA™ (ruxolitinib) cream, for topical use

Brief Summary of FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use: Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions]*.

MORTALITY
Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

THROMBOSIS
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral janus kinase inhibitors. Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients: with chronic or recurrent infection; with a history of a serious or an opportunistic infection; who have been exposed to tuberculosis; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis: No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C: The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

Major Adverse Cardiovascular Events (MACE): Major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke were observed in clinical trials of Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

Thrombosis: Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to patients treated with placebo. Many of these adverse reactions were serious and some resulted in death. Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia: Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

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 two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Eosinophil count increased 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in Trials 1 and 2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted. Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong Inhibitors of CYP3A4: Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Risk Summary: Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data: Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD); the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure. In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

Lactation

Risk Summary: There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5 elimination half-lives).

Data: Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

Pediatric Use: The safety and effectiveness of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age with mild-to-moderate atopic dermatitis. Use of OPZELURA in this age group is supported by evidence from Trials 1 and 2 which included 92 subjects aged 12 to 17 years. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age have not been established.

Juvenile Animal Toxicity Data: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

Geriatric Use: Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between patients less than 65 years and patients 65 years and older.

PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections: Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection. Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious.

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA.

Major Adverse Cardiovascular Events: Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis: Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

Thrombocytopenia, Anemia and Neutropenia: Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia or neutropenia *[see Warnings and Precautions]*.

Administration Instructions: Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration]*.

Advise patients to limit treatment to 60 grams per week.

Pregnancy: Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 *[see Use in Specific Populations]*.

Lactation: Advise a patient not to breastfeed during treatment with OPZELURA and for four weeks after the last dose *[see Use in Specific Populations]*.

Manufactured for:
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Quick TAKES

- The new 1726-nm wavelength is the first to target the sebaceous glands.
- The 1064-nm laser used in the microsecond domain does not affect pigment, so it can be used on all skin types.
- Photodynamic therapy offers an alternative to laser acne treatment, but adherence and phototoxicity may pose concerns.

Lasers Shine New Light on Acne Therapy

LINDA STOCUM | *Assistant Editor*

What advantages do lasers or energy-based devices (EBDs) have over topical, oral, and other acne treatments? David J. Goldberg, MD, JD, director of Skin Laser and Surgery Specialists of New York and New Jersey; past director of Mohs and Laser Research at Icahn School of Medicine at Mount Sinai in New York, New York; adjunct professor of law at Fordham University School of Law in New York City; and a member of the *Dermatology Times*® editorial advisory board, tackled this question during his presentation at the 11th annual New Frontiers in Cosmetic Medicine and Medical Dermatology symposium.[1]

Like prescription medications, lasers and EBDs have proved effective in treating acne, Goldberg said. However, these options may better suit the challenges of certain cases or individual patient preferences. An important factor for some patients and physicians, he noted, is that this technology reduces some problems with adherence—patients do not have to self-manage treatment on a daily or twice-daily basis. Because the physician performs the procedure, it is easier to track adherence and ensure optimal, standardized treatment delivery, he added.

Lasers and EBDs also provide alternatives for patients who may be concerned about adverse reactions related to systemic medications. The devices expand the menu of nonsystemic treatments for patients with acne who do not want to ingest oral medications or apply topical treatments, even those with lower absorption rates.

With lasers and EBDs, as with prescription medications, no individual tool meets every patient's needs. The most common types of lasers available are:

- Intense pulsed light;
- infrared;
- pulsed dye;
- potassium titanyl phosphate; and
- radiofrequency.

> "Light and the energy-based device acne treatments are areas that have improved and changed over the course of the last 2 decades. We're just beginning to enter a new era of exciting technology for these therapies."
>
> David J. Goldberg, MD, JD, *New York, New York*

The most used laser now, according to Goldberg, is the 1064-nm infrared laser. This device emits beams that are absorbed by the water in the sebaceous gland, which heats up, reducing sebum output. These lasers are used for hair removal in the millisecond domain, he continued, but affect acne in the microsecond domain. Because they are not absorbed by pigment, they are safe to use in all skin types and are nearly painless, he said.

Goldberg cited data from a 2020 study that enrolled 20 patients, placing 10 in an actively treated group and 10 in a sham group. The investigators aimed to examine the efficacy of the 650-microsecond, 1064-nm Nd:YAG laser. Each group received 3 treatments 2 weeks apart, plus an additional session 4 weeks after the third treatment. Among the 10 patients in the sham group, their condition either did not improve or worsened, whereas patients in the active group showed decreases in inflammatory and comedonal lesions, porphyrin count, and sebum production.[2]

Although the 1064 infrared laser is effective, he said, a new 1726-nm wavelength that is being evaluated shows promise. This is the first laser to target the sebaceous glands, according to Goldberg, who noted that data will be published soon. Photodynamic therapy expands the choices for some patients but can pose difficulties with adherence, pain level, and phototoxicity, he said.

"Laser and energy-based device acne treatments are areas that have improved and changed over the course of last 2 decades," Goldberg said. "We're just beginning to enter a new era of exciting technology for these therapies." ◀

Disclosures

Goldberg has received research grants from Aerolase; Cutera, Inc; and Sebacia, Inc.

References

1 Goldberg DJ. Laser treatment of acne: state of the art. new frontiers in cosmetic medicine & medical dermatology. Presented at: New Frontiers in Cosmetic Medicine and Medical Dermatology Symposium; November 12-14, 2021; Hasbrouck Heights, New Jersey, and virtual.

2 Kesty K, Goldberg DJ. 650 usec 1064nm Nd:YAG laser treatment of acne: a double-blind randomized control study. *J Cosmet Dermatol*. 2020;19(9):2295-2300. doi:10.1111/jocd.13480

Quick **TAKES**

- Children should be patted dry after bathing, but not completely, to optimize moisturizers' effectiveness.
- Emollients should be applied within 3 to 5 minutes of bathing to maximize water trapping.
- Look for moisturizers that contain ceramides.

Role of Emollients, Moisturizers in Eczema Treatment

LINDA STOCUM|*Assistant Editor*

Adelaide Hebert, MD, recently gave *Dermatology Times*® an overview of the eczema landscape which is based on her 37 years as chief of pediatric dermatology at McGovern Medical School at The University of Texas Health Science Center at Houston.

Q: How are emollients and moisturizers different? How do they work together to treat eczema?

I think of emollients and moisturizers as being identical. They are so critical in restoring the barrier. They're the fundamental cornerstone of all the guidelines currently available for atopic dermatitis [AD] management, [and] we really need to employ these. When children or families are impoverished, we can suggest agents that are found in the grocery store where they can use food stamps.

We tend to use whatever will restore that barrier. It may not be optimized care, but even the most impoverished patient in general can afford something in the realm of in the emollient/ moisturizer. I place special emphasis on those moisturizers that contain ceramides, because, in my experience, they have given me the best results for the patients for whom I provide care.

Q: What are some key counseling points regarding emollient and moisturizers?

Most importantly, find one that the child will tolerate. I'll generally recommend 2 or 3. In our clinic, we are allowed to provide samples, which I think is beneficial because a parent, before they spend any money, can try a sample on a child to see what they tolerate.

Sometimes it's a matter of personal preference. How does that emollient feel on the skin? How easy is it for the parent to apply that agent? We have broken skin [and] we know that skin creams which come in tubs are both cost effective and effective in repairing the barrier, but they are thicker. They're a little more work for the parents to apply. Sometimes the child will become fretful and won't tolerate that degree of rubbing over the time period required to get it to go into the skin.

Some emollients come as sprays. Some emollients come as foams and sometimes those are more tolerated by any individual patient. I'm not rigid in what the parent and the patient will use, as long as they put a moisturizer on at least twice a day because this makes such a difference. It's surprising if parents come in, and they haven't had that fundamental education, and giving them the right guidance, and the right product, can make a marked difference in the child's care.

I do try to avoid lotions, because they contain more water, and they can dry the skin out. If a lotion seems to be what the patient is tolerating and the skin regimen is going well again, I'm flexible, and try to allow them to use what they are most comfortable with. All these things come into play the affordability of the product [and] the ability to access it readily. We want the parents to be able to use the regiments that we outlined for them, and not make it so complicated, that it's difficult to adhere to and difficult to do daily.

Q: What does your office recommend for patients when it comes to over the counter products?

We use almost every product available in the over-the-counter space. We like the Eucerin Eczema Care. We use all the CeraVe products, those are easy to find and readily available. We also have patients who will use Cetaphil Restoraderm. We have some who prefer the Gold Bond products.

There are indeed many more products that contain ceramides that I haven't mentioned. We tend to have samples of these parents will often recognize these brand names, and they feel very comfortable with them. Sometimes patients are using a product that's good but doesn't get in their ceramides. We will ask them the next time they make a purchase to consider getting the agent that contains the ceramides as we think it will enhance the regimen that they're already conducting for their child.

Q: When should a health care professional refer to a dermatologist for more aggressive therapies?

Well, we like to treat eczema when it's not too profound. Obviously, if the primary care physician or the nurse practitioner [NP] is not comfortable and the child is not getting better, is having recurrent infections, is not sleeping or growing, or if that eczema seems in any way to not be able to be brought under control, we're happy to see those patients in our clinic.

I think virtually every dermatologist who cares for AD is well versed in both what current therapies are available and we have some emerging therapies that are extremely exciting. We are very blessed in the atopic realm that some new therapies have allowed us to bring many of these patients under better control, particularly if they're age 6 and older. Currently, I'm certainly conducting research on some oral medications in the JAK inhibitor class that I think will be a great improvement in our armamentarium. Again, many patients don't like to take shots and prefer pills, but we really must design a therapy that's going to be available for the patient while tolerated by the patient, of course covered by their insurance plan. ◀

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Quick **TAKES**

- Itch is the top complaint of patients with psoriasis.
- Treatment advances have tended to focus on achieving clear or almost clear skin.
- Inhibiting the phosphodiesterase 4 pathway shows promise for improving skin clearance and reducing itch.

Impact of Itch Sparks New Pipeline Direction

Skin sensitivity will be a factor in vehicles for new treatments.

MARY SCOVIAK | *Managing Editor*

The next wave of advances in topical therapies that treat psoriasis will focus not only on efficacy in achieving clear or almost clear skin but also on patients' top symptomatic complaint: chronic itch, said April Armstrong, MD, for a non-medical continuing education session supported by Arcutis Biotherapeutics and held October 23, 2021, at the 2021 Fall Clinical Dermatology Conference in Las Vegas, Nevada.[1,2]

Itch is an expected part of any physician-patient discussion about atopic dermatitis (AD) and should be for consultations about psoriasis as well, said Armstrong, who is a professor of dermatology (clinical scholar) and associate dean of clinical research in the Department of Dermatology at the Keck School of Medicine of the University of Southern California in Los Angeles.

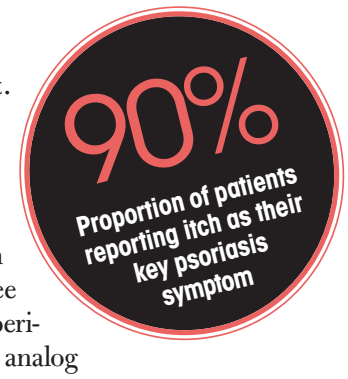
"For a long time, even some clinicians considered psoriasis a nonpruritic dermatosis. But patients—especially those with severe disease—tell us that itching is quite, quite bothersome," she said. "In fact, studies show that itch is the most burdensome and commonly reported symptom of psoriasis. Nearly 90% of patients reported itch as the key symptom in their disease."[1,2]

Armstrong recommended that physicians broaden the patient conversation beyond body surface area to include detailed questions on itch. "It's very important to ask patients about itch, including where they experience it," she advised. "Based on my experience, what's fascinating is that patients itch in their lesional areas but, importantly, also in their nonlesional skin. And that really tells us a few things."

She pointed to lines of evidence supporting the premise that the nonlesional skin of both patients with psoriasis and those with AD may not be normal and has the potential to flare up. "Oftentimes, there is a low level of immune hyperactivity as well as an increased number of neuropeptides in the area that mediate itch," Armstrong said. "So again, while we typically associate lesional skin with itch, we know that nonlesional skin can itch as well."

Numerous studies have demonstrated that itch has a ripple effect on quality-of-life and overall health, Armstrong noted. "As physicians, we need to talk to patients and their families about sleep disturbance relating to itch," she said. "In sleep studies that use nighttime videos, we see that in many cases, the patients unconsciously scratch throughout the night. In other cases, itch can relate to insomnia. It can create problems with falling asleep. Even when patients do sleep, the quality of sleep diminishes because the duration of time that they actually spend in the REM cycle is significantly reduced, so they feel overly tired or sleepy. Oftentimes, that can lead to poor performance during the day at work or school."

Armstrong recommended use of an itch scale to assess patient perceptions of severity. She prefers the 3 types commonly featured in clinical trials: The numeric scale, with ratings from 0 (no symptoms) to 10 (worst case possible), is the most widely used test. Armstrong also likes the verbal rating scale for use in the clinical setting—patients can describe the degree of itch they are experiencing. The visual analog scale, which presents patients with a line on which they mark an X where their itch ranks, is declining in popularity. "Technically, to do it correctly, you're supposed to use a ruler to measure the distance from the beginning to the end of the line. Who carries a ruler these days?" she commented.



Patient input also can aid in identifying the most effective treatment regimen. "For example, when assessing histaminergic itch vs nonhistaminergic itch, patients often notice that there's more description of burning, prickling, and stinging associated with nonhistaminergic itch. The quality of itch matters," Armstrong said

SOLUTIONS BEYOND STEROIDS

Under-recognition of the impact of itch has not just frustrated patients, it also has contributed to a gap in the development of treatment options. Although new medications have produced significant advances in reducing redness and scaling, leading to clear or almost clear skin for many patients, the pipeline for therapies that aim to address itch has been narrow, according to Arm-

“The challenge with regards to the development of topical therapies is really focused on a treatment that is effective not only in terms of decreasing the signs, the redness, and the scaling of psoriasis as well as reducing itch but also is formulated such that it has a minimal degree of sensitization for the skin itself.”

April Armstrong, MD, *Los Angeles, California*

strong. Topical steroids remain the No. 1 choice for treating plaque psoriasis, she said. “This drug class has proved to be effective in treating erythema and scaling,” she added. “Topical steroids also can reduce itch, although oftentimes that reduction is partial or not complete.”

Formulation is key in Armstrong’s view. Penetration enhancers such as propylene glycol significantly help move an active drug molecule into the skin. “The problem is that these penetration enhancers frequently can lead to skin irritation in some patients,” she said. Surfactants used for emulsification can also cause irritation and burning, according to Armstrong.

“So, the challenge with regards to the development of topical therapies is really focused on a treatment that is effective not only in terms of decreasing the signs, the redness, and the scaling of psoriasis as well as reducing itch but also is formulated such that it has a minimal degree of sensitization for the skin itself,” she said. “Itch, therapeutic targets for itch, and the therapies themselves have been really active areas of development lately.”

MOVING FORWARD FROM ANTIHISTAMINES

“When we as dermatologists think about itch, we typically think about histaminergic itch, so most of therapies targeted against itch are antihistamines,” Armstrong said. “That particular paradigm is quite valid when we’re thinking about chronic spontaneous urticaria, for example. However, when we’re thinking about conditions such as psoriasis and [AD], our clinical practice informs us that antihistamines do not work very well…to treat severe itch in our patients.”

There is hope on the horizon, she noted. The explosion of pipeline drugs aimed at AD has led to psoriasis treatments that offer solutions for itch. However, Armstrong cautioned against seeing these breakthroughs as panacea: “I want to highlight the fact that [AD] and psoriasis have different immunological pathways as their main drivers and that the quality of itch associated with each can be quite different.”[3,4]

In terms of AD, Armstrong said some of the mediators implicated in itch include IL-4, IL-13, IL-31, and—importantly—phosphodiesterase 4 (PDE4), as well as the JAK/STAT pathway. TSLP protein also has been connected with the pathogenesis or at least involvement of itch in AD.

“For psoriasis, some of the players are the same, but there are different ones as well,” she pointed out. “For example, PDE4 is one of the commonly shared mediators for itch. However, for psoriasis, we also see a bit greater involvement in the NK-1 receptor as well as *TRK4*.”

Turning to neurotrophic and neuronal factors related to AD and psoriasis, Armstrong discussed how the sensory nervous system mediates flow transmission of some of the fibers that play a role in the itch-scratch cycle.

External events such as trauma or infection also can trigger itch. Cytokine receptor signaling leads to the release of alarmins from keratin sites to alert the brain that something is happening, she said. “They can then go to the receptors on our nerves in the skin and bind to the receptors, resulting in transmission of the signal to our dorsal root ganglion in the brain as itching. So, as you can see here, PDE4 can be involved in the initial stage in terms of the reception of the danger signal. That’s 1 pathway.”

Immune cells provide another pathway. Although the helper T cell (T_H) 2 pathway is involved with AD and much of that particular signal transmission, PDE4 also plays a big role with regard to the transcription of downstream factors, such as IL-4, IL-13, and IL-31, which ultimately bind to the receptors on the neurons, Armstrong said. In her view, these combined factors point to PDE4 inhibitors as a pipeline drug class to watch. (On October 4, 2021, Arcutis Biotherapeutics a submitted a new drug application to the FDA for its topical PDE4 inhibitor, roflumilast cream [ARQ-151], for the treatment of mild to severe plaque psoriasis and AD. If approved, it would be the first topical PDE4 inhibitor for plaque psoriasis.[5])

“Potentially, the next generation of PDE4 inhibitors will really reduce the symptoms but be nonirritating. That’s something already being worked on,” she said. “The immune cells involving psoriasis are different [from those in AD]. Predominantly, we’re talking about T_H17 cells and some T_H1 cells. At least in part, these cells, through that PDE4 signaling, can go to stimulate the cutaneous nerves and then translate that into what we perceive as itch. The mediators and receptors overexpress psoriasis.

“We still have a lot to learn about itch, and there’s a lot unknown about this,” Armstrong concluded. “Our therapeutic targets are looking at these various mechanisms pretty closely. We also have room for therapies that offer patients vehicles that are nonirritating and that effectively treat all their symptoms as well as signs of disease. We need to use itch scales and track psoriasis’ impact on quality-of-life. And we need to offer patients support, especially kids who are very itchy. They can be quite miserable, so making sure that they have support with their family and that they’re connected with us as well as their pediatricians or mental health experts would be very helpful.” ◀

Disclosures

Armstrong is research investigator and/or scientific adviser to AbbVie, Almirall, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant Sciences, Dermira, Eli Lilly and Company, EPI Health, Incyte, Janssen, LEO Pharma, ModMed, Nimbus Therapeutics, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB. “Innovations in Topical Therapy: The Role of Vehicle in Treatment Decisions” was supported by Arcutis Biotherapeutics.

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Quick TAKES

- Patients treated with TNF blockers could see a dramatic reduction in cardiovascular disease.
- IL-23 blockers can be given less frequently, an injection every 2 or 3 months.
- The International Psoriasis Council put out a paper in 2021 recommending a change in severity classification.

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Top Tips for Managing Plaque Psoriasis

Experts explore the fine points of strategies to address this challenging condition in *Dermatology Times*®' *Around the Practice* series exclusively on dermatologytimes.com.

DermatologyTimes Around the PRACTICE

MARY SCOVIAK | *Managing Editor*

Dermatology Times® recently brought together a panel of experts to share unique insights on the nature of plaque psoriasis, how to make a more accurate and effective diagnoses, how to develop a more effective treatment plan, and how to choose which drugs would benefit which patients most.

Providing guidance on perspectives in plaque psoriasis management for 2 exclusive *Around the Practice* video sessions were: moderator Christopher Bunick (CB), MD, PhD, associate professor of dermatology, physician scientist at Yale University's Department of Dermatology in New Haven, Connecticut, and a member of *Dermatology Times*®' editorial advisory board, and panelists: Mark Lebwohl (ML), dean for clinical therapeutics at the Kimberly and Eric J. Waldman Department of Dermatology at the Icahn School of Medicine at Mount Sinai in New York, New York, and a member of *Dermatology Times*® editorial advisory board; Jashin Wu (JW), MD, founder and course director of the San Diego Dermatology Symposium, the Dermatology Refresher Symposium for Nurse Practitioners and Physician Assistants, the Skin Cancer Symposium and Symposium for Inflammatory Skin Disease, and the Dermatology Innovation Symposium; and Helen Torok (HT), MD, medical director of the Trillium Creek Dermatology Center in Medina, Ohio, and a *Dermatology Times*® editorial advisory board member.

Here are the key takeaways for improving patient outcomes.

ML: It appears that the inflammatory cytokines that are characteristic of plaque psoriasis also contribute to the development of psoriatic arthritis and cardiovascular disease, as well as a host of other systemic problems. In fact, there is very good evidence that started to emerge initially from registries around the world showing that patients treated with tumor necrosis factor [TNF] blockers ended up having a dramatic reduction in cardiovascular disease. Joel Gelfand first showed that myocardial infarctions were increased in patients with severe psoriasis more than a decade ago in a landmark article that was published in the *Journal of the American Medical Association* [JAMA].

Subsequently, data from registries showed as much as a 50% reduction in heart attacks in patients with psoriasis who had been treated with TNF blockers. Dr Wu, who is on our panel, also demonstrated similar findings in the Kaiser Permanente EMR. It was shown in several of the registries that other treatments like methotrexate also reduced cardiovascular disease, perhaps not as much but still they reduced cardiovascular disease. We don't have nearly as much registry data with the IL-17 blockers or IL-23 blockers because they are newer, but initial data emerging on the IL-17 blockers, which came out first, is showing some impact on cardiovascular disease. Some very good studies looked at atherosclerotic plaques in patients with psoriasis who had been treated with biologics and who had not been treated with biologics. In fact, there was a reduction in lipid-rich necrotic core and atherosclerotic plaques in patients on biologics, particularly those on IL-17 blockers.

CB: So, Dr Lebwohl, with this important information on cardiovascular disease in patients with psoriasis, does this impact how dermatologists and other physicians should actually be treating psoriasis patients?

ML: Well, I would say 1 of the first questions we ask patients who come to us is, "Do you have any joint pains?" If the answer is yes or it looks like they may have psoriatic arthritis… that should influence the selection of biologic therapy. I would be more inclined to go to, for example, with an IL-17 blocker or a TNF blocker in patients with psoriatic arthritis.

CB: You've mentioned TNF-alpha, IL-17, and IL-23. If you could, just take a moment and review some of the pathophysiology behind these cytokines and how they're connected with being treatment targets in psoriasis.

ML: TNF blockers are a bit more broadly immunosuppressive, and I don't usually go to TNF blockers first anymore because they have [black] box warnings. There is probably a small increase in malignancies and infections in patients on those drugs, not on the IL-17 blockers, with the exception of candidal infections, which are pretty minor and are not increased with the IL-23 blockers.

Having said that, the way IL-23 works is it causes upregulation of Th17 cells to make IL-17. And IL-17 is the key cytokine in the development of psoriasis. So, if you block IL-23, you indirectly block IL-17. What's more is that when you block IL-23, the Th17 cells either die or hibernate. They seem to wither away. So, once you stop an IL-23 blocker, it takes a while for the body to reconstitute those Th17 cells, and I believe that is why we see prolonged remissions after using IL-23 blockers. Of note, they can be given less frequently, so they are injected every 2 or 3 months but they're a little

Image courtesy of *Dermatology Times*®

slower than IL-17 blockers.

When you block IL-17, you're blocking the cytokine that is immediately responsible for the development of psoriasis. By blocking it, you get a very rapid response. Having said that, at least for the IL-17A blockers, which are secukinumab, and ixekizumab, the psoriasis seems to come back a little more frequently. They have to be injected at least once a month to maintain their response. Of note, the newest entry to the IL-17 family is a drug that blocks IL-17A and IL-17F. IL-17A is clearly a very potent inducer of psoriasis. IL-17F may not be as potent an inducer of psoriasis but it's more prevalent in psoriatic plaques. It seems that when you block both, you actually get an additive effect. The new IL-17A and IL-17F blocker, bimekizumab eventually is administered as infrequently as every 2 months. Not only is it fast but it also doesn't have to be given as often.

CB: Certainly, the IL-17A and F, the amount of each in the skin, and the amount of synergy between them is an important and interesting topic to discuss. Are you aware of any studies or is there any utility in actually combining or investigating an IL-23 and an IL-17 inhibitor?

ML: If I were going to combine agents, I don't think I would combine those 2, and I'm not aware of any studies combining them, I theoretically see a patient's psoriasis doing very well with IL-23 or IL-17 blockers and using IL-17 blockers for psoriatic arthritis. Now, guselkumab does have data that it is effective for psoriatic arthritis, so do the other IL-23 blockers as well— risankizumab and tildrakizumab. Guselkumab is approved already for psoriatic arthritis. But at least so far, the dose that is accepted today, which is every 8-week administration of 100 milligrams, looks like it might be as effective as the IL-17 blockers.

CB: Dr Wu, discuss for us a little bit about the not only clinical manifestations but a little bit about the progressive nature of psoriasis as a whole. Is there an importance of early diagnosis and treatment vs a later diagnosis and treatment? How do you see the progressive nature and start [seeing the] treatment impacting the actual clinical appearance of your patients?

JW: The clinical manifestations of psoriasis tends to be thick erythematous plaques, characteristically with a silvery scale on the elbows and knees. It can also be on the scalp. Those are probably the most common locations but [they] certainly can be outside of these areas as well. These patients, [may] scratch and have a little bit of bleeding where they're kind of picking off the silvery scale. [For] nail psoriasis, they can have nail pitting, patches, and onychomycosis like changes. Those are very common scenarios of the nails.

They can also have inverse psoriasis which is where the psoriasis is maybe a little bit less silvery, more of a macerated appearance. These would be in the armpit area, [or] the groin area. They can have pustular type psoriasis, so that could be generalized pustular psoriasis. That can be more of a medical emergency when they have almost whole-body psoriasis with pustules. They'll probably go to the [emergency department] and might have to be hospitalized. Then there's also the more localized palmar pustular psoriasis, usually on the palms and soles. That's a little bit more difficult variant to treat. They can also have erythrodermic psoriasis, again we have the whole body filled with psoriasis. Again, this could be more of a medical emergency.

[There is] also guttate psoriasis. These patients tend to be on the younger side. They have these teardrop-like lesions more on the trunk area. Usually, younger patients like children or adolescents, would have a strep throat infection first, in which case they could have the guttate flare. They could have it treated, or it will resolve on its own. But then if they have another strep throat infection, they can have another flare of guttate psoriasis. Here's 1 way where potentially you could prevent having future psoriasis. There are some studies that show that [if] they have a tonsillectomy, maybe that could potentially prevent the guttate psoriasis from becoming a plaque type psoriasis.

In terms of the progressive nature of the disease, certainly patients usually present with the skin disease first. On average, about 10 years later they can have the joint manifestations of psoriasis, psoriatic arthritis. With the skin manifestation, you can treat the disease. They may have some clearance and but there's no scarring per se. With psoriatic arthritis, that's different. If you don't treat the psoriatic arthritis, it can be slowly progressive and then form many deformities in their joints and they can really have loss of range of motions and severe issues. In general, it is definitely better to treat patients sooner rather than later. I actually advocate using a systemic agent if they have more severe disease.

CB: In your own practice, how often do you manage these patients with both plaque psoriasis and/or psoriatic arthritis with biologics by yourself vs actually bringing in a rheumatologist to help co-manage the patient?

JW: Generally speaking, if they have both severe psoriasis and psoriatic arthritis, I would manage it myself. I would typically put them on an IL-17 inhibitor or a TNF inhibitor, as Dr Lebwohl mentioned. However, if they have more mild disease of the skin but psoriatic arthritis, they may not necessarily qualify for one of these biologic agents based on the psoriasis itself. I may get rheumatology involved to see if they could be put on something other than a biologic first. But sometimes in those cases, the wait times for rheumatology is much longer than it is for dermatology, so I still may treat them with one of those agents myself.

CB: There's a lot of emphasis on body surface area, particularly documenting the psoriasis affected surface area in medical charting or notes in order to satisfy insurance companies that want a certain body surface area before they'll approve a biologic. I think that this personally may not be the right thing because you have some people that have scalp psoriasis and it's only localized on the scalp, and sometimes it can be very severe. I wanted your opinion on what you think about body surface area? What about these patients that have severe scalp psoriasis and quality-of-life [issues] psoriasis can have even in a very small body surface area affected?

JW: Traditionally, body surface area can be defined as less than 3% as mild disease, between 3% to 10% moderate disease, and then greater than 10% would be severe disease. For some patients I do feel that this is a reasonable way to characterize the severity of the disease but certainly not for all patients. As you mentioned, if they have really severe scalp disease, maybe that would be about 2% or 3% of the body. The International Psoriasis Council put out a paper in the last year or so where they did recommend changing the severity classification. Say they failed any topical agent, then they should be considered for any systemic agent at that point. They don't necessarily need to have a certain amount of body surface area per se. And really, if they have a poor quality of life or maybe they have that 1% but it's right in the middle of their face, that to me would be a reason they should get a systemic agent rather than purely topical agents. ◀

To watch the full *Around the Practice* video, visit **dermatologytime.com**

Quick **TAKES**

Multispectral imaging technology drives visualization of specific skin structures such as pigment distribution and vasculature.

High definition in close-up images shows subtle factors that otherwise may be difficult to see.

A cloud storage option for patient images takes the burden off the practice's server capacity and affords accessibility to review imagery and monitor lesion progression.

Digital Device Aids Skin Cancer Diagnostics

MARY SCOVIAK | *Managing Editor*

Skin cancer dermoscopy is getting a high-tech overhaul as the scope of innovation broadens from a singular focus on the stand-alone product to the development of a comprehensive medical, patient care, and workflow management platform. Next-generation launches such as the FDA-cleared Demetra (Barco) skin-imaging platform integrate advanced tools into a handheld device aimed at maximizing diagnostic and monitoring accuracy with the optimized accessibility of cloud storage and seamless flow of information into electronic health records (EHRs).

Leveraging that combined technology answers unmet needs on various fronts, Jodi E. Ganz, MD, told *Dermatology Times*®. She is managing partner of Olansky Dermatology & Aesthetics, with offices in Buckhead and Roswell, Georgia.

"Analog dermatoscopes pose some challenges in regard to skin cancer," Ganz said. One is that traditional devices generally use white light exclusively. Demetra signals a new direction for image capture with either white or multispectral light.

"Multispectral imaging lets me see a lot more of the architecture of the surface change," Ganz said. "It better reveals some subtler features of cell structure such as areas of higher relative concentration of pigment, such as melanin, and areas with a higher relative concentration of blood within the lesion. I wasn't seeing this with the naked eye and, sometimes, not even with my regular scope."

High-tech imaging systems such as Demetra add next-step functionality that not only captures more detailed visuals of the lesion and its cell structure but also provides access to analytical information to assess the patterns presented in the imaging. Rolled out in July 2021, Demetra's skin parameter maps (SPMs) can provide better insight into the inner structures of lesions. Driven by multispectral imaging technology, SPMs parse the dermatoscopic image into 3 individual maps showing pigment, blood, and scatter contrast.

Others center on imagery definition and accessibility, according to Ganz. "I never found a great way to capture the dermatoscopic images I was seeing with a traditional scope," she said. Ganz also cites problems with imaging multiple lesions in large skin areas such as the back and narrowly targeted sites such as fingernails and toenails, as well as parts of the body that are difficult to photograph clearly.

"I had no way to correlate the up close view of the lesion I was examining with a sharp enough image to make sure the pathologist would see what I saw on the other end," Ganz said

Nor was it easy to show patients detailed features of the lesion or cell structure to help them understand what those characteristics indicate in terms of being malignant or benign. "Because Demetra has a screen like a smartphone, I can show the patient exactly what I'm seeing in the exam," Ganz said. "If it is as simple as a keratosis, I can use the image and information it offers to reassure the patient. However, if a cell is suspicious, I can explain exactly why I recommend a biopsy of that lesion. I find patients are much more willing to have the biopsy after seeing the risk indicators."

Digital dermatoscopes allow dermatologists to appreciate changes in lesions using the comparison and lesion mapping features. Also, retaking the image at a follow-up visit is easily accomplished by lining up the original lesion with the saved ghost image from the original image.

"To me, as a dermatologist, the issue with dermoscopy is related to having a reputable dermatoscope and to the skill level of being able to 'read' and analyze what is seen within the skin with that particular instrument. They must become proficient in understanding the meanings of what is being seen at the skin surface," said Michael Gold, MD, founder of Gold Skin Care Center, Advanced Aesthetics Medical Spa, The Laser & Rejuvenation Center, and Tennessee Clinical Research Center, all in Nashville.

The technology involved in creating advanced digital devices transforms diagnostic equipment from an offline aid to the dermatologist to one that allows practice managers to facilitate information gathering and storage. "With an analog system, there is no integration [with other systems in the practice] other than verbal notes from the clinician," said Trent Renta, practice manager at Olansky Dermatology & Aesthetics, with offices in Buckhead and Roswell, Georgia. "With these new devices, images are taken and automatically uploaded to both the device's EHR and integrated with our practice's EHR software, where that information is stored as a record of the patient's entire history." By automating part of the process of image and information collection, the devices streamline practice workflows, allowing the team to spend less time inputting information into patients' EHRs.

Having access to that information also benefits patients. By, in some cases, being able to correctly diagnose a lesion as benign, dermatologists may be able to help patients avoid unneeded biopsies and reassure them that mapping and following the lesion is the correct course, according to Gold.

Ganz outlined the opposite scenario: that of a patient who already had some melanomas and then presented with a large pigmented lesion on her face. Understandably, she did not want it biopsied unless necessary, and Ganz had been monitoring the lesion with measurements and photographs. Using an advanced digital imaging tool, though, Ganz saw pigment variation that posed a concern. When shown the image, the patient agreed that it needed to be removed and biopsied, Ganz said.

The power of the cloud data means the advanced tool on devices can continue to improve with use. "What's next is continually using the data and imagery received to increase even further the sensitivity and specificity [on new] technology," Gold said. ◀

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Pigmentary New Drugs FROM PAGE 1

development as of November 30, 2021.[1] Although study outcomes for the topical JAK inhibitor ruxolitinib (Opzelura; Incyte Dermatology), which was FDA approved to treat atopic dermatitis (AD) in September 2021, and oral JAK inhibitors are getting the most attention, investigators are examining options such as combining topical prostaglandin F2α analogues with fractional CO2 and excimer lasers and pairing oral vitamin D with phototherapy, as well as exploring new approaches using red or UV light therapies.

Quick TAKES

- Pigmentary disorders are medical conditions, not cosmetic issues.
- Systemic steroids are not going away, but—if FDA approved—Janus kinase inhibitors offer hope for patients with vitiligo who fail standard therapies.
- Lasers with narrowband UV-B wavelengths, IL-15 blockers, and applications of tranexamic acid show promise.

The availability of wider choices opens the way for a more proactive patient conversation, Desai said. "Ask the patient what their goals are and then discuss how you, as the doctor partner, can help achieve those goals," he advised. "You need that information to develop an effective treat¬ment plan for that individual."

Desai and William Damsky, MD, PhD, assistant professor in the Department of Dermatology and Dermapathology at the Yale School of Medicine in New Haven, Connecticut, drilled down on diagnosing and treating vitiligo as part of an exclusive DermView series for dermatologytimes.com, which was supported by Incyte.[2]

Desai discussed how innovation in the armamentarium will address unmet needs, and that will influence the development of more customized treatment plans.

"Vitiligo is not a one-size-fits-all disease," Desai said. "It requires a multimodal therapeutic approach—which can be challenging. Some patients can't come in 3 times a week to get light box therapy, or twice a week to get targeted excimer laser. Some don't want to take oral antioxidants. Some don't want to take the steroids; they're worried about immunosuppression, especially during COVID-19. All those things I agree with."

He added, "I don't do PUV-A [psoralen and ultraviolet A] therapy anymore. I don't do any psoralen plus UV-A. I do use narrowband [UV-B phototherapy] extensively, and I also use targeted excimer phototherapy. Topical calcineurin inhibitors and topical steroids were largely the workhorse part of my practice, especially before the advent of the topical JAK inhibitors, which I use a lot off label. I'm excited that hopefully soon, we'll potentially have those FDA approved. Probably the medication that's the farthest along is ruxolitinib (Opzelura; Incyte), which is a JAK1/2 inhibitor, 1.5% cream. That's been studied now in phase 2 and phase 3 trials. It really looks quite promising. I want to emphasize quickly the work that was done using preclinical models to identify the key cytokines, like IL-15 that's so important—like interferon-gamma that are actually mediating melanocyte destruction in this disease, are so important in guiding the field toward these therapies."

The FDA accepted ruxolitinib's supplemental new drug application (sNDA) for priority review for use in patients 12 and older with vitiligo. The Prescription Drug User Fee Act (PDUFA) target action date is April 18, 2022.

Damsky also sees JAK inhibitors as an important option. "JAK proteins are really important in inflammatory and autoimmune disorders because they mediate signaling from multiple cytokines," he said. "JAK inhibitors block the activity of those cytokines. As opposed to, for example, a monoclonal antibody blocking drug that just targets 1 cytokine, JAK inhibitors are interesting because they can simultaneously inhibit multiple cytokines, so they can fend off the immune attack on multiple fronts."

"There are investigational programs with novel topical and oral JAK inhibitors, and I think it will be really exciting to look at how JAK, not only specificity, but the route with which it's administered, affects therapy," Damsky said. "We know IL-15 is involved in cytotoxic T-cell responses and it's involved in T-cell memory. There are a lot of reasons to think that blockade of this cytokine could help patients with vitiligo. There's a proof-of-concept study that's underway now looking at IL-15 blockade in patients with vitiligo, and we've all got our fingers crossed that it's going to work. The point about IL-15 in memory I think is an interesting one because one can conceive that if you were able to turn off that memory response, you may not only be looking at treatment for vitiligo, but you may be looking at long-lasting treatment. We all have our ears perked up, listening for how those clinical trials turn out."

Looking to the future, Damsky added that certain types of vitiligo may aid understanding of the condition overall. "I think segmental vitiligo is really, from a scientific perspective, potentially very informative. If we can understand why vitiligo is affecting a very restricted patch of skin, often just on one side of the body, I think we may garner additional insight into vitiligo pathogenesis as a whole." ◀

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> "We are truly on the cusp of some revolutionary changes, particularly as clinical trial results for topical and oral [JAK] inhibitors continue to evolve as possible treatments for vitiligo and other conditions."
>
> Seemal Desai, MD, FAAD, *Dallas, Texas*

DermatologyTimes®

Innovations in Topical Therapy:
The Role of Vehicle in Treatment Decisions

Speaker
James Q. Del Rosso, DO, FAOCD, FAAD

Research Director/Investigator
JDR Dermatology Research
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and Strategic Development Advanced
Dermatology & Cosmetic Surgery
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Top 20 Stories of 2021

1 Detectable Levels of Benzene Noted in Some Sunscreen Batches

Valisure, an independent laboratory that is now a pharmacy dedicated to batch testing medications before they reach consumers, found that 78 sunscreens and after-sun-care products contained benzene, a potential carcinogen.

Christopher Bunick, MD, PhD, associate professor of dermatology at Yale School of Medicine in New Haven, Connecticut, and a member of the *Dermatology Times*® editorial advisory board, commented on the situation: "There is not a safe level of benzene that can exist in sunscreen products. Even benzene at 0.1 ppm in a sunscreen could expose people to excessively high nanogram amounts of benzene."

2 Vaccine Patients Experiencing "Vaccine Arm" Days After Injection

There were increasing reports of vaccine recipients who experienced delayed cutaneous adverse effects (AEs) after receiving the first dose of a COVID-19 vaccine. Experts assured people that although the AE is uncomfortable, it is temporary and can be treated at home.

Esther Freeman, MD, director of global health dermatology at Massachusetts General Hospital in Boston, spoke with *Dermatology Times*® about her published case series in the *New England Journal of Medicine*[1] regarding these delayed reactions, which she suggested calling "vaccine arm."

3 Device Improves Skin Cancer Images

A study published in *Lasers in Surgery and Medicine*, the official journal of the American Society for Laser Medicine and Surgery, examined the improvements in quality of the content-aware image restoration (CARE) technology.[2]

Reflectance confocal microscopy, an optical microscopy method, can examine cellular details of human skin noninvasively, but because of the high costs of the machines, a more affordable solution was investigated.

4 Valisure Highlights Controversy of Benzene Contamination in Sunscreen Products

In this video interview, David Light, founder and CEO of Valisure, sat down with *Dermatology Times*® to discuss benzene in sunscreen products and the impact the news would have on the sun-protection industry. He discussed how the carcinogen was found, starting with 1 product and expanding to 78. He also talked about other sun-protection products being tested.

5 Guidance Issued for COVID-19 Vaccine Side Effects in Dermal Filler Patients

The American Society for Dermatologic Surgery (ASDS) released the report "Guidance Regarding SARS-CoV-2 mRNA Vaccine Side Effects in Dermal Filler Patients."[3]

"Patient safety is foremost in the practice of dermatology, and board-certified dermatologists take adverse effects seriously," said Mathew Avram, MD, JD, immediate past president of the ASDS. "This guidance is meant to be informational and helpful as we move forward during pandemic recovery efforts."

6 The Cutaneous Connection: Episode 24—Benzene Found in Multiple Sunscreen Products

This podcast produced by *Dermatology Times*® dove deeper into the sunscreen controversy, as some products were found to have 3 times the FDA limit of 0.02 mg/day (2 ppm) benzene contamination.

David Light highlighted key aspects of the news from his perspective as founder and CEO of Valisure, where benzene was discovered in multiple brands and batches of sunscreen.

7 Study: How Does AK Affect Long-Term cSCC Risk?

For a study published in *JAMA Dermatology*, investigators looked into the risk of cutaneous squamous cell carcinoma (cSCC) after diagnosis of actinic keratosis (AK) during long periods of follow-up.[4] Patients 49 years or younger with AK were 7 times more likely to receive a cSCC diagnosis than those without AK.

Physician Weighs In on Sunscreen Contamination Controversy 8

In a video interview, Bunick discussed the report revealing that certain batches of various sunscreen and after-sun-care products were contaminated with benzene. He offered a dermatologist's perspective on how concerned physicians and patients should be about the carcinogen.

Researchers Study Connection Between Psoriasis and COVID-19 11

At the American Academy of Dermatology Virtual Meeting Experience 2021 (AAD VMX 2021), Jeffrey Liu, BS, a medical student at Keck School of Medicine of the University of Southern California in Los Angeles, presented data on the association between systemic treatments and COVID-19 infection risk in patients with psoriasis.[4]

The study's objectives were to assess the risk of COVID-19 infection in adult patients with psoriasis vs the general population and assess risk of infection in patients treated with systemic therapies compared with those treated with topical therapies within the Symphony Health database, which is a cloud-based server.

Study Reveals How Consumers Look at Sunscreen Labels 9

In response to an FDA proposed rule that would make ingredient lists more prominent and easier to understand, findings published in *JAMA Dermatology* revealed how consumers examine the package information on sunscreen's active ingredients.

In 2019, the FDA issued a proposed rule, 84 FR 6204, which would be an amendment to the Sunscreen Innovation Act of 2014. The amendment would require listing active ingredients on the main panel of sunscreens, allowing consumers to more readily compare products and either select or avoid a given product accordingly.

Out of the 47 people in the study group, 13 participants (28%) said that sunscreen ingredients influenced their selection and 5 (11%) said it was the most importation information. However, 34 participants (72%) said that the sun protection factor (SPF) rating was the most important information.

Relation Between Skin Cancer Medication and Dermatologic Adverse Events 12

Jordan Siad, BA, a fourth-year medical student and researcher at Harvard Medical School in Boston, Massachusetts, presented a retrospective study at AAD VMX 2021 on the association between female sex and higher rates of dermatologic AEs among patients with melanoma receiving immune checkpoint inhibitor therapy.

Guidelines Address COVID-19 Vaccine Concerns Related to Dermal Fillers 10

After 3 patients in the Moderna COVID-19 vaccine trials reported facial or lip swelling after receiving the vaccine, the ASDA issued new guidelines stating that patients with a history of dermal filler injections should not avoid vaccinations.[3]

"Basically, what the FDA data showed was that there were 3 participants out of 15,184 patients who received 1 dose of the mRNA-1273 vaccine who developed either facial swelling or lip swelling, which was presumed to be related to the filler placement," Sue Ellen Cox, MD, coauthor of the guidance and ASDS president, said.

COVID-19 Induced Skin Challenges 13

Zoe Diana Draelos, MD, adjunct assistant professor in the Department of Dermatology at Duke University School of Medicine in Durham, North Carolina, and chief medical editor of *Dermatology Times*®, covered COVID-19–related skin challenges, including chapped lips, maskne (mask-related acne), and dry hands from excessive handwashing. She offered best-practice recommendations for treating these issues.[5]

ELLACOR System Cleared by FDA 14

The ellacor system by Cytrellis received the FDA's clearance for the treatment of moderate to severe wrinkles. The minimally invasive device removes micro areas of excess skin without surgery, thermal energy, or scarring.

The Cutaneous Connection: Episode 21—Oxytocin and Skin Aging 15

In this podcast episode, Nicole Hayre, MD, FAAD, a board-certified dermatologist and founder of the Cosmetic Dermatology Center in Tysons Corner, Virginia, discussed her research on the link between the so-called love hormone, oxytocin, and younger-looking skin.[6]

FDA Grants Orphan Drug Status to ITIL-168 for Melanoma 18

The FDA granted an orphan drug designation to the investigational tumor-infiltrating lymphocyte (TIL) therapy ITIL-168 for the treatment of patients with stage IIB to IV melanoma. ITIL-168 is described as an investigational, autologous cell therapy composed of TILs.

Study: SGX301 Demonstrates Efficacy for Treatment of Cutaneous T-Cell Lymphoma 16

Ellen Kim, MD, professor of dermatology at the University of Pennsylvania in Philadelphia, presented results of the FLASH study (NCT02448381) at AAD VMX 2021.[7]

The phase 3, multicenter, randomized, double-blind, placebo-controlled study aimed to determine the efficacy of SGX301 (synthetic hypericin ointment 0.25%; Soligenix), a topical photosensitizing agent, and radiation from fluorescent bulbs to treat patients with plaque or patch phase cutaneous T-cell lymphoma—specifically, mycosis fungoides.

Master Techniques to Treat Eye Issues 19

In her Cosmetic Conundrums column, Draelos answered questions regarding undereye pigmentation and undereye edema, as well as facials to treat these issues.

Pointers With Dr Portela: How to Get Rid of Brown Spots 20

Dustin Portela, DO, a board-certified dermatologist and dermatologic surgeon at Treasure Valley Dermatology and Skin Cancer Center in Boise, Idaho, highlighted a TikTok video poster's claim that brown spots on the skin, caused by lipofuscin, can be prevented by avoiding seed oils. He explained why this information is misleading in the video.

Emerging Agents Augment Melasma Modalities 17

Pearl E. Grimes, MD, director of The Grimes Center for Medical and Aesthetic Dermatology, director of the Vitiligo and Pigmentation Institute of Southern California, and clinical professor of dermatology at the David Geffen School of Medicine at UCLA, all in Los Angeles, as well as a *Dermatology Times*® editorial advisory board member, spoke about this topic at Maui Derm 2021. Her presentation highlighted new solutions to optimize melasma management and identified cautions that could negatively affect outcomes.

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7 Kim E. Visible light-activated topical hypericin ointment in CTCL: FLASH study results. Presented at: American Academy of Dermatology Virtual Meeting Experience 2021; April 23-25, 2021; virtual.

Quick TAKES

- Deucravacitinib may see approval in 2022.
- The big news in the AD drug pipeline is the potential 2022 approval of tralokinumab.
- OX40 antagonist is 1 phase 3 drug with the potential for disease modification.

Game Changers FROM PAGE 1

Janus kinase (JAK) inhibitor deucravacitinib (BMS-986165; Bristol Myers Squibb), a novel, oral, selective tyrosine kinase 2 (TYK2) inhibitor, might see an approval in 2022, Bunick said.

"This is a game changer because it is the first major new oral agent for psoriasis in years, joining commonly used methotrexate and apremilast [Otezla; Amgen]," Bunick said. "I think it has the potential to be the best of all of them. That's why people are paying attention."

JAK inhibitors remain a hot topic in dermatology. Long prescribed for rheumatoid arthritis, JAK inhibitors are new to dermatology, with an approval only last year for ruxolitinib (Opzelura; Incyte), a topical JAK for AD.

The FDA recently decided to add a black box warning on the drug class based on data showing elevated cardiovascular and cancer risks in rheumatoid arthritis patients.

"This has somewhat diminished the excitement and the breadth of how JAK inhibitors will be used in dermatology," Bunick said. "Whether that's right or wrong is a different debate. Dermatologists have a good history of working with medications that have black box warnings, and I don't think that dermatologists shy away from that." Ultimately it will depend on whether patients are comfortable taking JAK inhibitors once they have discussions with their dermatologists about risks vs benefits, according to Bunick.

In AD, the big news in the drug pipeline is the potential 2022 approval of tralokinumab (Adtralza; LEO Pharma), a human IgG4 monoclonal antibody. "It is a biologic injectable medication—an IL-13 inhibitor," Bunick said. Dupilumab (Dupixent; Sanofi and Regeneron Pharmaceuticals) is the only approved biologic option in AD. "Not every patient responds or has a durable response to dupilumab," Bunick said. "So having a second biologic in the [AD] space is essential for patient care."

Pfizer developed abrocitinib, a pipeline JAK1 inhibitor for AD, which is under FDA priority review. "Abrocitinib could be really effective but, again, the question comes back to the black box warning, what patients are going to be right for this medication and which patients are going to be OK taking it," Bunick said.

Emma Guttman-Yassky, MD, PhD, system chair and professor of dermatology at Icahn School of Medicine at Mount Sinai in New York, New York, spends her days researching pipeline dermatology medications and devices and caring for patients with life-altering skin diseases, including AD. What excites her most about the future is the possibility of disease modification, or treating moderate to severe skin diseases, then stopping a drug without having the disease return.

"Right now, when we stop treatments for patients who have moderate to severe disease, the disease comes back quite rapidly, usually by 4 to 6 weeks," Guttman-Yassky said.

OX40 antagonist is 1 drug initiating phase 3 trials with the potential for disease modification, according to Guttman-Yassky.

Anti-OX40 (KHK4083) maker Kyowa Kirin announced phase 2 results in February 2021 for its international study of 274 patients with moderate to severe AD, according to a February 18, 2021, company news release. "The study's primary end point was week 16, but they treated patients for 36 weeks, then followed patients for an additional 20 weeks off drug," Guttman-Yassky said. "They found that with the 2 highest doses, they were able to maintain Eczema Area and Severity Index (EASI) 75 responses in about 90% patients for another 20 weeks. I have seen some patients at Mount Sinai clear for 6 months."

An anti-CCR4 oral medication was shown in a small study to have potential for disease modification in AD patients. CCR4 is a chemokine receptor highly expressed by Th2 cells. AD patients took the drug for 4 weeks, then stopped and not only maintained results for another 2 weeks but continued to improve, while the placebo group worsened, according to Guttman-Yassky.

Mindera Health dermal intelligence might make a splash in the US market in 2022, according to Bunick.

Mindera Health takes a piece of the surface of the skin and uses genetic, transcriptomic, and other analyses to extract a patient's RNA, DNA, and proteins. "They are basically analyzing at the molecular level each patient's unique signature and predicting from that signature which medication may work best for the patient," Bunick said. "This is going to change how dermatologists work in the clinic, potentially for many different diseases."

A game changer for Miami, Florida, dermatologist Jill Waibel, MD, is the Ellacor micro-coring device by Cytrellis. "Micro-coring is not an energy device; it is an excisional technology," Waibel said. "Basically, the genius for this is that we can do something that is easier than a face-lift for skin laxity, including jowls. These are tiny micro-excisions that remove small cores of skin. When you remove these tiny skin cores, they biomechanically close immediately. The cores are so small—30 to 70 microns—[which] is below the level that causes a scar."

The FDA recently approved Ellacor, developed by dermatologist Rox Anderson, MD, for reduction of severe wrinkles in the mid to lower face and submental area.

"[T]he FDA doesn't really validate laxity. But I use Ellacore for laxity," Waibel said. "The treatment takes 14 to 20 minutes. The channels close in about 2 minutes and there is a little redness and pigment for about 3 days."

Waibel said she has seen impressive results using the device on the lower face and neck as well as to treat tattoos, stretch marks, and acne scars. "The limitation is that it is not a stand-alone treatment," Waibel said. "I do a lot of this in combination with resurfacing, where I can tighten the skin and get rid of the wrinkles."

Dermatologists might soon have an energy-based device option to treat acne, according to Waibel. Rox Anderson and dermatologist Emil Tanghetti, MD, developed the Accure laser, which is in the process for FDA approval. In 1 study, Accure treatment resulted in an average 80% lesion reduction at 3 months posttreatment.[1] "Acne patients do not want antibiotics, and we probably shouldn't be prescribing antibiotics because of their side effects. An energy-based treatment is exciting and that will happen in 2022, certainly with this laser leading the pack," Waibel said.

A new technology that is working "surprisingly well" for the generalized flushing of rosacea, the pigment of melasma, and more is the Sylfirm X (distributed by Benev) radiofrequency (RF) microneedling device, according to Houston, Texas–based cosmetic and dermatologic surgeon Suneel Chilukuri, MD. Dermatologist-developed Sylfirm X is a dual wave technology that has a short wave as well as a continuous wave pulse. It is the only device in the RF microneedling category that has a short pulse wave, he said.

Sylfirm X uses a unique bipolar uninsulated needle, eliminating the safety concerns noted with prior-generation uninsulated RF needles.

"By utilizing a depth of only 300 microns with a short pulse, we are able to improve the dermal-epidermal junction. The basement membrane gets tighter so there is less trans-epidermal water loss, which helps with rosacea. In addition, there is remodeling of the superficial vessels with subsequent clinical erythema reduction. With melasma, this short pulse activates the senescent fibroblasts in a safe manner. Clinical trials have shown that areas of hyperpigmentation in melasma have more senescent fibroblasts than surrounding areas," Chilukuri said. ◀

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