PSORIASIS
and Psoriatic Arthritis

A SUPPLEMENT TO
Dermatology News
OCTOBER 2020

New guidelines
on systemic nonbiologic therapies

Markers
of systemic inflammation

Clearance
beyond PASI 100

Screening
for psoriatic arthritis

New guidelines
on topical, alternative treatments

And more...

Commentaries by
Joel M. Gelfand, MD, MSCE
and Alan Menter, MD

Exploring new guidelines and scientific advances

By Joel M. Gelfand, MD, MSCE


Dr. Gelfand

YOU ARE NOT GOING to want to miss out on the chance to improve your ability to manage psoriasis by reading this update on the latest scientific advances. In fact, if you don't continue reading on, there's a chance your ability to manage psoriasis will get worse since you won't be up to date with the latest findings. See what I just did? I used a "loss frame" approach rooted in the principles of behavioral economics, which Ari Kassardjian demonstrated can be used to make patients more agreeable to treatment! (See page 7.) I will also cover some thought-provoking studies that uncover the invisible effects of psoriasis. These new findings remind us that, just because we don't see psoriasis on the skin of a patient who is "clear" or recognize the effects of systemic inflammation because their C-reactive protein is normal, there is always more than meets the eye when it comes to psoriasis. Finally, I will explore data on the first new mechanism of action for the topical management of psoriasis in decades and highlight practice-changing recommendations from the new American Academy of Dermatology–National Psoriasis Foundation guidelines for the management of psoriasis with nonbiologic systemic agents (wave goodbye to liver biopsies for methotrexate patients). Speaking of the NPF, take a look at the 22 recommendations their COVID-19 Task Force (full disclosure, I cochair this effort) just released to promote optimal management of psoriatic disease during the pandemic (www.psoriasis.org/covid-19-task-force-guidance-statements/). To keep up with the latest publications about psoriasis, I invite you to follow me on Twitter (@DrJoelGelfand) or LinkedIn (www.linkedin.com/in/drjoelgelfand/).

Dr. Gelfand is professor of dermatology and of epidemiology; vice chair of clinical research and medical director, Dermatology Clinical Studies Unit; and director of the Psoriasis and Phototherapy Treatment Center at the University of Pennsylvania, Philadelphia. His disclosures relevant to this supplement are serving as a consultant to Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Biologics, Novartis, Pfizer, and UCB (DSMB); receiving honoraria; receiving payment for continuing medical education related to psoriasis supported indirectly by Lilly, Ortho Dermatologics, and Novartis; and receiving research grants to the Trustees of the University of Pennsylvania from AbbVie, Boehringer Ingelheim, Celgene, Janssen, Novartis, Ortho Dermatologics, and Pfizer.

By Alan Menter, MD


Dr. Menter

ALL SIX OF THE American Academy of Dermatology–National Psoriasis Foundation psoriasis guidelines have now been published; most recently, the guidelines on systemic nonbiologic therapies; and topical therapies, alternative therapies, and severity measures (see pages 11 and 21). The others have focused on pediatrics, phototherapy, biologics, and comorbidities. These guidelines represent more than 3 years of collaboration and work with more than 20 dermatologist colleagues, a rheumatologist, cardiologist, and representatives from a patient advocacy organization, and are the first new such guidelines in the United States in 12 years. This is an exciting time in the area of psoriasis and psoriatic arthritis, as reflected in the guidelines, and the selection of stories in this supplement.

Dr. Menter is chairman of dermatology at Baylor Scott & White Health and clinical professor of dermatology at the University of Texas, both in Dallas. He is cochair of the American Academy of Dermatology Psoriasis Guideline Work Group. He is an adviser, a consultant, an investigator, and/or a speaker for Abbott Labs, Amgen, Boehringer Ingelheim, Celgene, Janssen Biotech, LEO Pharma, Eli Lilly, Merck, Novartis, Sun Pharma, and UCB; and he has received grants and/or honoraria from these companies.

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Psoriasis and Psoriatic Arthritis is a supplement to *Dermatology News*, an independent newspaper that provides practicing dermatologists with timely and relevant news and commentary about clinical developments in the field and about the impact of health care policy on the specialty and the physician's practice.

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Otezla® (apremilast) 30mg tablets

GETTING OTEZLA GETS EVEN EASIER

8 out of 10 commercially insured lives in the US have preferred access with **no biologic step** required for Otezla[1]

Otezla is listed as preferred, with no biologic step requirement, on:

Aetna Prescription Drug Benefit

Cigna Prescription Drug List

CVS Caremark Formularies*

Express Scripts National Preferred Formulary†

OptumRx ✓

Prime Therapeutics

UnitedHealthcare ✓

✓ Indicates no DMARD or biologic step-edit required

Contact your Otezla representative or visit *OtezlaPro.com* for a complete list of plans

*Basic, Standard, and Advanced Control Formularies.
†SafeGuardRx® Program has 1 biologic step for patients on certain Otezla® (apremilast) indications.
DMARD, disease-modifying antirheumatic drug.

INDICATIONS

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

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

IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

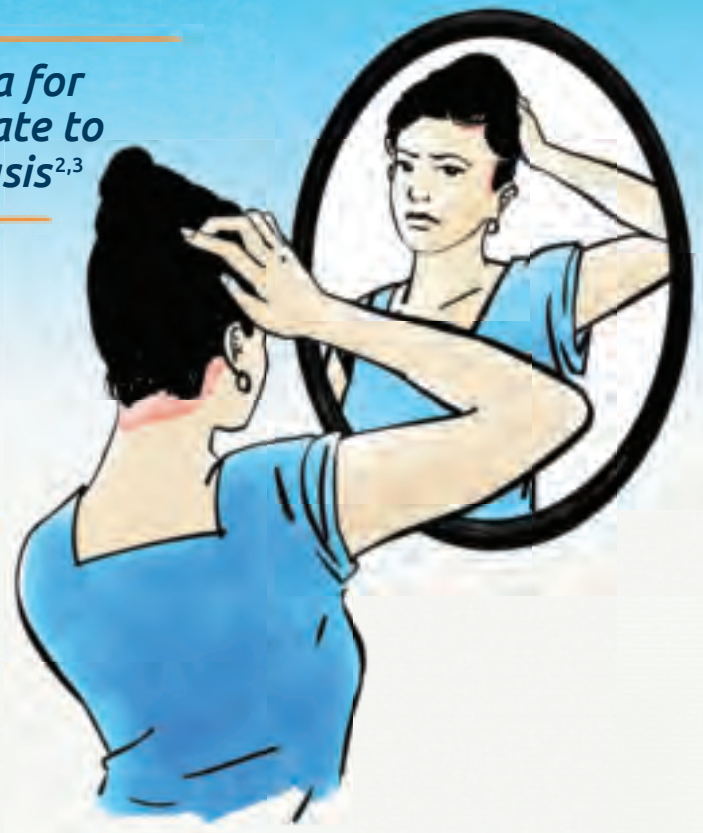
Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.

#1

PRESCRIBED

For patients starting plaque psoriasis or psoriatic arthritis treatment*

Otezla Clinical Data for Adults with Moderate to Severe Scalp Psoriasis[2,3]



THE ONLY ORAL THERAPY WITH DATA IN THE LABEL FOR SCALP PSORIASIS[2]

- **A FIRST STEP TO SYSTEMIC THERAPY FOR MODERATE TO SEVERE SCALP PSORIASIS**[1,2]
- **OTEZLA IS A NON-BIOLOGIC THERAPY WITH ORAL DOSING, A PROVEN EFFICACY AND SAFETY PROFILE, AND NO LABEL-REQUIRED LAB MONITORING**[2]

STYLE clinical trial[2,3]

Study design: Phase 3 multicenter, randomized, double-blind, placebo-controlled study of 303 patients with moderate to severe plaque psoriasis of the scalp. Patients were randomized 2:1 to Otezla® (apremilast) 30 mg twice daily (n=201) or placebo (n=102) for the placebo-controlled phase through week 16, then continued or switched to Otezla for the open-label extension phase through week 32. Treatment groups were stratified by baseline ScPGA score (3 [moderate] or 4 [severe]).
Selected inclusion criteria: Patients had moderate to severe plaque psoriasis of the scalp (ScPGA ≥3, SSA ≥20%), inadequate response or intolerance to ≥1 topical therapy for plaque psoriasis of the scalp, and moderate to severe plaque psoriasis (BSA involvement of ≥10%, sPGA ≥3, PASI score ≥12).

BSA, body surface area; PASI, Psoriasis Area and Severity Index; ScPGA, Scalp Physician Global Assessment; sPGA, static Physician Global Assessment; SSA, scalp surface area.

*Data includes information derived from Symphony Health Solutions. The unprojected claims dataset covers 60%-70% of all commercially insured claims, Medicare, Medicaid, and cash prescriptions. Patients are classified as New to Brand (NTB) if over the last 12-month period the patient had not been on their current "brand." NTB includes patients who have had no prior treatment history as well as patients who switched to a brand for the first time from a different prior therapy [April 2014 through April 2020].[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions

- Diarrhea, Nausea, and Vomiting: Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- Depression: Treatment with Otezla is associated with an increase in depression. During clinical trials 1.3% (12/920) of patients reported depression, compared to 0.4% (2/506) on placebo. Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur
- Weight Decrease: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla
- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

Adverse Reactions

- Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4)

For adult patients with moderate to severe plaque psoriasis

OTEZLA SIGNIFICANTLY IMPROVES SCALP RESPONSE[2,3]

STYLE primary endpoint: proportion of patients achieving an ScPGA response at week 16[2,3*]

Otezla patients **3x** as likely to achieve scalp improvement at week 16 *vs placebo in the STYLE study*

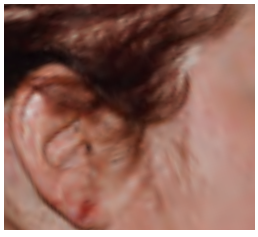
43.3% with Otezla® (apremilast) 30 mg BID (n=201)

vs (*P*<0.0001)

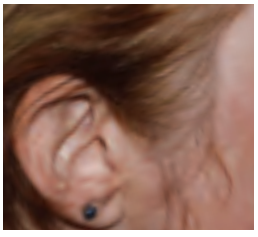
13.7% with placebo (n=102)

*ScPGA response was defined as the proportion of patients achieving an ScPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.

Results seen in an Otezla patient (scalp response)



Baseline



Week 16
ScPGA: 0†
3-point improvement in ScPGA score

†Actual clinical trial patient from STYLE.[1] Individual results may vary.

Adverse reactions[2,3]

- The most common adverse reactions (≥5%) from weeks 0 to 16 included diarrhea, nausea, headache, and vomiting
- The proportion of patients who discontinued treatment because of any adverse reaction was 6% for patients who received Otezla 30 mg twice daily and 3% for patients who received placebo
- Gastrointestinal adverse reactions that led to discontinuation of treatment were diarrhea (3% vs 0%), nausea (1.5% vs 1%), and vomiting (1.5% vs 0%) in the Otezla group, compared to placebo

Visit *OtezlaPro.com* for additional information

IMPORTANT SAFETY INFORMATION (cont'd)

Use in Specific Populations

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Otezla during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/
- Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Otezla and any potential adverse effects on the breastfed child from Otezla or from the underlying maternal condition
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

References: 1. Data on file, Amgen Inc. **2.** Otezla [package insert]. Thousand Oaks, CA: Amgen Inc. **3.** Van Voorhees A, Gold LS, Lebwohl M, et al. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: results of a phase 3b, multicenter, randomized, placebo-controlled, double-blind study. *J Am Acad Dermatol.* 2020. doi:10.1016/j.jaad.2020.01.072.

Please turn the page for Brief Summary of Full Prescribing Information.

Otezla® (apremilast) 30mg tablets

Brief Summary of Prescribing Information

OTEZLA® (apremilast) tablets, for oral use

PLEASE SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

CONTRAINDICATIONS

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation *[see Adverse Reactions (6.1)]*.

WARNINGS AND PRECAUTIONS

Diarrhea, Nausea, and Vomiting

There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

Depression

Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects while receiving OTEZLA, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of subjects treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated subjects. In the clinical trials, one subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease

During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (49/497) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo.

During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of subjects treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3/382) subjects treated with placebo.

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered *[see Adverse Reactions (6.1)]*.

Drug Interactions

Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

ADVERSE REACTIONS

Clinical Trials Experience

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

Psoriatic Arthritis Clinical Trials: OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials [Studies PsA-1, PsA-2, and PsA-3] of similar design in adult patients with active psoriatic arthritis *[see Clinical Studies (14.1)]*. Across the 3 studies, there were 1493 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was used over the first 5 days [see Dosage and Administration (2.1)]. Placebo patients whose tender and swollen joint counts had not improved by at least 20% were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or 30 mg twice daily at week 16 while OTEZLA patients remained on their initial treatment. Patients ranged in age from 18 to 83 years, with an overall median age of 51 years.

The majority of the most common adverse reactions presented below occurred within the first 2 weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

Adverse Reactions Reported in ≥2% of Patients on OTEZLA 30 mg Twice Daily and ≥1% Than That Observed in Patients on Placebo on Day 1-5 (Placebo %, OTEZLA %): Diarrhea[a] (1.2%, 9.3%), Nausea[a] (1.4%, 7.4%), Headache[a] (1.8%, 4.8%), Upper respiratory tract infection[b] (0.6%, 0.6%), Vomiting[a] (0.4%, 0.8%), Nasopharyngitis[b] (0.2%, 0.2%), Abdominal pain upper[b] (0.0%, 0.6%).

Adverse Reactions Reported in ≥2% of Patients on OTEZLA 30 mg Twice Daily and ≥1% Than That Observed in Patients on Placebo on Day 6-112 (Week 16) (Placebo %, OTEZLA %): Diarrhea[a] (1.6%, 7.7%), Nausea[a] (3.1%, 8.9%), Headache[a] (2.2%, 5.9%), Upper respiratory tract infection[b] (1.8%, 3.9%), Vomiting[a] (0.4%, 3.2%), Nasopharyngitis[b] (1.6%, 2.6%), Abdominal pain upper[b] (0.2%, 2.0%).

[a] Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache.

[b] Of the reported adverse drug reactions none were serious.

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies: **Immune system disorders:** Hypersensitivity, **Investigations:** Weight decrease, **Gastrointestinal Disorders:** Frequent bowel movement, gastroesophageal reflux disease, dyspepsia, **Metabolism and Nutrition Disorders:** Decreased appetite*, **Nervous System Disorders:** Migraine, **Respiratory, Thoracic, and Mediastinal Disorders:** Cough, **Skin and Subcutaneous Tissue Disorders:** Rash

*1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

Psoriasis Clinical Trials

The safety of OTEZLA was assessed in 1426 subjects in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days *[see Dosage and Administration (2.1)]*. Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years.

Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for subjects treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated subjects.

Adverse Reactions Reported in ≥1% of Subjects on OTEZLA and With Greater Frequency Than in Subjects on Placebo; up to Day 112 (Week 16) (Placebo %, OTEZLA %):
Diarrhea (6%, 17%), Nausea (7%, 17%), Upper respiratory tract infection (6%, 9%), Tension headache (4%, 8%), Headache (4%, 6%), Abdominal pain* (2%, 4%), Vomiting (2%, 4%), Fatigue (2%, 3%), Dyspepsia (1%, 3%), Decreased appetite (1%, 3%), Insomnia (1%, 2%), Back pain (1%, 2%), Migraine (1%, 2%), Frequent bowel movements (0%, 2%), Depression (0%, 1%), Bronchitis (0%, 1%), Tooth abscess (0%, 1%), Folliculitis (0%, 1%), Sinus headache (0%, 1%).

*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain. Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with OTEZLA.

OTEZLA was evaluated in a Phase 3, multicenter, randomized, placebo-controlled study (PSOR-3) in adults with moderate to severe psoriasis of the scalp *[see Clinical Studies (14.2)]*. A total of 302 subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. The most commonly reported adverse reactions that occurred at a higher rate in the OTEZLA group than in the placebo group were: diarrhea (31% vs. 11%), nausea (22% vs. 6%), headache (12% vs. 5%), and vomiting (6% vs. 2%). The proportion of subjects who discontinued treatment because of any adverse reaction during the 16 -week placebo-controlled period of the study was 6% for subjects who received OTEZLA 30 mg twice daily and 3% for subjects who received placebo. Gastrointestinal adverse reactions that led to discontinuation of treatment were diarrhea (3% vs 0%), nausea (1.5% vs 1%), and vomiting (1.5% vs 0 %) in the OTEZLA group compared to placebo.

DRUG INTERACTIONS

Strong CYP450 Inducers

Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy *[see Warnings and Precautions (5.3)] and Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Risk Summary

Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential.

Lactation

Risk Summary

There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed child from OTEZLA or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the 1493 patients who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis patients were 65 years of age and older, including 19 patients 75 years and older. No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

Of the 1257 subjects who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis subjects were 65 years of age and older, including 9 subjects who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly subjects ≥65 years of age and younger adult subjects <65 years of age in the clinical trials.

Renal Impairment

Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft–Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

Hepatic Impairment

Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

OVERDOSAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.OTEZLA.com or contact Amgen Medical Information at 1-800-772-6436.

Manufactured for:

Amgen Inc.
Thousand Oaks, CA 91320-1799 U.S.A

https://pat.amgen.com/otezla

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US-OTZ-20-0528

'Loss-framed' approach makes psoriasis patients more agreeable to treatment

By Jeff Craven

Emphasizing the potential harms of not taking a psoriasis treatment may make patients more likely to agree to start that therapy, according to research presented at the annual meeting of the Society for Investigative Dermatology, held virtually.

"We typically explain to patients the benefits of treatment," Ari A. Kassardjian, BS, of the University of Southern California, Los Angeles, said in his presentation. "However, explaining to them the harmful effects on their skin and joint diseases, such as exacerbation of psoriasis and/or psoriatic arthritis, could offer some patients a new perspective that may influence their treatment preferences; and ultimately, better communication may lead to better medication adherence in patients."

In the study he presented, explaining to patients possible outcomes without treatment was more effective in getting them to agree to treatment than was messaging that focused on the positive effects of a therapy (reducing disease severity and pain, and improved health).

He noted that the impact of framing choices in terms of gain or loss on decision-making has been measured in other areas of medicine, including in patients with multiple sclerosis where medication adherence is an issue (J Health Commun. 2017 Jun;22[6]:523-31). "Gain-framed" messages focus on the benefits of taking a medication, while "loss-framed" messages highlight the potential consequences of not agreeing or adhering to treatment.

The loss-framed message described the downsides of not taking medication.

In the study, Mr. Kassardjian and coinvestigators evaluated 90 patients with psoriasis who were randomized to receive a gain-framed or loss-framed message about a hypothetical new biologic injectable medication for psoriasis and psoriatic arthritis (PsA). More than half were male (64.4%), white (53.3%), and non-Hispanic or Latino (55.6%); and about one-fourth of the participants (27.8%) also had PsA.

The gain-framed message emphasized "the chance to reduce psoriasis severity, reduce joint pain, and improve how you feel overall," while the loss-framed message described the downsides of not taking medication – missing out "on the chance to improve your skin, your joints, and your overall health," with the possibility that psoriasis may get worse, "with worsening pain in your joints from psoriatic arthritis," and feeling "worse overall." Both messages included the side effects of the theoretical injectable, a small risk of injection-site pain and skin infections. After receiving the message, participants ranked their likelihood of

Continued on following page ▶

COMMENTARY BY DR. GELFAND: Which of the following options would you prefer: Option A: 100% chance of winning $500 or option B: 50% chance of winning $1,000? Okay, stop for a minute and reread the two options and select A or B before you go any further. I bet I know what option you selected (and no, I am not going to send you $500!). If you randomly choose from these options 1,000 times, each option will yield the same amount of money in the end; that's basic math and probability theory. So why is it that you probably selected option A? We humans are subject to a number of cognitive biases, including a strong preference to avoid loss (a principle of behavioral economics).

In other words, I don't want to lose $500 bucks for the chance of winning $1,000 even though the scenarios are essentially the same. And this is where Ari A. Kassardjian of the University of Southern California, Los Angeles, and his coinvestigators bring behavioral economics to psoriasis. In a paper he presented virtually (welcome to the new COVID-19 normal) at the 2020 Society for Investigative Dermatology meeting, they tested the impact of loss aversion on treatment preference in patients with psoriasis.

They randomized 90 patients to "gain-framed" messages focused on the benefits of taking a medication versus "loss-framed" messages which highlighted the potential consequences of not agreeing or adhering to treatment. In option A, the gain-framed message emphasized "the chance to reduce psoriasis severity, reduce joint pain, and improve how you feel overall," while option B, the loss-framed message, described the downsides of not taking medication – missing out "on the chance to improve your skin, your joints, and your overall health," with the possibility that psoriasis may get worse, "with worsening pain in your joints from psoriatic arthritis," and feeling "worse overall."

So which group do you think was more likely to indicate a preference for taking the medication? Option B of course! This study demonstrates that how we present choices to patients makes a big difference in the selections they make. There are of course many other ways we human are subject to cognitive biases, often to our own detriment. To learn more about this important topic you should read "Predictably Irrational" by Dan Ariely, PhD, (New York: HarperCollins Publishers, 2009).

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taking the medication on an 11-point Likert scale, with a score of 0 indicating that they would "definitely" not use the medication and a score of 10 indicating that they would "definitely" use the medication.

Scores among those who received the loss-framed message were a mean of 8.84, compared with 7.11 among patients who received the gain-framed message (between-group difference; 1.73; *P* less than .0001). In a comparison of patients with and without PsA, the between-group difference was 1.90 for patients with PsA (*P* less than .0001) and 1.08 for patients who did not have PsA ($P = .002$). In a comparison of responses of those with PsA and those without PsA, the between-group difference was 1.08 ($P = .03$). While PsA and non-PsA patients favored the loss-framed messages, "regardless of the framing type, PsA patients always responded with a greater preference for the therapy," Mr. Kassardjian said.

Gender also had an effect on responsiveness to gain-framed or loss-framed messaging. Both men and women ranked the loss-framed messaging as making them more likely to use the medication, but the between-group difference for women (2.00; $P = .008$) was higher than in men (1.49; $P = .003$). However, the total men compared with total women between-group differences were not significant.

"In clinical practice, physicians regularly weigh the benefits and risks of treatment. In order to communicate this information to patients, it is important to understand how framing these benefits and risks impacts patient preferences for therapy," Mr. Kassardjian said. "While most available biologics are effective and have tolerable safety profiles, many psoriasis patients may be hesitant to initiate these therapies. Thus, it is important to convey the benefits and risks of these systemic agents in ways that resonate with patients."

Mr. Kassardjian reports receiving the Dean's Research Scholarship at the University of Southern California, funded by the Wright Foundation at the time of the study. Senior author April Armstrong, MD, disclosed serving as an investigator and/or consultant for AbbVie, BMS, Dermavant, Dermira, Janssen, Kyowa Hakko Kirin, Leo Pharma, Eli Lilly, Modernizing Medicine, Novartis, Ortho Dermatologics, Regeneron, Sanofi, Sun Pharma, and UCB.

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SOURCE: Kassardjian AA. SID 2020, Abstract 489.

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Topical PDE-4 inhibitor for psoriasis effective in phase 2b trial

By Bruce Jancin

Once-daily topical roflumilast, a potent selective topical phosphodiesterase-4 inhibitor, brought marked improvement in signs and symptoms of chronic plaque psoriasis – including challenging lesions in tough-to-treat intertriginous areas – in a phase 2b, randomized, double-blind, vehicle-controlled clinical trial, Mark G. Lebwohl, MD, reported at the virtual annual meeting of the American Academy of Dermatology.

Clinical improvement occurred rapidly. And topical roflumilast's side-effect profile was essentially the same as in vehicle-treated controls, which suggests a potential major advantage for the novel drug in future clinical practice. After all, topical treatment is the mainstay of psoriasis therapy, but the current topical agents – high-potency corticosteroids, vitamin D derivatives, and retinoids – have long-term tolerability, efficacy, or side-effect issues, especially in treating sensitive skin areas, including the face and intertriginous areas.

Phosphodiesterase-4 (PDE-4) activity is elevated in psoriatic skin. Indeed, inhibition of PDE-4 via oral apremilast (Otezla) is an established strategy for improving psoriasis through down-regulation of inflammatory cytokines including tumor necrosis factor–alpha, interleukins-17 and -23, and interferon-gamma. Notably, however, roflumilast is orders of magnitude more potent than any other PDE-4 inhibitor. An oral version has been available for treatment of chronic obstructive pulmonary disease for nearly a decade.

The 12-week study included 331 patients with chronic plaque psoriasis who were randomized to once-daily 0.3% roflumilast cream, 0.15% roflumilast cream, or vehicle. Three-quarters of participants had a baseline Investigator Global Assessment (IGA) score of 3, indicative of moderate disease.

The primary endpoint was achievement of an IGA score of 0 or 1 (clear or almost clear) at week 6. The observed improvement was dose related, although both doses of roflumilast were significantly more effective than vehicle. However, peak improvement occurred at week 8, not week 6, with subsequent plateauing of response through week 12. A week 8 IGA of 0 or 1 plus at least a 2-grade improvement from baseline occurred in 32% of the high-dose roflumilast group, 25% of those on the 0.15% formulation, and 10% of controls.

"The effect in improvement was very rapid, with a statistically significant improvement compared to vehicle for both concentrations as early as week 2," said Dr. Lebwohl, professor and chair of the department of dermatology at the Icahn School of Medicine at Mount Sinai, New York.

A key secondary endpoint focused on treatment response in intertriginous areas, since "those are the areas where we really don't want to use steroids because of major irritation problems," he explained. At week 12, treatment success as defined by an intertriginous IGA score of 0 or 1 plus at least a 2-point improvement from baseline was seen in 86% of the 0.3% roflumilast cream group, 50% on low-dose therapy, and 29% of controls.

About 65% of subjects on high-dose

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COMMENTARY BY DR. GELFAND: We have seen an explosion of progress in the oral and biologic treatment of moderate to severe psoriasis. New agents targeting phosphodiesterase-4, Janus kinase, tumor necrosis factor, interleukin-17, and IL-23 have been approved by the Food and Drug Administration for management of psoriatic disease in the last 2 decades. How many products with new mechanisms of action have been approved for the topical treatment of psoriasis during this same time period? Zero.

Topical therapies remain a critical component of the management of psoriasis. First, 80% of patients with psoriasis have limited body surface area involved and, thus, are primarily managed with topical therapy. Second, even our best treatments for patients with moderate to severe psoriasis will fail to achieve 100% clearance in a large percentage of patients, and therefore, adjuvant topical treatment will be needed. Clearly, highly effective and safe topical agents remain an unmet medical need for our patients.

With this in mind, it was exciting to see phase 2b data of topical roflumilast, a potent selective topical phosphodiesterase-4 inhibitor. In a study of 331 patients, an Investigator Global Assessment of 0 or 1 plus at least a 2-grade improvement from baseline occurred in 32% of the high-dose 0.3% roflumilast group, 25% of those on the 0.15% formulation, and 10% of those on vehicle at week 8. Stated another way, you would need to treat about 5 patients with high-dose roflumilast cream for 8 weeks to achieve 1 extra good (but not great as in "clear") result in the skin (this statistic is known as the "number needed to treat" or "NNT").

Is your enthusiasm waning? Well, a key secondary endpoint focused on treatment response in intertriginous areas, which is an area especially challenging to treat because of concerns of atrophy (with topical corticosteroids) or irritation. At week 12, treatment success as defined by an intertriginous investigator global assessment score of 0 or 1 plus at least a 2-point improvement from baseline was seen in 86% of the high-dose roflumilast cream group, 50% on low-dose therapy, and 29% on vehicle (a more respectable NNT of 2 for the high-dose arm). Looking forward to phase 3 results of this agent!

Biologics may delay psoriatic arthritis

By Jim Kling

Treatment of psoriasis with biologics was associated with a reduced risk of developing psoriatic arthritis compared with conventional disease-modifying antirheumatic drugs (DMARDs), in a single-center retrospective analysis in Argentina that followed patients for almost 2 decades.

About 30%-40% of patients with psoriasis go on to develop psoriatic arthritis (PsA), usually on average about 10 years after the onset of psoriasis. One potential mechanism of PsA onset is through enthesitis, which has been described at subclinical levels in psoriasis.

"It could be speculated that treatment with biologics in patients with psoriasis could prevent the development of psoriatic arthritis, perhaps by inhibiting the subclinical development of enthesitis," Luciano Lo Giudice, MD, a rheumatology fellow at Hospital Italiano de Buenos Aires, said during his presentation at the virtual annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.

Although these results do not prove that treatment of the underlying disease delays progression to PsA, it is suggestive, and highlights an emerging field of research, according to Diamant Thaçi, MD, PhD, professor of medicine at University Hospital Schleswig-Holstein (Germany), who led a live discussion following a prerecorded presentation of the results. "We're going in this direction – how can we prevent psoriatic arthritis, how can we delay it. We are just starting to think about this," Dr. Thaçi said in an interview.

The researchers examined medical records of 1,626 patients with psoriasis treated at their center between 2000 and 2019, with a total of 15,152 years of follow-up. Of these patients, 1,293 were treated with topical medication, 229 with conventional DMARDs (methotrexate in 77%, cyclosporine in 13%, and both in 10%), and 104 with biologics, including etanercept (34%), secukinumab (20%), adalimumab (20%), ustekinumab (12%), ixekizumab (9%), and infliximab (5%).

They found that 11% in the topical treatment group developed PsA, as did 3.5% in the conventional DMARD group, 1.9% in the biologics group, and 9.1% overall. Treatment with biologics was associated with a significantly lower odds of developing PsA compared with treatment with conventional DMARDs (3 versus 17.2 per 1,000 patient-years; incidence rate ratio, 0.17; $P = .0177$). There was a trend toward reduced odds of developing PsA among those on biologic therapy compared with those on topicals (3 versus 9.8 per 1,000 patient-years; IRR, 0.3; $P = .0588$).

The researchers confirmed all medical encounters using electronic medical records and the study had a long follow-up time, but was limited by the single center and its retrospective nature. It also could not associate reduced risk with specific biologics.

The findings probably reflect the presence of subclinical PsA that many clinicians don't see, according to Dr. Thaçi. While a dermatology practice might find PsA in 2% or 3%, or at most, 10% of patients with psoriasis, "in our department it's about 50%-60% of patients who have psoriatic arthritis, because we diagnose it early," he said.

He found the results of the study encouraging. "It looks like some of the biologics, for example IL [interleukin]-17 or even IL-23 [blockers] may have an influence on occurrence or delay the occurrence of psoriatic arthritis."

Dr. Thaçi noted that early treatment of skin lesions can increase the probability of longer remissions, especially with IL-23 blockers. Still, that's no guarantee the same would hold true for PsA risk. "Skin is skin and joints are joints," Dr. Thaçi said.

Dr. Thaçi and Dr. Lo Giudice had no relevant financial disclosures.

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COMMENTARY BY DR. MENTER: This retrospective study found that patients with psoriasis treated with biologics had significantly lower odds of developing psoriatic arthritis, compared with those treated with conventional DMARDs. As Dr. Thaçi points out in this report, this is an emerging area of research, and the results probably reflect the presence of subclinical psoriatic arthritis.

An important clinical issue is that, if early psoriatic arthritis is left untreated, within a year, 50% of patients will go on to develop permanent joint destruction. Early psoriatic joint disease appears 10-15 years after the onset of skin disease, and it is absolutely essential that we as dermatologists work with our rheumatologist colleagues to prevent permanent joint destruction in our patients.

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roflumilast cream reported at least a 4-point reduction in the Worst Itch–Numerical Rating Scale by week 8, as did 58% of those on the low-dose version and 42% of controls. Another secondary endpoint – patient-reported burden of disease as captured in a Psoriasis Symptoms Diary – showed a significant divergence between both doses of roflumilast and vehicle as early as week 2.

"Adverse events were negligible," Dr. Lebwohl said. "There was only one discontinuation in the 0.3% arm, compared to none with 0.15% and two with vehicle." The phase 3 program is now recruiting participants.

The study was funded by Arcutis Biotherapeutics. Dr. Lebwohl reported receiving research funding from and serving as a consultant to that company and numerous others.

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AAD-NPF releases guidelines for systemic nonbiologic treatments of psoriasis

By Richard Mark Kirkner

It's been 11 years since the American Academy of Dermatology updated its guidelines for using systemic nonbiologic therapies for psoriasis, and now new guidelines recommend oral apremilast monotherapy and suggest a framework for a number of off-label treatments.

The guidelines, issued jointly with the National Psoriasis Foundation, were published in the Journal of the American Academy of Dermatology.

"I think we are way behind," Alan Menter, MD, chairman of the division of dermatology at Baylor University Medical Center, Dallas, and cochair of the guideline writing committee, said in an interview. "Most other countries update their guidelines every 1 or 2 years; we were 10 years behind." The guidelines for systemic nonbiologic drugs follow up psoriasis guidelines issued by the AAD and the NPF on pediatric patients issued earlier this year, and on phototherapy, biologic treatments, and management of comorbidities issued last year.

"A lot has happened in the last 10 years," said cochair Craig A. Elmets, MD, professor of dermatology at the University of Alabama at Birmingham. "While much of the interest is on biologic agents, nonbiologics are still used quite frequently, and the guidelines for their appropriate use have changed. Use of the guidelines provides people in the health profession with the most up-to-date evidence-based information so they can give their patients the best care."

The guidelines acknowledge that the medications it covers are still widely used, either by themselves or in combination with biologic agents; readily available; easy to use; and, in the case of older therapies, relatively cheap.

Methotrexate has been available since the 1970s. Given as an injection or taken orally, the guidelines recommend supplementation with folic acid to counteract methotrexate's side effects, particularly GI upset. The guidelines note that folic acid is less expensive than folinic acid. Combination therapy with methotrexate and tumor necrosis factor (TNF) inhibitors is more effective than methotrexate monotherapy, with a similar side-effect profile, the guidelines state.

Dr. Elmets

Methotrexate is more widely used outside the United States, "but it is a very good, quick fix and it's much safer in children and young people than it is in people with cardiovascular disease," Dr. Menter noted. "It's still the most commonly used drug worldwide because it's cheap, and you do have to worry about the long-term toxicity which is related the liver issues."

The guidelines say that subcutaneous administration of methotrexate "may be particularly useful" for patients on higher doses, which when taken orally, are associated with a higher risk of GI effects.

Dr. Menter referred to a 2017 study, which reported 41% of patients treated with subcutaneous methotrexate once a week achieved a Psoriasis Area and Severity Index 75 score of 41% after a year of treatment, compared with 10% of those on placebo (Lancet. 2017 Feb 4;389[10068]:528-37).

The guidelines rate strength of recommendation as class A for methotrexate for moderate to severe psoriasis in adults, recommend supplementation with folic or folinic acid to counteract GI complications and liver problems, and note that adalimumab and infliximab are more effective than methotrexate for cutaneous psoriasis. Class B recommendations for methotrexate and psoriasis include

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COMMENTARY BY DR. GELFAND: BIG news out of the new systemic nonbiologic joint AAD-NPF psoriasis treatment guidelines (full disclosure: I am the second author). There's a breadth of recommendations filling an astonishing 22 tables! But I will focus on one can't-miss detail, which is that we have completely revamped how to monitor for liver damage from methotrexate. Based on the new recommendations, liver biopsies should be a thing of the past for most of our patients. The new guidelines emphasize serology tests and noninvasive imaging to detect liver fibrosis before it becomes clinically significant. Here's what you need to know. First, assess the patient for risk factors for liver disease, many of which are common in psoriasis patients, such as obesity, diabetes, and hyperlipidemia. Next, in addition to your standard baseline labs for methotrexate, it is recommended to do a serologic test to identify signs of liver fibrosis. Options include fibrosis-4, an algorithm based on liver enzymes, platelet count, and age (available online), or patented tests such as FibroTest/FibroSure (BioPredictive), FibroMeter (Echosens), and Hepascore (Quest Diagnostics). Note that some of the patented tests require the patient to be fasting overnight. Depending on the results of the serologic test and the patient's liver disease risk factors, noninvasive imaging approaches such as FibroScan (Echosens), a vibration-controlled transient elastography may be recommended. Magnetic resonance elastography is a more accurate technique that should be considered if there is a technical failure with vibration-controlled transient elastography or in patients with a particularly high risk for failure such as body mass index of 40 kg/m^2 or greater. Details are in the guidelines.

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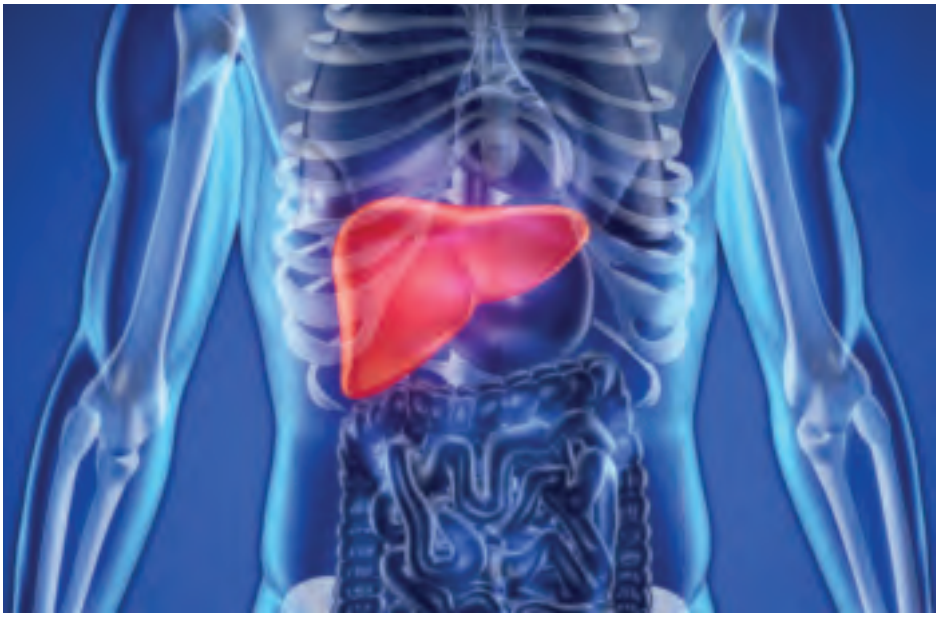
statements that patients should begin with a test dose, especially if they have impaired kidney function; methotrexate is effective for peripheral, but not axial, psoriatic arthritis (PsA); and TNF inhibitors are more effective than methotrexate for PsA.



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"We have completely revamped how to monitor for liver damage from methotrexate."

Approved by the Food and Drug Administration in 2014 for psoriasis, apremilast, which inhibits phosphodiesterase-4, is the newest drug in the recommendations. The guidelines recommend its use for moderate to severe psoriasis in adults, with a class A recommendation. Patients should start on a low dose and then build up to the 30-mg, twice-daily dose over 6 days and should be counseled about the risk of depression before starting treatment. Routine laboratory testing can be considered on an individual basis.

The guidelines also lay out three recommendations (and strength of recommendation) for cyclosporine, a drug that's been around since the 1990s: for severe, recalcitrant cases (class A); for erythrodermic, general pustular, and palmoplantar psoriasis (class B); and as short-term therapy for psoriasis flare in patients already on another drug (class C).

Acitretin is another longstanding therapy used mostly for palmar-plantar psoriasis, but it can also be used as monotherapy for plaque psoriasis as well as erythrodermic and pustular disease. It can also be used in combination with psoralens with UVA for psoriasis and combined with broadband UVB phototherapy for plaque psoriasis. The acitretin recommendations are class B.

The oral Janus kinase (JAK) inhibitor tofacitinib isn't specifically approved for psoriasis, but it is approved for RA, PsA, and ulcerative colitis. The drug targets the JAK-STAT signaling pathway that causes inflammation. The guidelines state that tofacitinib can be considered for moderate to severe psoriasis, but lists no strength of recommendation. The recommended dose is either 5 or 10 mg orally twice a day, with a caveat that the higher dose carries a higher risk of adverse events. Patients should be evaluated for getting a zoster vaccine before they begin therapy.

"We thought that, because there was probably a small chance that it might get approved for psoriasis, that we would discuss it briefly," Dr. Menter said of tofacitinib.

Another off-label use the guidelines address is for fumaric and acid esters, also known as fumarates, which are used to in Europe to treat moderate to severe psoriasis. Dimethyl fumarate is approved for relapsing forms of multiple sclerosis in the United States. The guidelines state that fumarates can be used for psoriasis, but offer no strength of recommendation. Side effects include gastrointestinal disturbance and flushing.

Other treatments that are also addressed in the guidelines include a host of systemic immunosuppressants and antimetabolites: azathioprine, hydroxyurea, leflunomide, mycophenolate mofetil, thioguanine, and tacrolimus, none of which are FDA approved for psoriasis. They're rarely used for psoriasis, but may have value in selected cases, the guidelines state.

Dr. Menter said that apremilast is the only oral drug in the guidelines, but they are the wave of the future for treating psoriasis. "I think there's a tremendous potential for new oral drugs – TK2 [thymidine kinase], the JAK inhibitors, and other drugs coming down the pipelines. The majority of patients, if you ask them their preference, would like to take an oral drug rather than an injectable drug. And it would be much easier for dermatologists, they wouldn't have to train patients on how to do the injections."

Dr. Menter and Dr. Elmets disclosed financial relationships with numerous pharmaceutical companies. Other authors/work group members also had disclosures related to pharmaceutical manufacturers, and several had no disclosures.

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SOURCE: Menter A et al. J Am Acad Dermatol. 2020 Jun;82(6):1445-86.

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*In the ERASURE study at week 12, 82% of patients in the COSENTYX 300-mg arm (n=245) achieved a PASI 75 response and 65% of patients achieved IGA 0 or 1 vs 4% and 2% in the placebo group (n=248), respectively.[1] In the FIXTURE study at week 12, 76% of patients in the COSENTYX 300-mg arm (n=327) achieved a PASI 75 response and 62% of patients achieved IGA 0 or 1 vs 5% and 3% in the placebo group (n=326), respectively.[1] In the FUTURE 2 study, for patients with active psoriatic arthritis treated with COSENTYX 300 mg (n=100), 150 mg (n=100), or placebo (n=98), ACR20 response at week 24 was 54%, 51%, and 15%, respectively.[1] In the ERASURE (N=738) and FIXTURE (N=1306) studies, among the patients who chose to participate (39%) in assessments of patient-reported outcomes, improvements in signs and symptoms related to itching, pain, and scaling at week 12 compared with placebo were observed using the Psoriasis Symptom Diary©.[1]

†NBRx share as prescribed by rheumatologists, allocated using Symphony Health patient longitudinal data to limit product use to *ICD-10* codes for PsA and/or PsO. NBRx is the IQVIA NPA New to Brand® measure showing the volume of prescriptions associated with first-time patient use of a product.[2]

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

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

Please see additional Important Safety Information on reverse.
Please see Brief Summary of full Prescribing Information on the following pages.

Cosentyx® (secukinumab)

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Infections

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

Exercise caution when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and COSENTYX should be discontinued until the infection resolves.

Pre-treatment Evaluation for Tuberculosis

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

Inflammatory Bowel Disease

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

Hypersensitivity Reactions

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

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

Vaccinations

Prior to initiating therapy with COSENTYX, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with COSENTYX should not receive live vaccines.

Non-live vaccinations received during a course of COSENTYX may not elicit an immune response sufficient to prevent disease.

MOST COMMON ADVERSE REACTIONS

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

References: 1. COSENTYX [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** IQVIA NPA Weekly Tracker as of December 2019. Data on File for step-by-step PsA share calculation by Novartis Pharmaceuticals Corp.

Please see additional Important Safety Information on the previous page.
Please see Brief Summary of full Prescribing Information on the following pages.

Cosentyx® (secukinumab)

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 8/20 COS-1393474

COSENTYX® (secukinumab) injection, for subcutaneous use
COSENTYX® (secukinumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

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

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

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

1.2 Psoriatic Arthritis

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

1.3 Ankylosing Spondylitis

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

1.4 Non-radiographic Axial Spondyloarthritis

COSENTYX is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

4 CONTRAINDICATIONS

COSENTYX is contraindicated in patients with a previous serious hypersensitivity reaction to secukinumab or to any of the excipients *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

COSENTYX may increase the risk of infections. In clinical trials, a higher rate of infections was observed in COSENTYX treated subjects compared to placebo-treated subjects. In placebo-controlled clinical trials in patients with moderate to severe plaque psoriasis, higher rates of common infections, such as nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with candida (1.2% versus 0.3%) were observed with COSENTYX compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis *[see Adverse Reactions (6.1)]*. The incidence of some types of infections appeared to be dose-dependent in clinical studies *[see Adverse Reactions (6.1)]*.

Exercise caution when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and COSENTYX should be discontinued until the infection resolves.

5.2 Pre-treatment Evaluation for Tuberculosis

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

5.3 Inflammatory Bowel Disease

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

5.4 Hypersensitivity Reactions

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

5.5 Risk of Hypersensitivity in Latex-Sensitive Individuals

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

5.6 Vaccinations

Prior to initiating therapy with COSENTYX, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with COSENTYX should not receive live vaccines.

Non-live vaccinations received during a course of COSENTYX may not elicit an immune response sufficient to prevent disease.

6 ADVERSE REACTIONS

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

- Infections *[see Warnings and Precautions (5.1)]*
- Inflammatory Bowel Disease *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

Plaque Psoriasis

A total of 3430 plaque psoriasis subjects were treated with COSENTYX in controlled and uncontrolled clinical trials. Of these, 1641 subjects were exposed for at least 1 year.

Four placebo-controlled Phase 3 trials in plaque psoriasis subjects were pooled to evaluate the safety of COSENTYX in comparison to placebo up to 12 weeks after treatment initiation, in Trials 1, 2, 3, and 4. In total, 2077 subjects were evaluated (691 to COSENTYX 300 mg group, 692 to COSENTYX 150 mg group, and 694 to placebo group) *[see Clinical Studies (14) in the full prescribing information]*.

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

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

Adverse Reactions	COSENTYX		Placebo (N = 694) n (%)
	300 mg (N = 691) n (%)	150 mg (N = 692) n (%)	
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)
Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)
Pharyngitis	8 (1.2)	7 (1.0)	0 (0)
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)
Rhinorrhea	8 (1.2)	2 (0.3)	1 (0.1)

Adverse reactions that occurred at rates less than 1% in the placebo-controlled period of Trials 1, 2, 3, and 4 through Week 12 included: sinusitis, tinea pedis, conjunctivitis, tonsillitis, oral candidiasis, impetigo, otitis media, otitis externa, inflammatory bowel disease, increased liver transaminases, and neutropenia.

Infections

In the placebo-controlled period of the clinical trials in plaque psoriasis (a total of 1382 subjects treated with COSENTYX and 694 subjects treated with placebo up to 12 weeks), infections were reported in 28.7% of subjects treated with COSENTYX compared with 18.9% of subjects treated with placebo. Serious infections occurred in 0.14% of patients treated with COSENTYX and in 0.3% of patients treated with placebo *[see Warnings and Precautions (5.1)]*.

Over the entire treatment period (a total of 3430 plaque psoriasis subjects treated with COSENTYX for up to 52 weeks for the majority of subjects), infections were reported in 47.5% of subjects treated with COSENTYX (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of subjects treated with COSENTYX (0.015 per patient-year of follow-up).

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

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

Inflammatory Bowel Disease

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

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

Hypersensitivity Reactions

Anaphylaxis and cases of urticaria occurred in COSENTYX treated patients in clinical trials *[see Warnings and Precautions (5.4)]*.

Psoriatic Arthritis

COSENTYX was studied in two placebo-controlled psoriatic arthritis trials with 1003 patients (703 patients on COSENTYX and 300 patients on placebo). Of the 703 patients who received COSENTYX, 299 patients received a subcutaneous loading dose of COSENTYX (PsA1) and 404 patients received an intravenous loading dose of secukinumab (PsA2) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled period of the trials in patients with psoriatic arthritis, the overall proportion of patients with adverse events was similar in the secukinumab and placebo-treatment groups (59% and 58%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the COSENTYX

groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, upper respiratory tract infection, headache, nausea, and hypercholesterolemia. The safety profile observed in patients with psoriatic arthritis treated with COSENTYX is consistent with the safety profile in psoriasis.

Similar to the clinical trials in patients with psoriasis, there was an increased proportion of patients with infections in the COSENTYX groups (29%) compared to placebo group (26%) *[see Warnings and Precautions (5.1)]*.

There were cases of Crohn's disease and ulcerative colitis that include patients who experienced either exacerbations or the development of new disease. There were three cases of inflammatory bowel disease, of which two patients received secukinumab and one received placebo *[see Warnings and Precautions (5.3)]*.

Ankylosing Spondylitis

COSENTYX was studied in two placebo-controlled ankylosing spondylitis trials with 590 patients (394 patients on COSENTYX and 196 patients on placebo). Of the 394 patients who received COSENTYX, 145 patients received a subcutaneous load of COSENTYX (study AS1), and 249 received an intravenous loading dose of secukinumab (study AS2) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled period of the trials in patients with ankylosing spondylitis, the overall proportion of patients with adverse events was higher in the secukinumab groups than the placebo-treatment groups (66% and 59%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the COSENTYX groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, nausea, and upper respiratory tract infection. The safety profile observed in patients with ankylosing spondylitis treated with COSENTYX is consistent with the safety profile in psoriasis. In a third controlled study of AS (study AS3), the safety profile of the 300 mg dose of COSENTYX was consistent with the safety profile of the 150 mg dose of COSENTYX.

Similar to clinical trials in patients with psoriasis, there was an increased proportion of patients with infections in the COSENTYX groups (31%) compared to the placebo group (18%) *[see Warnings and Precautions (5.1)]*.

In the original ankylosing spondylitis program, with 571 patients exposed to COSENTYX there were 8 cases of inflammatory bowel disease during the entire treatment period [5 Crohn's (0.7 per 100 patient-years) and 3 ulcerative colitis (0.4 per 100 patient-years)]. During the placebo-controlled 16-week period, there were 2 Crohn's disease exacerbations and 1 new onset ulcerative colitis case that was a serious adverse event in patients treated with COSENTYX compared to none of the patients treated with placebo. During the remainder of the study when all patients received COSENTYX, 1 patient developed Crohn's disease, 2 patients had Crohn's exacerbations, 1 patient developed ulcerative colitis, and 1 patient had an ulcerative colitis exacerbation *[see Warnings and Precautions (5.3)]*.

Non-radiographic Axial Spondyloarthritis

COSENTYX was studied in one randomized, double-blind, placebo-controlled non-radiographic axial spondyloarthritis trial with 555 patients (185 patients on with load COSENTYX, 184 patients on without load COSENTYX and 186 patients on placebo). The safety profile for patients with nr-axSpA treated with COSENTYX was overall similar to the safety profile seen in patients with AS and other previous experience with COSENTYX. Patients in nr-axSpA1 study who received the loading dosing regimen compared to those without the loading regimen, had higher incidence of infections and infestations (92 per 100 patient-years vs 72 per 100 patient years), including nasopharyngitis, upper respiratory tract infection and urinary tract infection, and gastrointestinal disorders (27 per 100 patient-years vs 22 per 100 patient-years), including gastritis, lower abdominal pain, colitis, diarrhea, and hematochezia.

6.2 Immunogenicity

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

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (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 incidence of antibodies to COSENTYX with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Patients treated with COSENTYX may not receive live vaccinations *[see Warnings and Precautions (5.6)]*.

7.2 Non-Live Vaccines

Patients treated with COSENTYX may receive non-live vaccinations. Healthy individuals who received a single 150 mg dose of COSENTYX 2 weeks prior to vaccination with a non-U.S. approved group C meningococcal polysaccharide conjugate vaccine and a non-U.S. approved inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive COSENTYX prior to vaccination. The clinical effectiveness of meningococcal and influenza vaccines has not been assessed in patients undergoing treatment with COSENTYX *[see Warnings and Precautions (5.6)]*.

7.3 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation.

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

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Specific markers detect psoriatic disease inflammation without elevated CRP

By Jake Remaly

Five serum markers detect systemic inflammation in patients with psoriatic disease in the absence of elevated C-reactive protein, according to a cross-sectional study of patients and healthy controls.

"Different clinical subsets of psoriatic disease based on skin, entheseal, and joint involvement are characterized by specific inflammation marker profiles," Maria V. Sokolova, MD, of Friedrich-Alexander University Erlangen-Nuremberg and University Clinic Erlangen (Germany) and colleagues reported in Arthritis Research & Therapy. "Treatment of psoriatic disease with cytokine inhibitors reduces these elevated levels of systemic inflammation markers."

Quantifying systemic inflammation in psoriatic disease has been a challenge, Dr. Sokolova and colleagues wrote. Levels of C-reactive protein (CRP), a commonly used measure of systemic inflammation, "are often low or absent." To examine other potential markers of systemic inflammation in psoriatic disease, they conducted cross-sectional and longitudinal studies that included healthy controls and patients with psoriatic disease. Patients had isolated or combined manifestations of psoriatic disease, including the skin, the entheses, and the joints. The researchers grouped patients by isolated psoriatic skin disease; isolated enthesitis; isolated arthritis; psoriatic skin disease with enthesitis; psoriatic skin disease with arthritis; arthritis and enthesitis; and combined psoriatic skin disease, arthritis, and enthesitis.

The researchers first assessed 10 potential markers using enzyme-linked immunosorbent assay: calprotectin, interleukin-22, IL-8, lipocalin 2, beta-defensin 2, IL-17, IL-23, vascular endothelial growth factors, LL37 (cathelicidin), and pentraxin 3. They measured the markers in 10 healthy controls and 10 patients with active polymorphic psoriatic arthritis. Five parameters – beta-defensin 2, lipocalin 2, IL-22, IL-8, and calprotectin – significantly differed between controls and patients with psoriatic disease. Lipocalin 2, beta-defensin 2, and IL-22 are associated with IL-17/IL-23 activation, and calprotectin and IL-8 are associated with innate immune cell activation. The other markers did not significantly differ or were not detectable in enough participants.

To validate the signals, the researchers measured the five parameters as well as CRP in 105 controls and 105 patients with psoriatic disease, including 15 patients in each of the seven disease pattern groups.

"As expected, CRP levels were normal in the majority of individuals," they wrote. The proportion of patients with CRP greater than 5 mg/L was 0% in isolated psoriatic skin disease, 0% in isolated enthesitis; 20% in isolated arthritis; 7% in psoriatic skin disease with enthesitis; 33% in psoriatic skin disease with arthritis; 27% in arthritis with enthesitis; and 33% in combined psoriatic skin disease, arthritis, and enthesitis.

"Only a subset of patients with arthritis, but not patients with skin or entheseal disease show elevated CRP," the researchers wrote. "In sharp contrast," beta-defensin 2 and lipocalin 2 were elevated in a majority of patients with monomorphic skin and entheseal disease, but not in joint disease.

"Both proteins were significantly correlated to the extent of skin disease and to a lesser extent also entheseal disease," they added. Calprotectin and IL-8 were elevated in a majority of patients with joint disease and correlated with the extent of arthritis. "IL-22 was elevated ... in all three manifestations of psoriatic disease," and the vast majority of patients with polymorphic disease had "widespread marker elevation," the researchers wrote.

"Overall, these results offer a new possibility to measure systemic inflammation in psoriatic disease," Dr. Sokolova and colleagues wrote.

The study was supported by the German Research Foundation and other grant and fellowship funding. The authors had no competing interests.

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SOURCE: Sokolova MV et al. Arthritis Res Ther. 2020;22:26.

COMMENTARY BY DR. GELFAND: How can it be that psoriasis patients can demonstrate such significant inflammation in their skin and joints on examination and have normal markers of inflammation, such as C-reactive protein, in their blood? Well, perhaps we are looking at the wrong biomarker (I know – shocker, right?). Sokolova et al. demonstrated this point by looking at a cohort of patients with psoriatic disease and varying clinical presentations, ranging from disease limited to the skin to disease involving the entheses and/or joints as well. They evaluated novel markers of systemic inflammation such as lipocalin 2, beta-defensin 2, interleukin-22, calprotectin, and IL-8 and found that these were all markedly elevated in these patients, compared with healthy controls, despite having a normal CRP. Beta-defensin 2 and lipocalin 2 are both IL-17–regulated mediators, whereas calprotectin and IL-8 are related to innate immunity. IL-22 is produced by Th22 cells and contributes to inflammation in lupus, rheumatoid arthritis, and psoriasis. These data suggest that, when it comes to looking for systemic inflammation associated with psoriasis in the clinic, we should believe our own eyes and not the results of CRP.

Beyond PASI 100: Striving for molecular clearance

By Bruce Jancin

All PASI 100 responses to psoriasis therapy are not the same, Andrew Blauvelt, MD, declared at the virtual annual meeting of the American Academy of Dermatology.

He presented a first-of-its-kind study that potentially opens the door to a new, more rigorous standard for treatment success in psoriasis: not simply cleared lesional skin as captured by a Psoriasis Area and Severity Index (PASI) 100 response, but also clearance of residual psoriasis signs and symptoms – as well as what he termed "molecular clearance."

"We've found that clearing skin with drugs utilizing different mechanisms of action may lead to differential consequences for our patients," observed Dr. Blauvelt, a dermatologist and clinical trialist who is president of the Oregon Medical Research Center, Portland.

A PASI 100 response, traditionally considered an elusive goal for the great majority of patients with severe psoriasis, can now often be achieved using today's top-tier, high-performance biologics. But Dr. Blauvelt and his coinvestigators are interested in pushing even beyond PASI 100 to a new frontier of therapeutic benefit.

"Nothing like this analysis has ever been done before."

He presented a secondary analysis of the previously reported VOYAGE 1 and 2 head-to-head randomized trials of guselkumab (Tremfya) versus adalimumab (Humira) for treatment of moderate to severe psoriasis (J Am Acad Dermatol. 2017 Mar;76[3]:405-17, 418-31). This new analysis, which focused exclusively on PASI 100 responders by week 24, demonstrated that patients with a PASI 100 response to guselkumab, an interleukin (IL)-23 inhibitor, had significantly fewer persistent symptoms and signs of psoriasis than those whose skin clearance was attained using adalimumab, a tumor necrosis factor (TNF) inhibitor.

Courtesy Dr. Andrew Blauvelt

Dr. Andrew Blauvelt

Moreover, the investigators showed that the gene expression profile of PASI 100 responders who were free of signs and symptoms was more normalized than that of patients with residual symptoms despite their cleared skin.

The analysis included 16 participants in the VOYAGE trials who achieved PASI 100 at week 24 on guselkumab and 5 who did so on adalimumab. At baseline and again at week 24, these individuals completed the Psoriasis Symptoms and Signs Diary (PSSD). Also, biopsies of lesional and nonlesional skin were obtained at baseline and of cleared lesional skin at week 24 for transcriptomic microarray analysis

COMMENTARY BY DR. GELFAND: Two of my patients are 100% clear of their psoriasis. Does it matter which cytokine I targeted with a biologic to achieve this outstanding response when both patients now have completely clear skin? In this provocative preliminary study presented at the virtual AAD meeting by Andrew Blauvelt, MD, the answer may be yes!

The researchers did a subanalysis of psoriasis patients treated with either guselkumab (IL-23 inhibitor) or adalimumab (TNF-alpha inhbitor) who achieved PASI 100 at week 24 in the Voyage 1 and 2 randomized controlled trials. First, they observed that about half of patients whose skin was clear of psoriasis have residual skin symptoms. This statistical finding very much parallels what I see in clinic where patients with 100% clear skin tell me they can "feel" their psoriasis when they are approaching their next shot, despite being clear.

Provocatively, the investigators observed 10 insufficiently normalized genes in the skin of psoriasis patients who achieved clear skin but still had underlying symptoms, which demonstrates a plausible mechanistic explanation for the subjective complaints. Second, more guselkumab-treated patients achieved symptom-free and sign-free status, compared with adalimumab-treated patients, at week 24 and fewer genes were insufficiently normalized in guselkumab-treated patients than in adalimumab-treated patients.

This analysis is a reminder that psoriasis patients with clear skin are not necessarily clear of their psoriasis. More work needs to be done to determine the clinical significance of residual skin symptoms in patients with psoriasis who achieve clear skin. How clinically important are these residual symptoms? Do they need to be treated, and if so, how? And perhaps most important, are they a marker that the patient will eventually lose response to their biologic?

of the expression of many thousands of genes.

Persistent psoriasis symptoms despite cleared skin

The PSSD involves patient ratings of various psoriasis symptoms and signs. Total scores can range from 0 (symptom- and sign-free) up to 100. At week 24, a significantly higher proportion of guselkumab-treated PASI 100 responders had a total PSSD score of zero: 55%, versus 43% in the adalimumab group. This was consistently true across the board for each of the individual signs and symptoms assessed. For example, 61% of the guselkumab group gave themselves a zero for itch, as did 50% of the adalimumab group. Sixty-four percent on guselkumab and 52% on adalimumab reported being free of redness. And 78% of the guselkumab group reported being pain-free, compared with 69% with adalimumab, Dr. Blauvelt reported.

Gene expression analysis

At baseline, more than 2,300 dysregulated genes were identified in lesional skin while functioning normally in nonlesional skin. The great majority of these initially dysregulated genes became normalized in cleared lesional skin in PASI 100 responders at week 24. However, 25 of the genes remained dysregulated in cleared lesional skin, meaning they displayed less than 75% of normal function. Ten of these 25 genes with dysregulated expression at follow-up showed abnormal function in patients with residual symptoms despite cleared skin, but they functioned normally in those without persistent symptoms. This raises the possibility that the residual symptoms of psoriasis were attributable to the abnormal gene functioning, according to Dr. Blauvelt.

Of note, 9 of the 10 dysregulated genes in cleared lesional skin of patients with residual symptoms were present in the adalimumab group; these included 2 genes localized to the epidermal differentiation complex as well as the psoriasis-specific proline-rich 9 gene known as PRR9, which is induced by IL-17A. In contrast, only four genes, none of which were localized to the epidermal differentiation complex, were insufficiently normalized in the cleared lesional skin of guselkumab-treated PASI 100 responders.

"Nothing like this analysis has ever been done before," the dermatologist observed. "It's a pilot study. Perhaps with more data like this, we'll be using this type of information in clinical practice to go beyond clearing patients' skin."

Dr. Blauvelt reported serving as a scientific adviser to and paid clinical investigator for Janssen, which sponsored the study, as well as for roughly two dozen other pharmaceutical companies.

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Christine Langer/Thinkstock

Ultrasound improves specificity of psoriatic arthritis referrals

By Bianca Nogrady

The use of ultrasound in screening for psoriatic arthritis in patients with psoriasis could reduce the number of unnecessary referrals to rheumatologists, according to a research letter published in the British Journal of Dermatology.

Up to one-third of patients with psoriasis have underlying psoriatic arthritis (PsA), but half of all patients with psoriasis experience nonspecific musculoskeletal complaints.

"Different screening tools have been developed for the dermatology practice to distinguish patients with a higher likelihood of having PsA; however, the low specificities of these tools limit their use in clinical practice," wrote Dilek Solmaz, MD, and colleagues at the University of Ottawa.

In this prospective study, 51 patients with psoriasis were screened for referral to a rheumatologist using the Early Arthritis for Psoriatic Patients and Psoriasis Epidemiology Screening Tool questionnaires. They also underwent a limited ultrasound scanning of wrists, hands, feet, and the most painful joint, which was reviewed by experienced rheumatologists.

Bogdanhoda/Thinkstock

A dermatologist was asked to make a decision on referral based on the questionnaire data alone, then invited to revisit that decision after viewing the ultrasound results. When basing their decision on the questionnaires only, the dermatologist decided to refer 92% of patients to a rheumatologist. Of these patients, 40% were subsequently diagnosed with PsA, which represented a sensitivity of 95% but specificity of just 9%.

After reviewing the ultrasound data, the dermatologist revised their recommendations and referred only 43% of patients. Of these, 68% were later diagnosed with psoriatic arthritis. Among the patients who were not referred after the ultrasound review, five were diagnosed with PsA, but two had isolated axial involvement with no peripheral joint disease. Excluding these two cases, the sensitivity decreased to 88% but specificity increased to 77%.

"Screening tools in psoriasis that have high sensitivities usually have low specificities, which means a higher number of patients to be referred to rheumatology than needed," the authors wrote. "Our study demonstrated that a musculoskeletal [ultrasound] based on a predefined protocol improves the referrals made to rheumatology."

The authors did note that the ultrasounds were reviewed by experienced rheumatologists, so the results might not be generalizable to less-experienced sonographers without experience in musculoskeletal disorders.

The study was funded by AbbVie. One author declared receiving funding for a fellowship from UCB. Two authors declared honoraria and advisory consultancies with the pharmaceutical sector, including AbbVie.

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SOURCE: Solmaz D et al. Br J Dermatol. 2019 Nov 28. doi: 10.1111/bjd.18515.

COMMENTARY BY DR. MENTER: In this study of patients with psoriasis, which evaluated ultrasound as a screening tool for psoriatic arthritis (PsA), specificity was increased when dermatologists reviewed joint ultrasound results plus results of screening questionnaires, compared with questionnaires alone, which the investigators noted could reduce unnecessary referrals to rheumatologists.

Most dermatologists in clinical practice do not have regular access to ultrasound, but they do have a definitive role in assessing their psoriasis patients for psoriatic joint disease at each and every visit. Ask patients about early morning joint stiffness, which disappears after 30-40 minutes of waking up (a classic sign), and then do a quick evaluation. Check the fingers and toes for dactylitis, which affects the hands and feet equally, and press on each joint to check for tenderness. While the patient is standing up, have them turn in the opposite direction and look at the heels to see if there is a difference; for example, one Achilles that is swollen and red, compared with the other. Then, take your thumb and index finger, starting at the base of the calf, and gently rub down to the heel to check for tenderness in the Achilles tendons. I check for tenderness in the heel by pressing on the talus bone, and ask the patient to lift up his or her heel; plantar fasciitis is an early sign of PsA. Finally, take your thumb and press on the sacroiliac joint to check for sacroiliitis, common in patients with PsA. This exam can be done in a minute or less, and can effectively diagnose early joint disease in patients with psoriasis, which can prevent permanent joint damage.

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

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

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

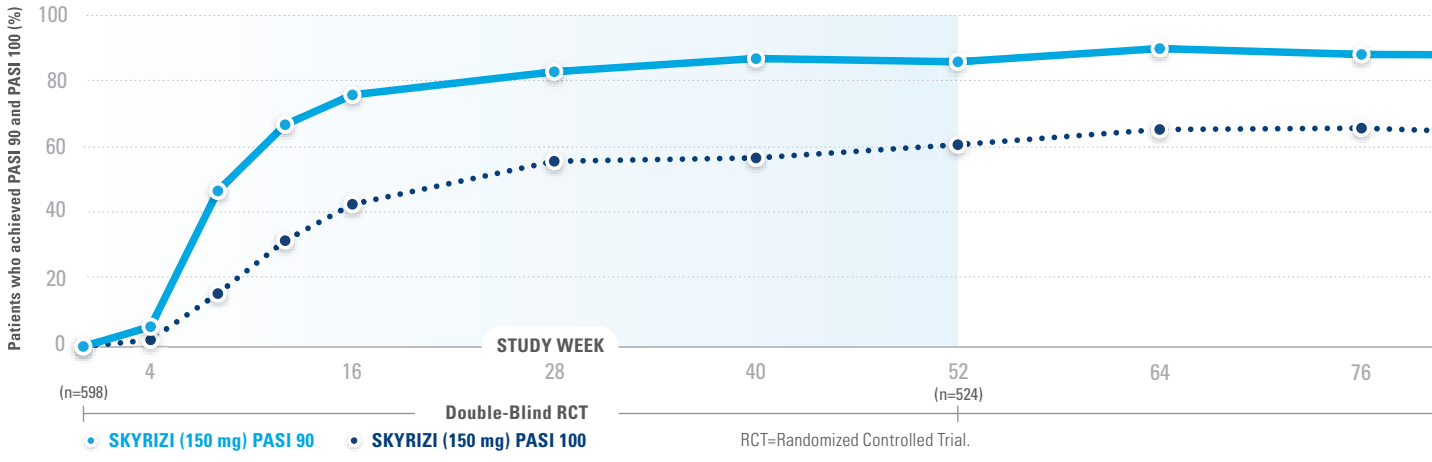
NRI=Non-Responder Imputation.

Study Design: UltIMMa-1 (N=506) and ultIMMa-2 (N=491) were replicate phase 3, randomized, double-blind, placebo- and active-controlled studies to evaluate the efficacy and safety of SKYRIZI (150 mg) vs placebo over 16 weeks and biologic active control over 52 weeks in adult patients with moderate to severe plaque psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous injections at Weeks 0, 4, and every 12 weeks thereafter.[2]

CONSISTENT PASI 90/100 RATES AT 2.5 YEARS IN OPEN-LABEL EXTENSION[4]

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

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



RCT=Randomized Controlled Trial.

INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

Infection

- SKYRIZI™ (risankizumab-rzaa) may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.
- In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Pre-Treatment Evaluation for Tuberculosis (TB)

- Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate

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MAINTENANCE OF RESPONSE

Skyrizi™
risankizumab-rzaa
75mg/0.83mL Injection

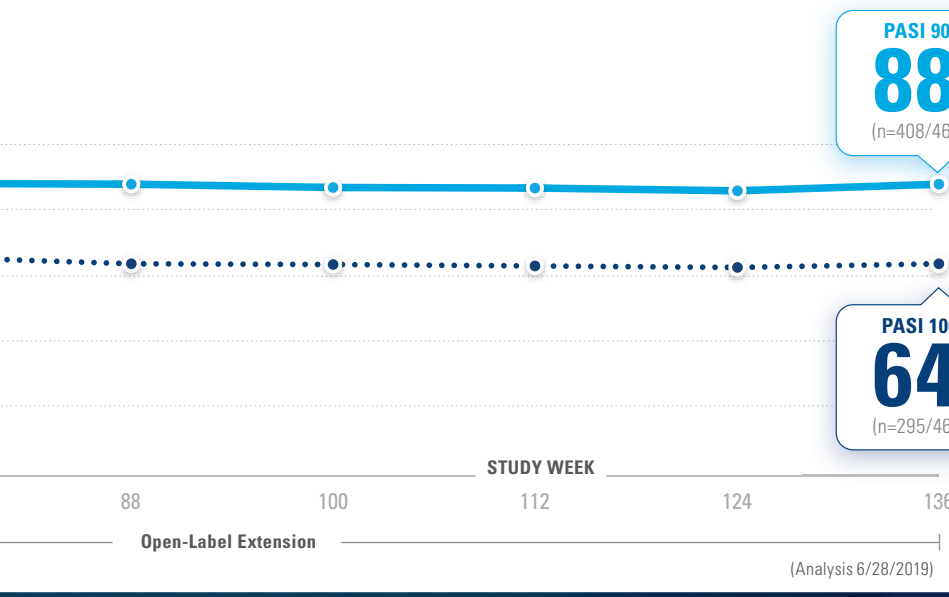
AT WEEK 52

In the randomized controlled trials, among patients who achieved PASI 90 and PASI 100 at Week 16, level of response was maintained at Week 52 by 88% (n=398/450) and 80% (n=206/258), respectively.[1]

AT WEEK 136

In an observed analysis,* among patients who achieved PASI 90 and PASI 100 at Week 52 and had available data at Week 136 in the open-label extension, level of response was maintained at Week 136 by 94% (n=375/398) and 82% (n=232/282), respectively.[4]

*Analysis conducted 8/6/2019.



KEY VARIABLES (AS MEASURED EVERY 12 WEEKS) OF OLE

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

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

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

course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Immunizations

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

Adverse Reactions

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

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

References: 1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **2.** Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650-661. **3.** Lebwohl M, Bachelez H, Valdecantos WC, Wu T, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis: an integrated analysis of UltIMMa-1 and UltIMMa-2. Poster presented at: American Academy of Dermatology Annual Meeting; March 1-5, 2019; Washington, DC. **4.** Data on file, ABVRRTI69209.

 North Chicago, IL 60064 US-SKZD-200054 January 2020 Printed in U.S.A.

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

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infections

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

The rate of serious infections for the SKYRIZI group and the placebo group was ≤ 0.4%. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the IMMHANCE study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Immunizations

Prior to initiating therapy with SKYRIZI, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with SKYRIZI. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS

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

- Infections *[see Warnings and Precautions]*

Clinical Trials Experience

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

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

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

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical studies.

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

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

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis

[b] Includes: headache, tension headache, sinus headache, cervicogenic headache

[c] Includes: fatigue, asthenia

[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth

[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

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

Specific Adverse Drug Reactions

Infections

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

Safety through Week 52

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

Immunogenicity

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

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

DRUG INTERACTIONS

Live Vaccinations

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with SKYRIZI.

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

PATIENT COUNSELING INFORMATION

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

Infections

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

Administration Instruction

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

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

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

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA
US License Number 1889

Ref: 20063596-R1 Revised March, 2020

LAB-3552 **MASTER**

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Registry data reveal temporal relationship between psoriasis symptoms and PsA onset

By Sharon Worcester

Psoriasis type and patient age at presentation among patients with psoriatic arthritis predict the timing of arthritis symptom synchronicity, according to findings from the Psoriatic Arthritis Registry of Turkey International Database.

However, in those who develop arthritis symptoms first, age at onset is not predictive of psoriatic arthritis (PsA) symptom synchronicity, Umut Kalyoncu, MD, reported at the 2019 annual meeting of the American College of Rheumatology.

Of 1,631 patients from the registry, 1,251 had psoriasis first, 71 had arthritis first, and 309 had synchronous onset, which was defined as the onset of both psoriasis and arthritis symptoms within a 12-month period. The time from skin disease to PsA was 155.6 months, –67.4 months, and 1.8 months, among the groups, respectively, and the mean age at PsA onset was similar, ranging from about 41 to 42 years in those who developed arthritis first, said Dr. Kalyoncu, of the department of rheumatology at Hacettepe University, Ankara, Turkey.

However, the mean age of PsA onset among those who developed psoriasis first was 29.4 years, compared with 46.3 years in those who developed arthritis first.

"So there is a really big difference between psoriasis beginning age," he said.

PsA types also differed by onset symptoms: Axial involvement was more common with arthritis-first onset at 38.0%, compared with 28.8% for psoriasis-first and 27.8% for synchronous onset). Oligoarthritis occurred more often with arthritis-first onset (45.1% vs. 30.7% and 29.4%, respectively), and polyarthritis occurred less often with arthritis-first onset (33.8% vs. 49.4% and 47.6%, respectively), he said.

Psoriasis type also differed among the groups: Pustular skin involvement was more common in arthritis-first patients (18.3% vs. 11.9% and 16.5% of psoriasis-first and synchronous-onset patients), scalp lesions as the initial lesion were more common in psoriasis-first patients (48.3% vs. 35.2% of arthritis-first patients and 39.8% of synchronous-onset patients), and genital involvement was present more often in arthritis-first patients (12.7% vs. 6.2% and 4.9% of psoriasis-first and synchronous-onset patients).

A family history of psoriasis or PsA was more common in psoriasis-first patients.

Early-onset (type 1) psoriasis was more common in psoriasis-first patients (74% vs. 28.1% and 51.8% of arthritis-first and synchronous-onset patients), whereas late-onset (type 2) psoriasis was more common in arthritis-first patients (71.9% vs. 26.0% and 48.2% for psoriasis-first and synchronous-onset patients).

A family history of psoriasis or PsA was more common in psoriasis-first patients (35.6% vs. 26.3% and 28.2% of arthritis-first and synchronous-onset patients), Dr. Kalyoncu said.

Treatment types did not differ between the groups.

Multiple linear regression analysis for the time elapsed from psoriasis to PsA symptom synchronicity, with all other independent variables set to baseline values, showed an overall intercept interval of 66 months, but with nail involvement, family history, or plaque psoriasis, the interval was extended by 28, 24, and 20 months, respectively. However, the presence of pustular psoriasis decreased the intercept interval by 28 months.

A temporal relationship between the onset of skin psoriasis and PsA is a well-known feature of psoriatic disease, with prior studies showing that the majority of cases involve psoriasis-first onset, Dr. Kalyoncu said, adding that heterogeneity in musculoskeletal and skin involvement is also a known feature.

However, little is known about the role of genetics, he noted.

Therefore, he and his colleagues used the Psoriatic Arthritis Registry of Turkey International Database, which was established in 2014 and now also includes data from patients in Canada and Italy, to explore the associations between disease characteristics and the temporal relationship of skin and musculoskeletal disease.

Based on the findings, age at the onset of psoriasis was the main factor that determined PsA symptom synchronicity, he said.

"We know that HLA-Cw6 is important in genetic susceptibility of psoriatic arthritis, but it is important only for early-onset arthritis, not late-onset psoriasis," Dr. Kalyoncu said. "So our results make an indirect contribution [to the understanding of] these genetic and immunochemical differences between early-onset and late-onset psoriasis, and we need further future studies about this topic."

Dr. Kalyoncu reported having no relevant disclosures.

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SOURCE: Kalyoncu U et al. Arthritis Rheumatol. 2019;71(suppl 10), Abstract 2854.

New psoriasis guidelines focus on topical and alternative treatments, and severity measures

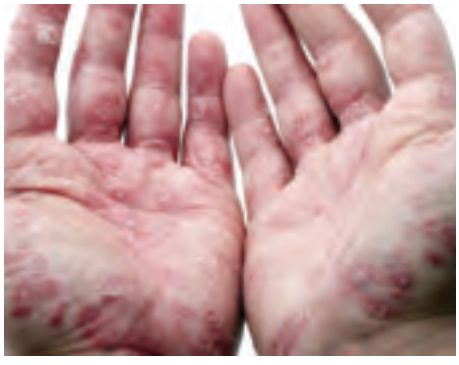
By Heidi Splete

Topical agents, alternative medicine, and disease severity assessment are the subjects of the latest updated set of guidelines for the management and treatment of psoriasis issued jointly by the American Academy of Dermatology and the National Psoriasis Foundation.

The guidelines, published in the Journal of the American Academy of Dermatology, focus on treatment for adults, and follow the release of other AAD-NPF guidelines on biologics for psoriasis, psoriasis-related comorbidities, pediatric psoriasis, and phototherapy in 2019, and earlier this year, guidelines for systemic nonbiologic treatments.

The latest guidelines' section on topical treatment outlines evidence for the efficacy, effectiveness, and adverse events related to topical steroids, topical tacrolimus and pimecrolimus, vitamin D analogues, tazarotene, moisturizers, salicylic acid, anthralin, coal tar, combinations with biologic agents, and combinations with nonbiologic treatments (methotrexate, cyclosporine, acitretin, and apremilast).

The guidelines noted the "key role" of topical corticosteroids in treating psoriasis "especially for localized disease," and include a review of the data on low-, moderate-, high-, and ultrahigh-potency topical steroids for psoriasis.



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In general, all topical steroids can be used in combination with biologics, according to the guidelines, but the strongest recommendations based on the latest evidence include the addition of an ultrahigh-potency topical corticosteroid to standard-dose etanercept for 12 weeks. Currently, 11 biologics are approved by the Food and Drug Administration for the treatment of psoriasis.

In addition, "while not FDA approved for psoriasis, the topical calcineurin inhibitors tacrolimus and pimecrolimus are often employed in the treatment of psoriasis," can be helpful for "thinner skin such as facial and intertriginous areas," and can be steroid sparing when used for more than 4 weeks, according to the guidelines.

Don't discount the role of patient preferences when choosing topical treatments, the authors noted. "The optimal vehicle choice is the one the patient is mostly likely to use."

The guidelines also address the evidence for effectiveness, and adverse events in the use of several alternative medicines for psoriasis including traditional Chinese medicine, and the herbal therapies aloe vera and St. John's wort, as well as the potential role of dietary supplements including fish oil, vitamin D, turmeric, and zinc in managing psoriasis, and the potential role of a gluten-free diet.

In general, research on the efficacy, effectiveness, and potential adverse effects of these strategies are limited, according to the guidelines, although many patients express interest in supplements and herbal products. For example, "Many patients ask about

Continued on following page ▶

COMMENTARY BY DR. MENTER: Published in July, this guideline is the sixth and final of the new American Academy of Dermatology–National Psoriasis Foundation guidelines, and includes a review of all available topical therapies. The paper includes 275 references and a total of 41 tables, including 1 listing classes 1 through 6 topical corticosteroids, with information on the available vehicles for each; other tables summarize level of evidence for vitamin D analogues, and combinations of topical agents with biologics.

Patients with mild to moderate psoriasis account for 80% of our psoriasis population. Therefore, despite all the attention surrounding the biologics, topical treatments remain the major agents for treatment of the average psoriasis patient, who does not have moderate to severe psoriasis.

We now have a number of nonsteroidal agents available, which may not work as quickly as the potent topical steroids, but work well for long-term maintenance therapy, discussed in the guideline. These include vitamin D_3 preparations. Everyone wants to achieve clearance quickly, but we have to help patients maintain long-term efficacy, which topical steroids by themselves do not do.

Also, as we point out in the guidelines, and as referenced in this story, for those with mild to moderate disease, who need daily treatment, you have to find a daily preparation with a vehicle – such as an ointment, cream, gel, foam, lotion, or spray – that is a viable option, taking into account patient preferences, which can have an impact on adherence to treatment.

We review alternative treatments, including traditional Chinese medicine, aloe vera, and fish oil and omega-3 fatty acid supplements. As discussed in the guideline, we do not have good clinical data on the effectiveness of many of these options.

Psoriasis topical combination maintenance strategy hits mark at 1 year

By Bruce Jancin

A proactive long-term strategy of maintenance therapy involving twice-weekly application of combined calcipotriene and betamethasone dipropionate spray foam was safe and effective in patients with moderate plaque psoriasis in the international, randomized PSO-LONG clinical trial, Mark Lebwohl, MD, reported at the virtual annual meeting of the American Academy of Dermatology.

The median time to first relapse – the primary study endpoint – was 56 days in patients randomized to the twice-weekly fixed-dose combination calcipotriene 0.005% and betamethasone dipropionate 0.064% foam (Enstilar), a significantly better outcome than the median 30 days for controls assigned to foam vehicle. Moreover, it took 169 days for 75% of patients on the combination foam to experience their first relapse: three times longer than in controls, added Dr. Lebwohl, principal investigator for PSO-LONG and professor and chair of the department of dermatology at the Icahn School of Medicine at Mount Sinai, New York.

The positive results "could have been predicted," he said in an interview. "But what really distinguishes this study from others is that no one before has ever done a placebo-controlled, double-blind trial with a topical steroid that lasted a year. This is a first, and we've shown that if you limit treatment to twice a week you get dramatic improvements in efficacy at no cost in terms of safety."

The combination spray foam is approved by the Food and Drug Administration as once-daily therapy in psoriasis patients aged 12 years and older, but only for up to 4 weeks because of safety concerns regarding longer use of the potent topical steroid. However, psoriasis is a chronic disease. The PSO-LONG trial was designed to study the impact of a for-now still-investigational long-term maintenance treatment strategy.

The open-label run-in period of the study included 640 adults with plaque psoriasis, 82% of whom had moderate disease at baseline as rated by Physician Global Assessment (PGA). Participants applied the combination foam once daily for 4 weeks. At that point, 80% of them had achieved a PGA rating of clear or almost clear with at least a two-grade improvement from baseline; these 521 responders were then randomized to 52 weeks of double-blind treatment with the combination foam or vehicle foam. Anyone who relapsed went on 4 weeks of once-daily active treatment with the combination foam, then returned to their original treatment arm.

The risk of a first relapse during the course of 1 year was 43% lower with the combination foam than in controls. The relapse rate over the year was 46% lower. Patients in the active-treatment arm spent an average of 256.5 days in remission during the year, compared with 222 days in controls.

"That's more than 1 month more time in remission during the year with active treatment. And remember, if patients flared, they went on daily therapy for a month," the dermatologist noted.

The rate of treatment-related adverse events was similar in the two groups at 2.8 events per 100 patient-years in the combination foam arm and 4.5 per 100 patient-years in controls. The twice-weekly active-treatment group had no increase in stretch marks, telangiectasias, skin atrophy, serum calcium, or abnormalities of the hypothalamic-pituitary-adrenal axis.

Dr. Lebwohl reported receiving an institutional research grant to conduct the trial from LEO Pharma, the study sponsor, as well as serving as a consultant to and researcher for the company.

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▶ *Continued from previous page*

the overall role of vitamin D in skin health. Rather than adding oral vitamin D supplementation, topical therapy with vitamin D agents is effective for the treatment of psoriasis," the authors noted.

In addition, they noted that mind/body strategies, namely hypnosis and stress reduction or meditation techniques, have been shown to improve symptoms and can be helpful for some patients, but clinical evidence is limited.

The guidelines also addressed methods for assessing disease severity in psoriasis. They recommended using body surface area (BSA) to assess psoriasis severity and patient response to treatment in the clinical setting. However, BSA is a provider assessment tool that "does not take into account location on the body, clinical characteristics of the plaques, symptoms, or quality of life issues," the authors noted. The Psoriasis Area and Severity Index (PASI) measures erythema, induration, and scaling and is more suited to assessing psoriasis severity and response to treatment in clinical trials rather than in practice, they said.

The updated guidelines were designed by a multidisciplinary work group of psoriasis experts including dermatologists, a rheumatologist, a cardiologist, and representatives from a patient advocacy organization.

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SOURCE: Elmets CA et al. J Am Acad Dermatol. 2020 Jul 29. doi: 10.1016/j.jaad.2020.07.087.

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