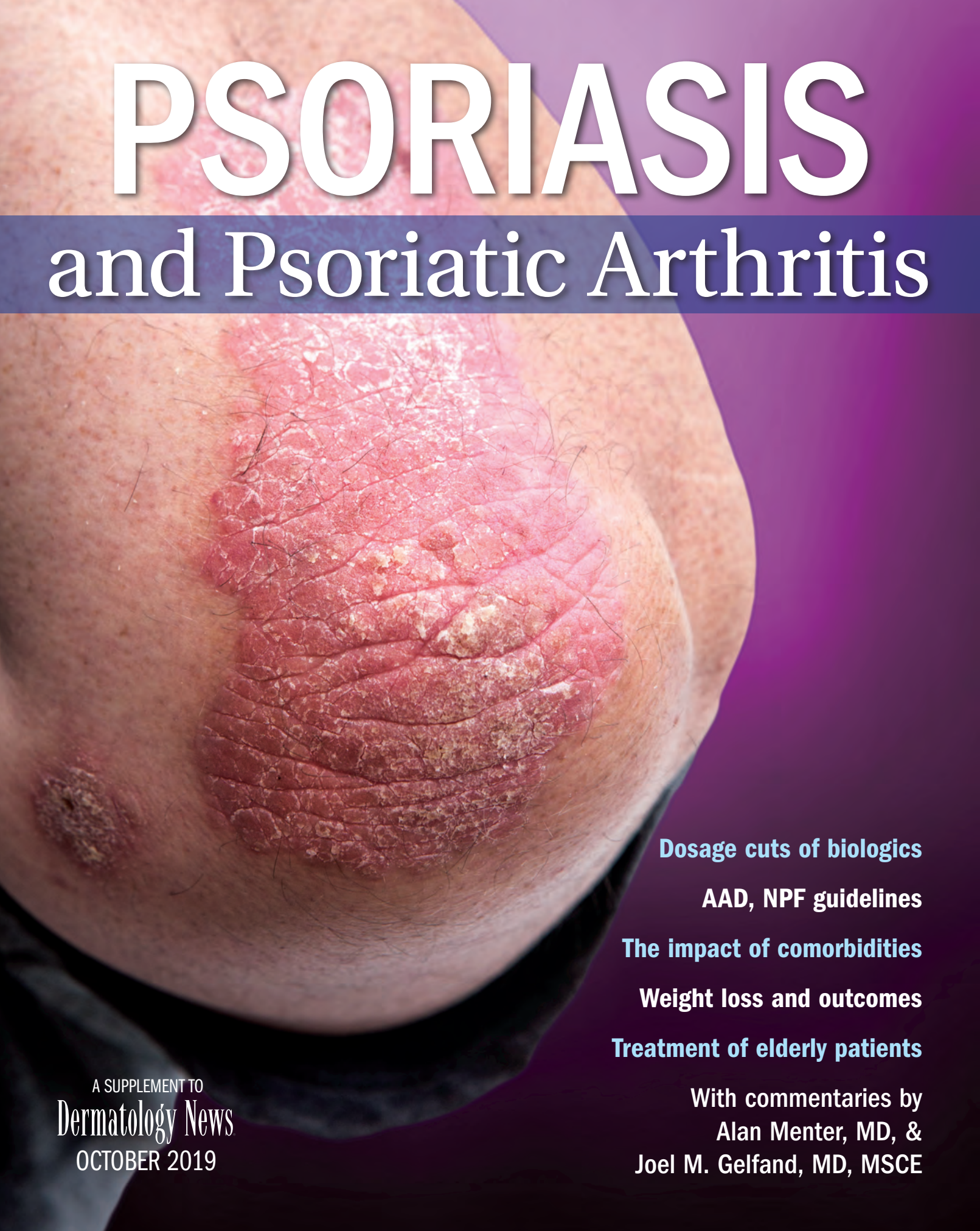
PSORIASIS

and Psoriatic Arthritis



Dosage cuts of biologics

AAD, NPF guidelines

The impact of comorbidities

Weight loss and outcomes

Treatment of elderly patients

With commentaries by
Alan Menter, MD, &
Joel M. Gelfand, MD, MSCE

A SUPPLEMENT TO
Dermatology News
OCTOBER 2019

Advances in psoriasis, psoriatic arthritis

BY ALAN MENTER, MD

Over the past 6 months, we have had three psoriasis guidelines articles published in the Journal of the American Academy of Dermatology: Biologics, Comorbidities and Phototherapy, which are covered in stories in this supplement (pages 8 and 18). Over the next 6 months, three more will be published, on pediatric psoriasis, nonbiologic systemic therapies, and topical therapies. Our committee of more than 20 colleagues have been working on these guidelines for the past 2 years, in partnership with the National Psoriasis Foundation. With the interleukin-23 (IL-23) inhibitor risankizumab recently approved, we now have a total of 11 biologic agents approved for moderate to severe psoriasis: four tumor necrosis factor–alpha drugs (etanercept, infliximab, adalimumab, and certolizumab), one IL-12/23 inhibitor (ustekinumab), three IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab), and three IL-23 inhibitors (guselkumab and tildrakizumab, in addition to risankizumab). The big and important question now is which drug will work best, not just in the short term but for the long term for each individual patient with various forms of psoriasis, with or without psoriatic arthritis.

DR. MENTER

Finally, with the 12 psoriasis comorbidities fully discussed in the recent guideline on this topic (J Am Acad Dermatol. 2019 Apr;80[4]:1073-113), will any individual biologic drug have the ability to reduce these comorbidities, especially cardiovascular disease?

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 has been an adviser, a consultant, an investigator, and/or a speaker for companies that include AbbVie, Allergan, Anacor, Boehringer Ingelheim, Celgene, Dermira, Galderma, Janssen Biotech, LEO Pharma, Eli Lilly, Menlo, Novartis, Pfizer, Promius, Regeneron and Sun Pharma; and he has received grants and/or honoraria from these companies.

BY JOEL M. GELFAND, MD, MSCE

The pace of discovery and advances in psoriasis is breathtaking. Each week there are roughly 50 new publications in the peer-reviewed scientific literature about psoriasis, with new discoveries about its treatment, pathophysiology, genetics, and comorbidities emerging rapidly. In this review I will cover just some of these important developments, ranging from new clinical trial designs (making our data more reflective of our day-to-day practice), new American Academy of Dermatology psoriasis guidelines on biologics, and for the first time in the AAD's history, identification and management of comorbidities in psoriasis, to novel approaches to evaluating the impact of our treatments on cardiovascular disease and new and emerging risk factors for psoriatic arthritis. Despite these advances, large treatment gaps remain, highlighted by one study of undertreatment of psoriasis in older individuals as well as another paper evaluating the use of complementary and alternative medicines by our patients, which are frequently turned to because of our inability to produce long-term remission in most cases. Want to keep up with the latest publications about psoriasis? I invite you to follow me on Twitter (@DrJoelGelfand) or LinkedIn (linkedin.com/in/drjoelgelfand). Until then, I hope you enjoy these brief reviews about some very important developments in psoriasis.

DR. GELFAND

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 Bristol-Myers Squibb, Boehringer Ingelheim, Janssen Biologics, Novartis, UCB (DSMB), and Pfizer; 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, Janssen, Novartis, Celgene, Ortho Dermatologics, and Pfizer.

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- 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

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- 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)

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

*Following a 5-day titration, the recommended maintenance dosage is 30 mg twice daily.

† To receive a free bridge supply of Otezla, patients must have an on-label diagnosis and be denied or waiting for coverage.

‡ Certain restrictions apply; eligibility not based on income, must be 18 years or older. This offer is not valid for persons eligible for reimbursement of this product, in whole or in part under Medicaid, Medicare, or similar state or federal programs. Offer not valid for cash-paying patients. People who are not eligible can call **1-844-4OTEZLA** to discuss other financial assistance opportunities.

BSA, body surface area; ESTEEM, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment.

References: 1. Otezla [package insert]. Summit, NJ: Celgene Corporation. **2.** Papp K, Reich K, Leonardi CL, et al. *J Am Acad Dermatol.* 2015;73(1):37-49.

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

OTEZLA® (apremilast) tablets, for oral use

RX Only

The following is a Brief Summary of the Prescribing Information; see Full Prescribing Information for complete product information.

4 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)]*.

5 WARNINGS AND PRECAUTIONS
5.1 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.

5.2 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.

5.3 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)]*.

5.4 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)]*

6 ADVERSE REACTIONS
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 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. 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. 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. 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.

7 DRUG INTERACTIONS
7.1 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)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 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.

8.2 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.

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

8.5 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.

8.6 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.

8.7 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.

10 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.

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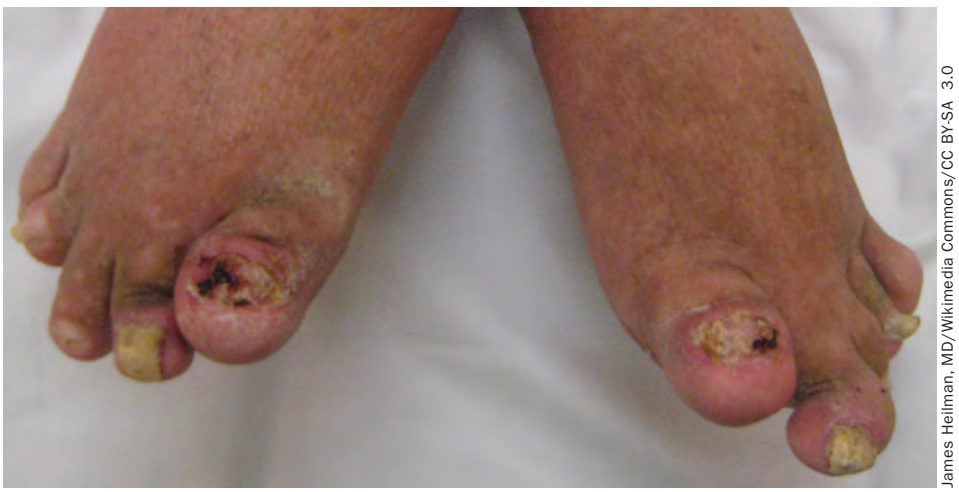
Pat. http:www.celgene.com/therapies

Based on APRPI.007 OTZ_PsA_PsO_HCP_BSv.007 07_2019

Family history of psoriasis, psoriatic arthritis linked to unique phenotypes

BY ANDREW D. BOWSER
FROM ARTHRITIS CARE & RESEARCH



James Heilman, MD/Wikimedia Commons/CC BY-SA 3.0

Family histories of psoriasis and of psoriatic arthritis have different effects on skin phenotypes, disease severity, and musculoskeletal features, the results of a retrospective cohort study suggest.

A family history of psoriasis was associated with younger onset of psoriatic disease and the presence of enthesitis, while by contrast, a family history of psoriatic arthritis (PsA) was associated with lower risk of plaque psoriasis and higher risk of deformities, according to Dilek Solmaz, MD, of the University of Ottawa and her coauthors, who reported their findings in Arthritis Care & Research.

"The link between family history of psoriasis/psoriatic arthritis and pustular/plaque phenotypes may point to a different genetic background and pathogenic mechanisms in these subsets," the investigators wrote.

Most, if not all, previous studies evaluating family history have grouped psoriasis and PsA together, according to Dr. Solmaz and her colleagues, rather than looking at the individual effects of psoriasis or PsA family history that may lead to unique disease phenotypes, as was done in the present study.

The investigators based their retrospective analysis on patients recruited in a longitudinal, multicenter database in Turkey and Canada. The mean age of patients in the study was 48 years; nearly 65% were female.

Out of 1,393 patients in the database, 444 had a family history of psoriasis or PsA. That included 335 patients with a psoriasis-only family history and 74 with a family history of PsA; another 35 patients weren't sure about having a family history of PsA or psoriasis and were left out of the analysis.

Plaque psoriasis was more common in individuals with a family history of only psoriasis, while pustular psoriasis was more common in those with a PsA family history, the investigators reported.

In multivariate analyses, having a family member with psoriasis was a risk factor for younger age of psoriasis onset (odds ratio, 0.976; 95% confidence interval, 0.964-0.989; *P* less than .001), as well as a higher risk for enthesitis (OR, 1.931; 95% CI, 1.276-2.922; $P = .002$) when compared against patients without a family history of psoriasis.

Patients with a family history of PsA were more likely to have deformities (OR, 2.557; 95% CI, 1.250-5.234; *P* less than .010) and lower risk of plaque-type psoriasis (OR, 0.417; 95% CI, 0.213-0.816; *P* less than .011) than patients without a family history of PsA.

Disease onset was earlier among patients with a family history of psoriasis at a mean of 28.1 years versus 31.9 years for those with a family history of PsA (*P* less than .001).

Dr. Solmaz and her colleagues reported no conflicts of interest related to the research, which was supported in part by the Turkish Society for Rheumatology, the Scientific and Technological Research Council of Turkey, and Union Chimique Belge.

dermnews@mdedge.com

SOURCE: Solmaz D et al. Arthritis Care Res (Hoboken). 2019 Jan 25. doi: 10.1002/acr.23836.

Commentary by Dr. Menter:
This is an interesting study of 1,393 patients with approximately 33% having a family history of psoriasis or psoriatic arthritis. Having a family member with psoriasis was associated with a younger age of psoriasis onset and interestingly, a higher risk of enthesitis, a common early manifestation of psoriatic arthritis. Pustular psoriasis, a rare form of psoriasis, was found to be more common in patients with a family history of psoriatic arthritis. With over 50 genes now part of psoriasis genotypes, the important question still remains: What important factors trigger the onset of psoriasis in genetically predisposed patients?

AAD, NPF update use of phototherapy for psoriasis

BY HEIDI SPLETE
FROM THE JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

Phototherapy remains a viable element of psoriasis care for many patients, used alone or in conjunction with other treatments, according to updated guidelines issued jointly by the American Academy of Dermatology and the National Psoriasis Foundation.

"Phototherapy serves as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications or simply seeking an adjunct to a failing regimen," wrote working group cochair Craig A. Elmets, MD, professor of dermatology at the University of Alabama at Birmingham, and coauthors.


DR. ELMETS

The guidelines, which focus on phototherapy for adults with psoriasis, join a multipart series on psoriasis being published this year in the Journal of the American Academy of Dermatology.

The working group used an evidence-based model to examine efficacy, effectiveness, and adverse effects of the following modalities: narrow-band ultraviolet B (NB-UVB); broadband ultraviolet B (BB-UVB); targeted phototherapy using excimer laser and excimer lamp; psoralen plus ultraviolet A (PUVA) therapy, including topical, oral, and bath PUVA; photodynamic therapy (PDT); Grenz-ray therapy; climatotherapy; visible-light therapy; Goeckerman therapy; and pulsed-dye laser/intense pulsed light.

NB-UVB, which can be used to treat generalized plaque psoriasis, refers to wavelengths of 311-313 nm. The recommended treatment is two or three times a week, with a starting dose based on skin phenotype or minimal erythema dose. Although oral PUVA has shown higher clearance rates, compared with NB-UVB, NB-UVB has demonstrated fewer side effects. NB-UVB also has shown effectiveness for psoriasis in combination with medications including oral retinoids, "particularly useful in patients at increased risk for skin cancer," the working group wrote. Genital shielding and eye protection are recommended during all phototherapy sessions to reduce the risk of cancer and cataracts, they emphasized.

BB-UVB, an older version of NB-UVB, is still effective for generalized plaque psoriasis as monotherapy, but evidence does not support additional benefit in combination with other treatments, and overall BB-UVB is less effective than either NB-UVB or oral PUVA, the working group said.

For treatment of localized psoriatic lesions, some evidence supports the ability of targeted UVB therapy to improve lesions in fewer treatments and at a lower cumulative dose, compared with nontargeted phototherapy, for palmoplantar plaque psoriasis and palmoplantar pustulosis. Excimer lasers also have shown effectiveness against scalp psoriasis, the working group noted. However, "there is insufficient evidence to recommend the excimer laser rather than topical PUVA for treatment of localized plaque psoriasis," they said.

PUVA treatments are available as topical creams, or they can be taken orally, or mixed with bath water. All forms of PUVA include psoralens, photosensitizing agents that prepare target cells for the effects of UVA light. Topical PUVA has demonstrated particular effectiveness for palmoplantar psoriasis, the working group noted, but there is a risk of phototoxicity, so it has become less popular, they added. Similarly, evidence supports effectiveness of oral and bath PUVA, but all forms are used less frequently because of the increased availability of NB-UVB phototherapy, they said.

PDT is primarily used to destroy premalignant or malignant cells, and in theory "PDT-induced apoptosis of T lymphocytes could lead to reductions in inflammatory cytokines and, in turn, to improvement of psoriasis," the working group noted. However, "clinical studies have failed to find significant benefit" of PDT using either 5-aminolevulinic acid (ALA) or methyl aminolevulinic acid (MAL) for psoriasis, or any significant benefits of MAL-PDT for nail psoriasis.

Quality of life and disease severity should be discussed with patients along with efficacy and safety information.

The Grenz ray is an effective, but rarely used, treatment in which 75% of long-wavelength ionizing radiation is absorbed by the first 1 mm of skin and 95% is absorbed within the first 3 mm of skin to protect the deeper tissues from radiation. Although more alternatives are available, Grenz rays can be used for psoriasis patients unable to tolerate UV therapy, according to the working group.

Climatotherapy involves temporary or

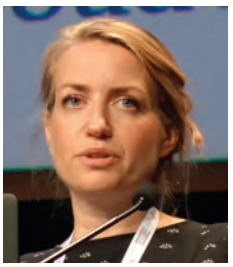
Continued on following page ▸

CONDOR: Most can reduce their dose of biologics

BY BRUCE JANCIN
REPORTING FROM THE EADV CONGRESS

PARIS – Two-thirds of psoriasis patients with stable low disease activity while on full-dose biologic therapy can successfully undergo biologic dose reduction with long-term maintenance of disease control and no adverse consequences, Juul van den Reek, MD, PhD, reported at the annual congress of the European Academy of Dermatology and Venereology.

She presented the results of the CONDOR trial, the first-ever formal, randomized, controlled trial of tightly regulated dose reduction of biologics, compared with usual-care standard-dose therapy. "Our current advice is we think you can try to reduce the dose because there are a lot of patients who benefit from this," declared Dr. van den Reek, a dermatologist at Radboud University, Nijmegen, the Netherlands.


DR. VAN DEN REEK

The advantages of this strategy are twofold: lower expenditures for this costly collection of medications and less exposure to any long-term, drug-related health risks, she noted.

CONDOR was a Dutch, six-center, 12-month, open-label, unblinded, noninferiority, randomized trial including 111 patients. Participants had to have stable low disease activity as defined by both Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores of 5 or less for at least 6 months while on standard-dose etanercept (Enbrel), adalimumab (Humira), or ustekinumab (Stelara) prior to enrollment. In fact, the av-

Continued on following page ▸

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permanent relocation of the patient to a part of the world with a climate that could be favorable for psoriasis because of the unique effects of environmental factors in those areas. The evidence to support climatotherapy is both subjective and objective, but considered safe.

Visible light has been associated with improvement in erythema in psoriasis, with hyperpigmentation as the only notable side effect based on the evidence reviewed. However, the working group found the current evidence insufficient to recommend the use of intense pulsed light for treating psoriasis.

Goeckerman therapy, a method that combines coal tar and UVB phototherapy, has shown safety and effectiveness for patients with recalcitrant or severe psoriasis, and remains a recommended treatment, according to the working group research. However, this method is underused, especially in the United States, because of the messiness of the application, challenge of insurance reimbursement, and investment of time for outpatient care, the work group noted.

Pulsed-dye laser treatment is effective for nail psoriasis, and reported adverse effects have been mild, according to the working group.

Overall, the guidelines emphasize that quality of life and disease severity should be considered and discussed with patients along with efficacy and safety information so they can make informed decisions about adding phototherapy to a current regimen or switching among modalities.

The guidelines have no funding sources. Several coauthors disclosed relationships with multiple companies, including manufacturers of psoriasis products; however, a minimum of 51% of the work group had no relevant financial conflicts to disclose, in accordance with AAD policy. Work group members with potential conflicts recused themselves from discussion and drafting of recommendations in the relevant topic areas. Alan Menter, MD, chairman of dermatology at Baylor Scott & White Health and clinical professor of dermatology at the University of Texas, both in Dallas, is the other cochair of the work group.

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SOURCE: Elmets CA et al. J Am Acad Dermatol. 2019 Jul 18. doi: 10.1016/j.jaad.2019.04.042.

Commentary by Dr. Menter:
With two new AAD-NPF psoriasis guidelines recently published (biologics and comorbidities), the third guideline (phototherapy) was recently published, also in the Journal of the American Academy of Dermatology. The final three guidelines (topical therapies, systemic oral therapies, and pediatric psoriasis) also will be published over the next few months.
The Phototherapy Guideline includes all issues and recommendations for both narrow-band and broadband UVB therapies, PUVA, targeted phototherapy (such as the excimer laser), Grenz-ray therapy, Goeckerman therapy, and pulsed-dye laser therapies. With approximately 75% of our psoriasis population having mild to moderate disease versus 25% having moderate to severe psoriasis, the use of phototherapy in mild to moderate forms of psoriasis remains an important aspect of psoriasis treatment, both in the dermatologist's practice as well as in home phototherapy for individual patients.

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erage baseline PASI score was less than 2, with a DLQI of 0.

Participants were randomized to usual care – the customary approved dose of biologic therapy – or a drop down to 67% of that dose, achieved through prolongation of the dosing interval. If the reduced-dose patients kept their PASI and DLQI scores at 5 or less for 3 months straight, they dropped further to 50% of their original dose. However, patients who exceeded those thresholds were immediately returned to their previously effective dose.

The primary endpoint in this noninferiority trial was the difference in mean PASI scores between the dose-reduction and usual-care groups at 12 months. The prespecified margin for noninferiority was a difference of 0.5 PASI points. And that's where the results get dicey: The mean difference turned out to be 1.1 PASI points in favor of usual care, meaning that, according to the study ground rules, dose reduction was not statistically noninferior. In hindsight, however, that 0.5-point margin was ill considered and too narrowly defined.

"Within the chosen margins, the dose-reduction strategy seemed inferior. But what is the clinical relevance of a mean difference of 1.1 PASI points, when the accepted minimal clinically important difference is 3.2 points?" Dr. van den Reek observed.

There was no significant between-group difference in DLQI scores at 12 months. Nor did the two study arms differ in terms of the prespecified secondary endpoint of persistent disease flares as defined by a PASI or DLQI greater than 5 for 3 consecutive months: Five patients in the reduced-dose group and three in the usual-care arm experienced such flares. There were no serious adverse events or other safety signals related to the intervention.

At 12 months, 50% of patients in the dose-reduction group were well maintained on 50% of their original approved-dose biologic and another 17% were doing well on 67% of their former dose.

Session chair Dedee Murrell, MD, professor of dermatology at the University of New South Wales, Sydney, noted that neither patients nor dermatologists were blinded as to treatment status in CONDOR. She then asked the question on everybody's minds: Was there any loss of treatment efficacy when patients in the dose-reduction arm needed to resume higher-dose therapy?

No, Dr. van den Reek replied. She added that planned future CONDOR analyses include a cost-effectiveness determination as well as measurement of serum drug levels and identification of antidrug antibodies, information that might prove helpful in identifying an enriched population of patients most likely to respond favorably to biologic dose reduction. In addition, CONDOR-X, a long-term extension study, is ongoing in order to learn how patients on reduced-dose biologics fare after the 12-month mark.

The CONDOR trial was funded by the Netherlands Organization for Health Research and Development; Dr. van den Reek reported having no financial conflicts of interest.

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Commentary by Dr. Gelfand:

The CONDOR trial is a new breed of study in dermatology – that of the pragmatic clinical trial. What are pragmatic trials? They are typically large-scale, simple, randomized, controlled trials designed to be embedded in and reflect real-world practice. In dermatology, we are used to efficacy trials, typically those designed with a myriad of inclusion and exclusion criteria, which are used to gain regulatory approval. An efficacy trial asks the question, "Can a treatment work under ideal circumstances?" In contrast, a pragmatic trial measures effectiveness of a treatment under real world conditions in which patients may be sicker, less motivated to adhere to the regimen, and the prescriber may have less experience with the disease and or treatment.

Are effectiveness trials needed in dermatology? Absolutely! Studies demonstrate that about a third of patients who go on systemic treatments for psoriasis would not have met entry criteria for trials of biologics and that psoriasis patients on biologic treatments in routine clinical practice who would not have met typical trial entry criteria have lower improvements in PASI and a higher rate of serious adverse events.

As for CONDOR, these investigators conducted a pragmatic trial in routine clinical practice to determine if patients with an excellent response to biologic treatment of psoriasis could successfully undergo dose reduction. Patients with PASI and DLQI scores of less than 5 for at least 6 months were randomized to usual care (maintenance of their dose) or a dose reduction in their biologic and followed for 12 months. Ultimately, the study was too small (remember earlier I noted that these trials need to be large) to definitively demonstrate that dose reduction is not noninferior to maintenance of the biologic dose.

The study did demonstrate that dose reduction can be done while successfully maintaining response in the skin in some patients; however, we are unable to predict which patients can successfully use this strategy, and we do not know if there will be long-term harms, such as failing to respond if disease recurs. Ultimately, this study is unable to inform clinical practice but is a step in the right direction of bringing psoriasis trials to real-world conditions. Want to learn more about pragmatic trials? Check out the Light Treatment Effectiveness (LITE) study we are doing in collaboration with the National Psoriasis Foundation. LITE is a pragmatic trial of home vs. office phototherapy for the treatment of plaque or guttate psoriasis in 1,050 patients aged 12 years or older and is funded by the Patient Centered Outcomes Research Institute (details at www.thelitestudy.com).

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Move Better[1*]

Feel Better[1*]

For moderate to severe plaque psoriasis and active psoriatic arthritis

LauraLee, actual COSENTYX patient since 2015

Treatment success is more than a PASI score

See what else is possible at Complete-Cosentyx-Approach.com

*In the ERASURE study at Week 12, 82% of patients in the COSENTYX 300-mg arm (n=245) achieved a PASI 75 response vs 4% in the placebo group (n=248).[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 51%, 54%, and 15%, respectively.[1] In the ERASURE (N=738) and FIXTURE (N=1306) studies, among the subjects 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]

PASI=Psoriasis Area Severity Index; ACR=American College of Rheumatology.

Reference: 1. Cosentyx [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2018.

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.

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

Hypersensitivity Reactions

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

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

Vaccinations

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

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

MOST COMMON ADVERSE REACTIONS

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

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

Cosentyx® (secukinumab)

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 8/19 COS-1378409

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.

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 and ankylosing spondylitis *[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 and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX. In an exploratory study in 59 patients with active Crohn's disease, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group. Patients who are treated with COSENTYX should be monitored for signs and symptoms of inflammatory bowel disease *[see Adverse Reactions (6.1)]*.

5.4 Hypersensitivity Reactions

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

5.5 Risk of Hypersensitivity in Latex-sensitive Individuals

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

5.6 Vaccinations

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

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

6 ADVERSE REACTIONS

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

- Infections *[see Warnings and Precautions (5.1)]*
- 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 300 mg (N = 691) n (%)	COSENTYX 150 mg (N = 692) n (%)	Placebo (N = 694) 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.

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 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)]*.

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.

Manufactured by:
Novartis Pharmaceuticals Corporation
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T2018-93

Positive PsA screens occur often in psoriasis

BY AMY KARON
FROM THE JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY

One out of eight patients with psoriasis had a positive screen for possibly undiagnosed psoriatic arthritis, according to an analysis of data from a prospective registry.

The finding highlights the need for better psoriatic arthritis screening among patients with psoriasis, said Philip J. Mease, MD, of the University of Washington, Seattle, and associates. The simple, five-question Psoriasis Epidemiology Screening Tool (PEST) used in this study could be deployed in general or dermatology practices to identify psoriasis patients who might need a rheumatology referral, they wrote. The report is in the Journal of the European Academy of Dermatology and Venereology.


DR. MEASE

Up to 30% of patients with psoriasis have comorbid psoriatic arthritis, but many such cases go undiagnosed, and even a 6-month diagnostic delay can worsen peripheral joint erosion and physical disability. This study included 1,516 patients with psoriasis seen at 114 private and academic practices in 34 states that participate in the independent, prospective Corrona Psoriasis Registry. A total of 904 patients without dermatologist-reported psoriatic arthritis responded to the validated PEST, which assesses risk of psoriatic arthritis by asking whether the test taker has been told by a doctor that he or she has arthritis and whether they have experienced swollen joints, heel pain, pronounced and unexplained swelling of a finger or toe, and pitting of the fingernails or toenails. Each "yes" response is worth 1 point, and total scores of 3 or higher indicate risk of psoriatic arthritis. A total of 112 (12.4%) had a score of 3 or higher.

The average age of patients who met this threshold was 53 years, 4 years older than those who did not ($P = .02$). Patients with PEST scores of 3 or more also had a significantly longer duration of psoriasis and were significantly more likely to have nail disease and a family history of psoriasis. Demographically, they were more likely to be white, female, and unemployed. They had significantly higher rates of several comorbidities, including depression and anxiety, cardiovascular disease, obesity, and serious infections. Finally, they reported having significantly more pain and fatigue and significantly worse health-related quality of life.

The study did not account for possible confounding. "Further research is needed to characterize patients by individual PEST score and to assess outcomes over time," the researchers wrote. "The use of screening tools can be beneficial in the detection of psoriatic arthritis, and comprehensive efforts to validate them in multiple clinical settings must continue, along with collection of critical feedback from patients and clinicians."

PEST scores of 3 or more were linked to longer duration of psoriasis and nail disease and a family history of psoriasis.

Corrona and Novartis designed and helped conduct the study. Novartis, the chief funder, participated in data analysis and manuscript review. Dr. Mease disclosed research funding from Novartis and several other pharmaceutical companies. He also disclosed consulting and speakers bureau fees from Novartis, Corrona, and several other companies.

dermnews@mdedge.com

SOURCE: Mease PJ et al. J Eur Acad Dermatol Venereol. 2019 Mar 5. doi: 10.1111/jdv.15443.

Commentary by Dr. Menter:
In a study of 904 psoriasis patients who did not have a diagnosis of psoriatic arthritis, the PEST (Psoriasis Epidemiology Screening Tool) was performed; 1 out of 8 of these psoriasis patients had a positive PEST screen for psoriatic arthritis. As the vast majority of psoriatic arthritis cases become evident only 10-15 years after the onset of their skin disease, and if left untreated, more than 50% of patients with untreated joint disease will progress to permanent joint destruction, it is imperative that all dermatologists screen for psoriatic arthritis at each and every visit to prevent permanent joint destruction. Using the PEST screening tool and evaluating for dactylitis and enthesitis is not a difficult task for dermatologists and will take less than 2 minutes of time at each visit.

AAD, NPF release two joint guidelines on treatment, management of psoriasis

BY JEFF CRAVEN
FROM THE JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

The American Academy of Dermatology and the National Psoriasis Foundation have jointly released two new guidelines on the management and treatment of psoriasis with a focus on biologics and comorbidities.

These guidelines are the first of two papers to be published in the Journal of the American Academy of Dermatology (JAAD), with four more guidelines on psoriasis to be published later this year in JAAD on phototherapy, topical therapy, nonbiologic systemic medications, and treatment of pediatric patients.

The guideline on biologics updates the 2008 AAD guidelines on psoriasis. In an interview, Alan Menter, MD, co-chair of the guidelines work group and lead author of the biologics paper, said the guidelines for biologics were needed because of major advances with the availability of new biologics over the last decade. For example, three tumor necrosis factor–alpha (TNF-alpha) inhibitors were available in 2008, but that number has increased to 10 biologics and now includes agents such as those targeting interleukin (IL)-12/IL-23, IL-17, and IL-23.

In addition, the new guidelines from AAD were developed to represent improvements in the management of patients with moderate to severe psoriasis as well as the relationship between psoriasis and related comorbidities.

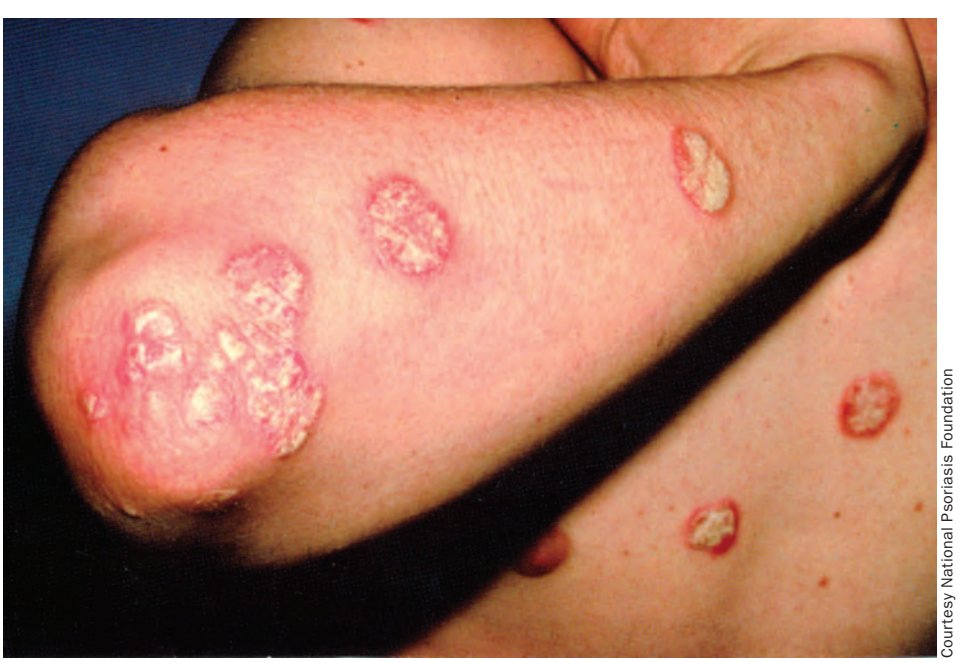
"Major advances in new biologic drugs [are] now available to patients, plus [there have been] significant advances in our understanding of comorbid conditions," such as cardiovascular comorbidities, said Dr. Menter, chairman of dermatology at Baylor Scott & White Health and clinical professor of dermatology at the University of Texas, both in Dallas.

clinical professor of dermatology, University of Texas, both in Dallas.

The working group for each set of guidelines consisted of dermatologists, patient representatives, a cardiologist, and a rheumatologist. The biologic guidelines working group analyzed studies published between January 2008 and December 2018 and issued a series of recommendations based on published evidence for the effectiveness, adverse events, and switching for Food and Drug Administration–approved TNF-alpha inhibitors (etanercept, infliximab, adalimumab, certolizumab, and TNF-alpha biosimilars); IL-12/IL-23 inhibitors (ustekinumab); IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab); and IL-23 inhibitors (guselkumab and tildrakizumab, and risankizumab, which is still under FDA review) for monotherapy or combination therapy in patients with moderate to severe psoriasis.

The biologic guidelines noted that, while FDA-approved biologics were deemed safe overall for patients with moderate to severe psoriasis, dermatologists should recognize the adverse effects of these therapies, monitor for infections, and counsel their patients against modifying or discontinuing therapy without first consulting a dermatologist. In general, the working group noted that failure with one biologic does not necessarily mean that a patient will experience failure with a different biologic, even among TNF-alpha and IL-12/IL-23 inhibitors. However, reduced efficacy for a patient receiving a specific TNF-alpha inhibitor may predict reduced efficacy when switching to a different TNF-alpha inhibitor, they said.

In the psoriasis comorbidity guideline, the working group examined the therapeutic interventions for psoriasis-related comorbidities such as psoriatic arthritis (PsA), cardiovascular disease, metabolic syndrome, and inflammatory bowel disease. They also provided recommendations on the effect of psoriasis on mental health, quality of life, and lifestyle choices such as smoking and alcohol use.



Courtesy National Psoriasis Foundation

With respect to cardiovascular disease, the dermatologist should ensure that patients are aware of the association between risk factors for cardiovascular disease and psoriasis, and that they undergo screening for these risk factors, consider lifestyle changes to reduce risk of cardiovascular disease, and consult with cardiologists and primary care providers based on individual risk, the guideline states. The working group recommended that patients with psoriasis undergo screening for hypertension, diabetes, and hyperlipidemia based on national guidelines, with more frequent screening recommended for patients with psoriasis greater than 10% body surface area or who are eligible for systemic or phototherapy.

In both the biologic and the comorbidity guidelines, the working groups stressed the importance of patient education and the role of the dermatologist in educating patients so that shared decision making can occur. They noted that education was related to improved quality of life for these patients.

"Both the comorbidities guidelines and the biologic guidelines will help educate the psoriasis population with input from dermatologists in clinical practices," Dr. Menter said.

However, both working groups noted there are still significant gaps in research, such as the effects of treatment combinations for new biologics and the lack of biomarkers that would identify which biologics are best suited for individual psoriasis patients.

There is also little known about the complex relationship between psoriasis and its comorbidities, and how psoriasis treatment can potentially prevent future disease. To ensure treatment of psoriasis-related comorbidities, dermatologists should consider psoriasis as a systemic disease with multiple comorbidities and interact with primary care doctors, cardiologists, and other providers involved in the care of the patients, Dr. Menter said.

There were no specific funding sources reported for the guidelines. Several authors reported relationships with industry, including pharmaceutical companies with drugs and products involving psoriasis, during the development of the guidelines. If a potential conflict was noted, the working group member recused himself or herself from discussion and drafting of recommendations, according to the paper. Dr. Menter's disclosure includes serving as a consultant, speaker, investigator, and adviser for, and receiving honoraria from, multiple pharmaceutical companies.

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SOURCES: Menter A et al. J Am Acad Dermatol. 2019 Feb 13. doi: 10.1016/j.jaad.2018.11.057. Elmets CA et al. J Am Acad Dermatol. 2019 Feb 13. doi: 10.1016/j.jaad.2018.11.058.

Commentary by Dr. Gelfand:

Tremendous advances have been made in the management of psoriasis, and the new AAD guidelines (full disclosure, I am an author of these guidelines) could not have come soon enough to catch up to all of the progress that is reflected in our practices and the outcomes we can achieve for our patients. The first new AAD psoriasis guideline focuses on biologics. Since the last AAD guidelines, new biologics targeting IL-17 and IL-23 have been approved, offering previously unimagined levels of efficacy for management of a complex immune-mediated disease. For perspective, about 80%-90% of patients can expect to achieve clear or almost clear skin with newer agents, whereas treatment efficacy of biologics for psoriatic arthritis, rheumatoid arthritis, and inflammatory bowel disease lag far behind these astonishing results.

The biologics guidelines provide evidence-based recommendations that support our daily practice, such as use of adalimumab or ustekinumab at higher doses than recommended by the FDA label, or use of secukinumab in adults with moderate to severe plaque psoriasis affecting the nails or moderate-to-severe palmoplantar plaque psoriasis, or guselkumab use as a monotherapy option in adults with scalp, nail, and plaque-type palmoplantar psoriasis. These evidence-based recommendations should enhance patient access to treatment for some of our most difficult-to-treat cases. The second guideline is about comorbidity and is the first of its kind issued by AAD. It is now well established that psoriasis patients have an increased risk of several major medical issues with diabetes and major cardiovascular events being most pressing as evidence-based prevention strategies exist. Moreover, we now know that a simple measurement of body surface area (BSA) affected by psoriasis is predictive of mortality and diabetes in a "dose-response" manner independent of other risk factors (see work from my lab, Psoriasis and the risk of diabetes: A prospective population-based cohort study. Wan MT et al. J Am Acad Dermatol. 2018 Feb;78[2]:315-22.e1.and Objective measures of psoriasis severity predict mortality: A prospective population-based cohort study. Noe MH et al. J Invest Dermatol. 2018 Jan;138[1]:228-30. doi: 10.1016/j.jid.2017.07.841). A key recommendation that clinicians should adopt in clinical practice centers about identification and management of cardiovascular risk factors in patients with psoriasis. For example, consider early and more frequent screening for hypertension, type 2 diabetes mellitus, and hyperlipidemia in candidates for systemic or phototherapy or who have psoriasis involving greater than 10% BSA. Moreover, risk score models should be adapted by introducing a 1.5 multiplication factor when the patient meets either disease severity of BSA greater than 10% or candidate for systemic or phototherapy. These recommendations can often be best put into practice by working closely with the patient's primary care team. Stay tuned for more AAD psoriasis guidelines on oral medications, pediatrics, and more!

Flu vaccination lags among patients with psoriasis

BY JIM KLING
FROM THE JOURNAL OF INVESTIGATIVE DERMATOLOGY

Psoriasis patients are more vulnerable to systemic infections, including influenza-related pneumonia, but a new study shows that they are less likely to receive the influenza vaccine than patients with RA.

Vaccination rates were higher in psoriasis patients aged over 50 years, those who were female, and those with other chronic medical conditions, however.

Megan H. Noe, MD, of the department of dermatology at the University of Pennsylvania, Philadelphia, and her coauthors referred to recent evidence suggesting that psoriasis involves systemic inflammation that increases the risk of comorbidities and that hospitalization rates for serious infections, including lower respiratory tract infections and pneumonia, are higher among adults with psoriasis than those who do not have psoriasis.

To compare influenza vaccination rates in psoriasis patients with those among patients with other chronic diseases, they conducted a cohort study, drawing from administrative and commercial claims data from OptumInsight Clinformatics Data Mart. They examined all adult patients with psoriasis, RA, or chronic hypertension who required oral antihypertensive medication. The study population included individuals tracked during the 2010-2011 flu season and 24 months prior (September 2008 to March 2011). This year was chosen because it was labeled as a "typical" season by the Centers for Disease Control and Prevention.

The primary outcome was a claim for an influenza vaccine, and covariates included age, length of residency, gender, and a clinical history of a range of conditions known to be associated with greater risk of influenza complications.

The population included 17,078 patients with psoriasis, 21,832 with RA, and 496,972 with chronic hypertension. After sex and age were controlled, the probability of getting a flu vaccine was similar between psoriasis and hypertension patients, but RA patients were more likely to be vaccinated than patients with psoriasis (odds ratio, 1.08; 95% confidence interval, 1.03-1.13). But the likelihood varied with age: 30-year-old patients with RA were more likely than a 30-year-old psoriasis patient to get a flu shot (OR, 1.30; 95% CI, 1.18-1.45), while a 70-year-old patient with RA was about as likely to get the flu vaccine as a 70-year-old patient with psoriasis.

Female psoriasis patients were more likely to get a flu shot than males (OR, 1.29; 95% CI, 1.20-1.38). Among the psoriasis patients, having some medical comorbidities were linked to a greater likelihood of being vaccinated, including asthma (OR, 1.58; 95% CI, 1.40-1.77), chronic liver disease (OR, 1.23; 95%, 1.03-1.47), diabetes (OR, 1.48; 95% CI, 1.36-1.63), HIV (OR, 3.68; 95% CI, 2.06-6.57), history of malignancy (OR, 1.21; 95% CI, 1.09-1.34), and psoriatic arthritis (OR, 1.40; 95% CI, 1.25-1.58).

There was no association between the use of an oral systemic therapy or biologic treatment and vaccination rates.

The authors suggested that psoriasis patients, especially younger ones, may not get adequate counseling on the value of the flu vaccine from their physicians. Studies have shown that, among the American public, health care providers are the most influential source of information about the flu vaccine. Among younger patients, the dermatologist may be a psoriasis patient's primary health care provider, so it is important for dermatologists to counsel patients about the recommended vaccines, the authors wrote.

"Further research understanding why adults with psoriasis do not receive recommended vaccinations will help to create targeted interventions to improve vaccination rates and decrease hospitalizations in adults with psoriasis," they concluded.

The study relied on administrative claims, so the results may not be generalizable to patients with insurance types other than those in the database or who are uninsured, the authors noted.

This study was funded by the National Psoriasis Foundation, the Dermatology Foundation, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Dr. Noe and three other authors did not report any disclosures, the fifth author reported multiple disclosures related to various pharmaceutical companies.

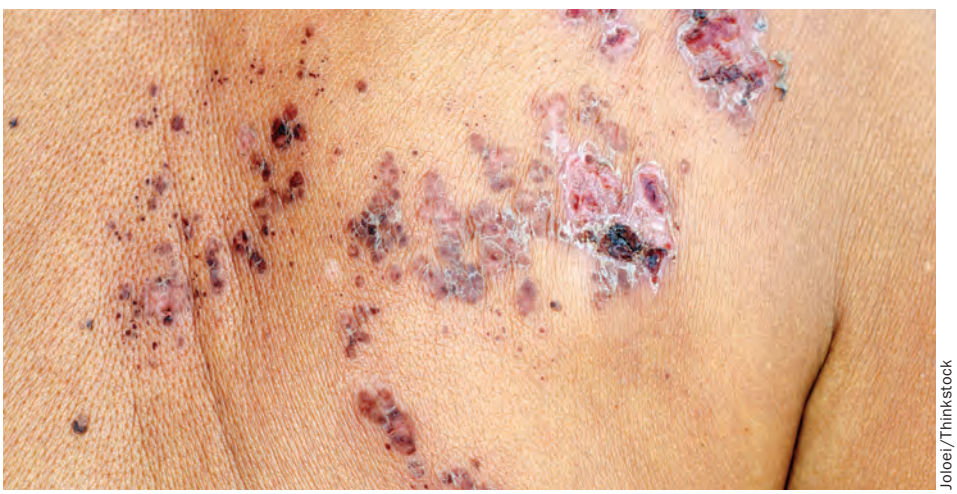
dermnews@mdedge.com

SOURCE: Noe MH et al. J Invest Dermatol. 2018 Oct 10. doi: 10.1016/j.jid.2018.09.012.

Commentary by Dr. Menter:
In this interesting study, 17,078 psoriasis patients, 12,832 patients with rheumatoid arthritis, and 496,972 patients with chronic hypertension were studied relating to flu vaccinations in all three populations. The incidence of flu vaccinations was similar between psoriasis patients and hypertension patients, but was lower in psoriasis patients versus rheumatoid arthritis patients. Because of the systemic inflammatory nature of psoriasis, the incidence of respiratory tract infections makes it essential for dermatologists to instruct their psoriasis patients to undergo flu vaccinations annually.

Herpes zoster risk increased with some psoriasis, psoriatic arthritis treatments

BY BIANCA NOGRADY
FROM THE JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY


Joloei/Thinkstock

All individuals with psoriasis or psoriatic arthritis aged over 50 years should receive the recombinant herpes zoster vaccine, according to a systematic review and consensus recommendations from the National Psoriasis Foundation.

Emily Baumrin, MD, of Brigham and Women's Hospital, Boston, and her coauthors reviewed 41 studies of herpes zoster in people with psoriasis or psoriatic arthritis according to treatment modality. Their report is in the Journal of the American Academy of Dermatology.

Overall, psoriasis was associated with an increased rate of herpes zoster when compared with the general population: 13.3 cases per 1,000 patient-years for psoriasis and 15.9 for psoriatic arthritis, compared with 8.5 in healthy controls after adjustment for age, sex, and systemic medications. Most of this increased incidence was seen in patients with more severe disease: Those with mild disease who were not receiving systemic therapy had a risk similar to that of healthy controls.

However, one study suggested much of the increased risk of herpes zoster in psoriasis was accounted for by immunosuppressive therapy; when those patients were excluded, there was an 8% increase in risk.

The authors found that people whose psoriasis was treated with tofacitinib (Xeljanz) had a two- to threefold increased risk of herpes zoster, compared with those treated with tumor necrosis factor (TNF) inhibitors or conventional synthetic disease-modifying antirheumatic drugs (DMARDs).

Corticosteroids – either alone or in combination with DMARDs – were also associated with significant increases in the risk of herpes zoster. Patients treated with TNF inhibitor monotherapy had a risk of herpes zoster similar to that of those treated with conventional synthetic DMARDs or no synthetic therapy.

On the question of immunization, the authors pointed to guidelines recommending use of the live attenuated zoster vaccine (Zostavax) in immunocompetent patients or those on low-dose immunosuppression, although they noted that the vaccine is currently contraindicated for patients on biologic DMARDs.

They also examined the evidence for the use of the recently released nonlive recombinant herpes zoster vaccine (Shingrix) in immunocompromised patients, which found no evidence of vaccine-related serious adverse events in individuals with HIV and low CD4 cell counts and in autologous hematopoietic stem cell transplant recipients.

Given this, they recommended that the recombinant vaccine be administered to all patients aged over 50 years

Continued on page 23 ▸

Commentary by Dr. Menter:
Psoriasis patients on systemic or biologic therapies are at an increased risk for herpes zoster, making it imperative that dermatologists explain to their psoriasis patients on these therapies the absolute need for herpes zoster vaccinations. In this review of 41 herpes zoster cases in patients with either psoriasis or psoriatic arthritis, there were 13.3 cases of herpes zoster per 1,000 patient-years in psoriasis patients and 15.9 for psoriatic arthritis patients versus only 8.5 cases per 1,000 patient-years in healthy controls. The more severe the psoriasis/psoriatic arthritis, the higher the incidence of herpes zoster was found. Fortunately, the new herpes zoster recombinant vaccine (Shingrix) has been shown to not cause side effects in immunocompromised patients, such as those who have HIV infection or who have had a transplant, and thus, can be safely used and recommended for our psoriasis patients on systemic or biologic therapies.

Cordran® Tape

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INDICATION AND USAGE

CORDRAN® Tape (Flurandrenolide Tape, USP) is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses, particularly dry, scaling localized lesions.

IMPORTANT SAFETY INFORMATION

Topical corticosteroids are contraindicated in patients with a history of hypersensitivity to any of the components of these preparations. Use of CORDRAN® Tape is not recommended for lesions exuding serum or in intertriginous areas.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Use over large surface areas, prolonged use, and the addition of occlusive dressings augment systemic absorption. Pediatric patients may absorb proportionately larger amounts of topical corticosteroids and thus may be more susceptible to systemic toxicity.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Patients receiving a large dose applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression, and therapy should be modified or discontinued as appropriate.

Topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively for pregnant patients or in large amounts or for prolonged periods of time. Caution should be exercised when topical corticosteroids are administered to a nursing woman.

Local adverse reactions may occur more frequently with the use of occlusive dressings. These reactions are listed in approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis. Reactions that may occur more frequently with occlusive dressings include: maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

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

IT STICKS. IT STAYS. IT WORKS.*

*CORDRAN Tape should be applied on clean and dry skin. It should always be cut, never torn. Topical corticosteroids are contraindicated in patients with a history of hypersensitivity to any of the components of these preparations. CORDRAN Tape is not recommended for lesions exuding serum or in intertriginous areas. Replacement of the tape every 12 hours produces the lowest incidence of adverse reactions, but it may be left in place for 24 hours if it is well tolerated and adheres satisfactorily. If irritation or infection develops, the use of CORDRAN Tape should be discontinued and appropriate antimicrobial therapy instituted, as necessary.[3]

USCOT0384c 08-2019

References:

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almirall

Not an actual patient, results may vary.

CORDRAN TAPE BRIEF SUMMARY OF PRESCRIBING INFORMATION

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION FOR CORDRAN® TAPE (Flurandrenolide Tape, USP)

This brief summary does not include all the information needed to use Cordran Tape safely and effectively. See full Prescribing Information for Cordran Tape.

INDICATIONS AND USAGE

For relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, particularly dry, scaling localized lesions.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in patients with a history of hypersensitivity to any of the components of these preparations. Use of Cordran Tape is not recommended for lesions exuding serum or in intertriginous areas.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using urinary-free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete on discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, so that supplemental systemic corticosteroids are required. Pediatric patients may absorb proportionately larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see Pediatric Use under PRECAUTIONS). If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatologic infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, Cordran Tape should be discontinued until the infection has been adequately controlled.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression: Urinary-free cortisol test, ACTH stimulation test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Usage in Pregnancy: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively for pregnant patients or in large amounts or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical-corticosteroid-induced HPA axis suppression and Cushing's syndrome than do mature patients because of a larger skin surface area to body weight ratio. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma-cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis.

The following may occur more frequently with occlusive dressings: maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

Manufactured for:
Almirall LLC
Exton, PA 19341.

Revised: 10/2018

USCOT0291 03-2019

almirall

Comorbidities may cut effectiveness of psoriasis biologics

BY BRUCE JANCIN
REPORTING FROM THE EADV CONGRESS

PARIS – The more comorbid conditions present in patients with moderate to severe plaque psoriasis, the less likely they are to achieve complete clearance in response to biologic therapy, according to the results of the prospective, observational PSO-BIO-REAL study.

The clinical importance of this finding lies in the fact that comorbidities are highly prevalent among patients with moderate to severe psoriasis. Indeed, fully 64% of the 846 participants in PSO-BIO-REAL had at least one major comorbid condition at baseline, Finn Ziegler said at the annual congress of the European Academy of Dermatology and Venereology.

"I think this reflects a picture that has been seen in other studies," noted Mr. Ziegler, director of global patient access at Leo Pharma in Ballerup, Denmark.

The purpose of the 12-month PSO-BIO-REAL (PSOriasis treated with BIOlogics in REAL life) study was to assess the effectiveness of a variety of biologic agents in a real-world population typical of patients encountered in routine clinical practice, as opposed to more restrictive format of often-cited randomized trials, which generally feature a lengthy list of exclusions. One-third of participants were from the United States, with the rest drawn from four Western European countries. Their mean age was 47 years, with an 18.4-year history of psoriasis and a baseline Psoriasis Area and Severity Index (PASI) score of 14.3.

Sixty percent of participants were starting treatment with a biologic agent for the first time. The other 40% had prior biologic experience. At physician discretion, 61% of enrollees were put on a tumor necrosis factor inhibitor, either etanercept (Enbrel), adalimumab (Humira), or infliximab (Remicade); 30% initiated treatment with the interleukin-12/23 inhibitor ustekinumab (Stelara); and 9% received secukinumab (Cosentyx), an interleukin-17 inhibitor.

The five most common comorbid conditions present at baseline were hypertension, present in 33.5% of participants; psoriatic arthritis (PsA), present in 28.1%; hyperlipidemia, 20.9%; diabetes, 13.9%; and depression, present in 13.7% of the psoriasis patients.

Baseline comorbidities were significantly more common among the biologic-experienced patients. For example, their prevalence of hypertension was 42%, compared with 28% in the biologic-naive group. PsA was present in 35% of the biologic-experienced and 23% of the biologic-naive patients. Nineteen percent of biologic-experienced patients had diabetes at baseline, as did 11% of the biologic-naive group.

During the 12-month study, 3.7% of patients developed a new comorbidity, the most common being anxiety, hypertension, PsA, depression, and hyperlipidemia.

The primary outcome in the study was the complete clearance rate – a PASI 100 response – at 6 months. It ranged from a high of 31% in patients with no baseline comorbid conditions to a low of 16.5% in those with three or more. The results were similar at 12 months.

Conversely, an inadequate therapeutic response as defined by a PASI 50 or less at 6 months occurred in 15% of psoriasis patients with no baseline comorbidities, 27% with one, 35% with two comorbid conditions, and 28% with three or more.

The major caveat regarding this study is that the observed association between comorbid conditions and complete clearance rates doesn't prove causality, Mr. Ziegler noted.

The PSO-BIO-REAL study was sponsored by Amgen, AstraZeneca, and Leo Pharma. Mr. Ziegler is a Leo executive.

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SOURCE: Ziegler F. EADV Congress, Abstract FC04.01.

Continued from page 19

with psoriasis or psoriatic arthritis, and to those aged under 50 years who were being treated with tofacitinib, systemic corticosteroids, or combination systemic therapy.

There were insufficient data to draw conclusions about the impact of treatment with the interleukin-12/23 blocker ustekinumab (Stelara) on herpes zoster risk, but the authors noted that there was a trend toward an increased risk. They found no increase in the risk of herpes zoster with interleukin-17 inhibitors (ixekizumab [Taltz], secukinumab [Cosentyx], and brodalumab [Siliq]) and interleukin-23 (p19 subunit) inhibitors (guselkumab [Tremfya], tildrakizumab [Ilumya], and risankizumab) but noted an absence of long-term safety data for these drugs.

Four authors declared advisory, consultancy, or speaker positions with the pharmaceutical sector.

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SOURCE: Baumrin E et al. J Am Acad Dermatol. 2019 Mar 15. doi: 10.1016/j.jaad.2019.03.017.

Weight loss cuts risk of psoriatic arthritis

BY BRUCE JANCIN
REPORTING FROM THE ACR ANNUAL MEETING

CHICAGO – Overweight and obese psoriasis patients have it within their power to reduce their risk of developing psoriatic arthritis through weight loss, according to a large British longitudinal study.

Of the three modifiable lifestyle factors evaluated in the study as potential risk factors for the development of psoriatic arthritis in psoriasis patients – body mass index, smoking, and alcohol intake – reduction in BMI over time was clearly the winning strategy, Neil McHugh, MD, said at the annual meeting of the American College of Rheumatology.

"Weight reduction amongst those who are obese may have the potential to greatly reduce their risk of psoriatic arthritis."

The message from this study of 90,189 incident cases of psoriasis identified in the U.K. Clinical Practice Research Datalink was unequivocal: "If you're overweight and have psoriasis and you lose weight, you reduce your chance of developing a nasty form of arthritis," said Dr. McHugh, professor of pharmacoepidemiology and a rheumatologist at the University of Bath (England).

"As psoriatic arthritis affects around 20% of people with psoriasis, weight reduction amongst those who are obese may have the potential to greatly reduce their risk of psoriatic arthritis in addition to providing additional health benefits," he added.


DR. MCHUGH

Among the more than 90,000 patients diagnosed with psoriasis, 1,409 subsequently developed psoriatic arthritis, with an overall incidence rate of 2.72 cases per 1,000 person-years. Baseline BMI was strongly associated in stepwise fashion with subsequent psoriatic arthritis. Psoriasis patients with a baseline BMI of 25-29.9 kg/m^2 were at an adjusted 1.76-fold increased risk of later developing psoriatic arthritis, compared with psoriasis patients having a BMI of less than 25. For those with a BMI of 30-34.9 kg/m^2, the risk of subsequent psoriatic arthritis was increased 2.04-fold. And for those with a baseline BMI of 35 kg/m^2 or more, the risk was increased 2.42-fold in analyses adjusted for age, sex, psoriasis duration and severity, history of trauma, and diabetes.

In contrast, the risk of developing psoriatic arthritis wasn't significantly different between psoriasis patients who were nonsmokers, ex-smokers, or current smokers. And while there was a significantly increased risk of developing psoriatic arthritis in psoriasis patients who were current drinkers, compared with nondrinkers, the risk in ex-drinkers and heavy drinkers was similar to that in nondrinkers, a counterintuitive finding Dr. McHugh suspects was a distortion due to small numbers.

While the observed relationship between baseline BMI and subsequent risk of psoriatic arthritis was informative, it tells only part of the story, since body weight so often changes over time. Dr. McHugh and his coinvestigators had data on change in BMI over the course of 10 years of follow-up in 15,627 psoriasis patients free of psoriatic arthritis at the time their psoriasis was diagnosed. The researchers developed a BMI risk calculator that expressed the effect of change in BMI over time on the cumulative risk of developing psoriatic arthritis.

"We were able to show that, if for instance you started with a BMI of 25 at baseline and ended up with a BMI of 30, your risk of psoriatic arthritis goes up by 13%, whereas if you start at 30 and come down to 25, your risk decreases by 13%. And the more weight you lose, the greater you reduce your risk of developing psoriatic arthritis," the rheumatologist explained in an interview.

Indeed, with more extreme changes in BMI over the course of a decade following diagnosis of psoriasis – for example, dropping from a baseline BMI of 36 kg/m^2 to 23 kg/m^2 – the risk of developing psoriatic arthritis fell by close to 30%.

Dr. McHugh reported having no financial conflicts regarding this study, funded by the U.K. National Institute for Health Research.

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SOURCE: Green A et al. Arthritis Rheumatol. 2018;70(Suppl 10). Abstract 2134.

Dose-response effect seen for weight loss in PsA

BY BRUCE JANCIN
REPORTING FROM RWCS 2019

MAUI, HAWAII – Serious weight loss brings big improvement in psoriatic arthritis in obese patients, at least short term, according to a Swedish, single-arm, prospective, proof-of-concept study.

A dose-response effect was evident: the greater the lost poundage, the bigger the improvement across multiple dimensions of psoriatic arthritis.

The short-term efficacy was eye-catching, especially in view of the well-recognized increased prevalence of obesity in psoriatic arthritis patients. But the jury is still out as to the long-term impact of this nonpharmacologic therapy, Eric M. Ruderman, MD, said at the 2019 Rheumatology Winter Clinical Symposium.

He has spoken with the Swedish investigators and was happy to learn they're continuing to follow study participants long term.

"That's going to be the key, right? Because if you do this for 12 weeks, like every other fad crash diet, and then you let the weight go right back on again, you haven't really accomplished anything. I think the key will be what happens at a year," according to Dr. Ruderman, professor of medicine and associate chief for clinical affairs in the division of rheumatology at Northwestern University, Chicago.


DR. RUDERMAN

The study included 46 obese psoriatic arthritis patients who signed on for a structured, medically supervised very-low-energy diet lasting 12-16 weeks, depending upon their baseline obesity level. The commercially available liquid diet (Cambridge Weight Plan Limited) is a type of therapy widely prescribed by Swedish physicians, clocking in at a mere 640 kcal/day.

Following completion of the strict very-low-energy diet, patients were gradually reintroduced to a less-draconian, solid-food, energy-restricted diet, to be followed through the 12-month mark. The full 12-month protocol was supervised by staff in the obesity unit at Sahlgrenska University Hospital in Gothenburg, Sweden. The 12-month results will be presented at the annual European Congress of Rheumatology in Madrid.

Of the 46 starters, 41 made it to the 6-month follow-up assessment. At that point they'd lost a median of 18.2 kg, or 18.6% of their baseline body weight. Their body mass index had dropped from an average of 35.2 to 29.8 kg/m^2. And their psoriatic arthritis had improved significantly. For example, their median Disease Activity Score using 28 joint counts based upon C-reactive protein (DAS28-CRP) decreased from 2.9 at baseline to 2.4 at 6 months, with American College of Rheumatology 20, 50, and 70 responses of 51.2%, 34.1%, and 7.3% while disease-directed medications were held constant (Arthritis Res Ther. 2019 Jan 11;21[1]:17. doi: 10.1186/s13075-019-1810-5).

The investigators reported the very-low-energy diet phase was generally well tolerated. A total of 34 of the 41 patients deemed it "easier or much easier" than expected, prompting Dr. Ruderman to comment: "Because they thought it was going to be awful."

Dr. Ruderman reported serving as a consultant to numerous pharmaceutical companies.

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Commentary by Dr. Menter:

In two important studies relating to weight loss in our obese psoriasis population (average weight internationally of 90 kg and average BMI of 30), patients who are able to lose weight had a lower chance of developing subsequent psoriatic joint disease. In the first study, a British study of over 90,000 psoriasis patients, 1,409 patients subsequently developed psoriatic arthritis. Patients with a baseline BMI of 25-30 were at a 1.76-fold increased risk of developing psoriatic arthritis compared to patients with a BMI of less than 25. For obese patients with a BMI of 30-35 the risk of subsequent joint disease was increased 2.04-fold. For patients with a BMI greater than 35/m^2 the increased risk of subsequent joint disease was 2.42-fold.

In a study done in Sweden, similar results were noted when patients were placed on a very tight diet lasting up to 16 weeks. At 6 months, the average weight loss was 182 kg. The subsequent assessment of joint disease activity was significantly reduced after 6 months.

Thus, because of the obesity and metabolic syndrome issues associated with psoriasis, not just driven by overeating or alcohol use, but part of the systemic nature of psoriasis, it is essential that we, as dermatologists, do all we can to help our psoriasis population lose weight. In our Baylor, Dallas Gastric Bypass surgery, each patient lost over 100 pounds with their cholesterol levels, blood pressure, and blood glucose levels all dramatically improved.

EULAR keeps csDMARDs as top PsA drugs

BY MITCHEL L. ZOLER
REPORTING FROM EULAR 2019 CONGRESS

MADRID – The draft revision of the European League Against Rheumatism's recommendations for managing psoriatic arthritis sticks with the group's already-existing conviction that psoriatic arthritis treatment best starts with an NSAID, and if that fails, follow with a conventional synthetic antirheumatic drug such as methotrexate, a position in stark contrast with the 2018 recommendation from the American College of Rheumatology to first treat with a tumor necrosis factor (TNF) inhibitor.

For patients with psoriatic arthritis (PsA) manifesting with polyarthritis, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) "should be first," and should "start rapidly" if brief, initial treatment with an NSAID proves inadequate, Laure Gossec, MD, PhD, said while presenting a draft version of an update to the PsA management recommendations from EULAR at the European Congress of Rheumatology.

The EULAR recommendations-revision panel had about the same advice for managing PsA patients with oligoarthritis, monoarthritis, or peripheral arthritis. For oligo- and monoarthritis, "consider a csDMARD after failing NSAIDS, but also consider the patient's prognostic factors," like structural damage, and dactylitis. For PsA patients with peripheral arthritis, "it still makes sense to keep csDMARDs as the first-line treatment," said Dr. Gossec, professor of rheumatology at Pitie-Salpétriere Hospital and Sorbonne University, Paris. Once published, the revision will replace existing EULAR recommendations from 2015 (Ann Rheum Dis. 2016 Mar;75[3]:499-510).


DR. GOSSEC

The list of csDMARDs she cited included not just methotrexate, still the top csDMARD, but also sulfasalazine and leflunomide as alternatives, she noted, with methotrexate also the preferred csDMARD for patients with skin involvement. When a PsA patient fails at least one csDMARD, then switching to a biologic DMARD is recommended. For a patient with skin involvement, a drug that targets interleukin (IL)–17 or IL-12 and -23 is preferred. If skin involvement is not a major issue, then treatment with a TNF inhibitor is equally valid, she said.

The 2018 PsA management guideline from the American College of Rheumatology (ACR) proposed a strikingly different sequence, endorsing initial treatment with a TNF inhibitor first over all other options,


vgajic/Getty Images

including methotrexate and other "oral small molecules" (the ACR term for csDMARD), and also including NSAIDs (Arthritis Rheumatol. 2019 Jan;71[1]:5-32).

This schism between EULAR and the ACR could be seen as predictable, given the different constraints the two societies have set for themselves.

"EULAR recommendations take into account drug costs; the ACR guideline is supposed to be agnostic to costs," explained Philip J. Mease, MD, a rheumatologist at Swedish Medical Center in Seattle and a member of the ACR panel that wrote the 2018 PsA guideline.

In fact it was a study Dr. Mease recently led and reported results from that provided the most recent and perhaps best assessment of a TNF inhibitor, compared with methotrexate, as initial treatment for PsA, with findings that suggest that, although the advice from the two societies may sharply differ, the viewpoints of both groups are evidence based.

The SEAM-PsA (Study of Etanercept and Methotrexate in Subjects With Psoriatic Arthritis) trial randomized 851 PsA patients receiving their first treatment to methotrexate only, the TNF inhibitor etanercept (Enbrel) only, or both drugs. The study's two coprimary outcomes, the ACR 20 and minimal disease activity responses after 24 weeks, showed that etanercept monotherapy produced these responses in 61% and 36% of patients, respectively, while methotrexate monotherapy produced response rates of 51% and 23%, respectively. Both these differences between etanercept monotherapy and methotrexate monotherapy were statistically significant. Combining methotrexate with etanercept did not produce a significant improvement over etanercept alone.

Interpreting the meaning of this finding for clinical practice "depends on the lens you look through," Dr. Mease said in an interview. "A lot of patients respond to methotrexate, which is good when treatment resources are challenged. But when there is no resource challenge, the data support going straight to a TNF inhibitor."

"We carefully looked at the SEAM-PsA trial results, which provide some of the only data we have on methotrexate" for PsA.

Dr. Gossec confirmed the importance of the SEAM-PsA findings in the writing panel's decision during discussion of the draft, replying to a question about consideration of the study's findings. "We carefully looked at the SEAM-PsA trial results, which provide some of the only data we have on methotrexate" for PsA. "We felt that the results were in favor of methotrexate's efficacy, and therefore did not go against our proposal to keep a graduated approach starting with a csDMARD."

Patients who fail to receive adequate relief from a csDMARD could then try a biologic DMARD – a TNF inhibitor, IL-17 inhibitor, or IL-12/23 inhibitor, Dr. Gossec said. When skin involvement is minimal, any of these options are possible, she said. If skin involvement is significant, the panel recommended preferentially using an IL-17 or IL-12/23 inhibitor based on head-to-head trials in patients with psoriasis, she said.

When a biologic DMARD is not appropriate or fails, another option is to then try a targeted synthetic DMARD, such as a Janus kinase inhibitor. When none of these options are appropriate, or they all fail, another option for patients with mild oligo- or monoarthritis or in patients with limited skin involvement is apremilast (Otezla), a phosphodiesterase-4 inhibitor. The draft recommendations also advise clinicians to be sure to distinguish fibromyalgia pain from enthesitis involvement, and they introduce the possibility of, with "great caution," tapering down DMARD treatment in PsA patients who show sustained remission.

Dr. Gossec and Dr. Mease have both been consultants to and received honoraria from several companies. SEAM-PsA was sponsored by Amgen, the company that markets Enbrel.

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Commentary by Dr. Menter:

The European League Against Rheumatism (EULAR) has recently proposed recommendations for the initial therapy of psoriatic arthritis that is in stark contrast with American College of Rheumatology (ACR) 2018 Guidelines. Thus, EULAR proposes that patients with early-onset psoriatic arthritis should be initially treated with a conventional synthetic disease- modifying antirheumatic drug (csDMARD) including not only methotrexate but also sulfasalazine and leflunomide as alternatives.

The ACR guidelines in contrast endorse the initial therapy with a tumor necrosis factor–alpha inhibitor for early PsA versus methotrexate and other small molecules. A significant reason for this contrast between the European and U.S. guidelines for PsA relate predominantly to cost issues with EULAR proposing DMARDs prior to TNF-alpha agents because of the major cost differences.

Over 50% of patients with early PsA are likely to progress to permanent joint destruction if not placed on a TNF-alpha agent. Methotrexate will certainly reduce joint symptoms but, unfortunately, will not reduce the incidence of joint destruction.

For adult patients with active psoriatic arthritis (PsA)

Skin Clearance Clinical Trial Data

- Most HUMIRA-treated patients with active PsA who presented with psoriatic skin involvement demonstrated proven skin clearance (PASI 75) at Week 24 and sustained this response rate at Week 48[1,3,4,†]

Protection Against Further Joint Damage and Signs and Symptoms Clinical Trial Data

- Most HUMIRA-treated patients demonstrated proven and sustained protection against further joint damage (change in mean baseline mTSS) at Week 48. Additionally, many patients experienced proven improvement in signs and symptoms, as defined by ACR20, at Week 12[1,3,4,‡,§,ǁ,¶]

Indication[1]

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

Safety Considerations[1]

Serious Infections: Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies: Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

*Injection site pain immediately following injection as measured using a 0-10 cm Visual Analog Scale: HUMIRA 40 mg/0.4 mL vs HUMIRA 40 mg/0.8 mL.

†Patients enrolled in the clinical trial, who had a minimum of 3% body surface psoriatic skin involvement, were assessed for PASI 75; Week 48 data is based on an analysis from open label extension.

‡ACR20 indicates an improvement of at least 20% in tender joint count, swollen joint count, and at least 3 of the other ACR parameters.

§Modified total Sharp score (mTSS) measures narrowing, as well as radiographic changes specific to patients, including DIP joints, with a maximum score of 570.

‖No radiographic progression defined as a change in modified total Sharp score (mTSS) of ≤0.5 from baseline.

¶Extrapolated analysis. For HUMIRA-treated patients who did not have an mTSS at Week 48, mTSS was imputed by linear extrapolation using the baseline and Week 24 scores. The mTSS was used by the reader blinded to treatment group to assess the radiographs.

Safety Considerations[1] (cont'd)

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

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

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

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HUMIRA® adalimumab

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

SERIOUS INFECTIONS

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

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

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

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

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

MALIGNANCY

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

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

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

HEPATITIS B VIRUS REACTIVATION

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

NEUROLOGIC REACTIONS

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

HEMATOLOGIC REACTIONS

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

CONGESTIVE HEART FAILURE

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

AUTOIMMUNITY

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

IMMUNIZATIONS

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

ADVERSE REACTIONS

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

References: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc. **2.** Singh J, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheum.* 2018;0:1-28. **3.** Mease PJ, Gladman DD, Ritchlin CT, et al; for the Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2005;52(10):3279-3289. **4.** Gladman DD, Mease PJ, Ritchlin CT, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum.* 2007;56(2):476-488. **5.** Nash P, Vanhoof J, Hall S, et al. Randomized crossover comparison of injection site pain with 40 mg/0.4 or 0.8 mL formulations of adalimumab in patients with rheumatoid arthritis. *Rheumatol Ther.* 2016;3(2):257-270.

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

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HUMIRA® adalimumab

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

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

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

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

INDICATIONS AND USAGE

Rheumatoid Arthritis

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

Juvenile Idiopathic Arthritis

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

Psoriatic Arthritis

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

Ankylosing Spondylitis

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

Adult Crohn's Disease

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

Pediatric Crohn's Disease

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

Ulcerative Colitis

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

Plaque Psoriasis

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

Hidradenitis Suppurativa

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

Uveitis

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

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

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

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

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

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

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

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

Monitoring

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

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

Invasive Fungal Infections

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

Malignancies

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

Malignancies in Adults

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

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

Non-Melanoma Skin Cancer

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

Lymphoma and Leukemia

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

Malignancies in Pediatric Patients and Young Adults

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

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

Hypersensitivity Reactions

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

Hepatitis B Virus Reactivation

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

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

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

bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

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

Heart Failure

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

Autoimmunity

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

Immunizations

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

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

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

Infections

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

Tuberculosis and Opportunistic Infections

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

Autoantibodies

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

Liver Enzyme Elevations

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

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

Immunogenicity

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

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

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

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

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

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

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

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

Anti-adalimumab antibodies were measured in clinical trials of subjects with moderate to severe HS with two assays (an original assay capable of detecting antibodies when serum adalimumab concentrations declined to < 2 mcg/mL and a new assay that is capable of detecting anti-adalimumab antibody titers in all subjects, independent of adalimumab concentration). Using the original assay, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%. Using the new titer-based assay, anti-adalimumab antibody titers were measurable in 61% of HS subjects treated with HUMIRA. Antibodies to adalimumab were associated with reduced serum adalimumab concentrations. In general, the extent of reduction in serum adalimumab concentrations is greater with increasing titers of antibodies to adalimumab. No apparent association between antibody development and safety was observed.

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

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

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

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

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

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

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

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

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

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster. In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

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

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

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

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

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.
In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

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

Adult Crohn's Disease Clinical Studies

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

Pediatric Crohn's Disease Clinical Studies

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

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

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

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

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

Ulcerative Colitis Clinical Studies

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

Plaque Psoriasis Clinical Studies

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

Hidradenitis Suppurativa Clinical Studies

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

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

Uveitis Clinical Studies

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

Postmarketing Experience

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

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

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

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

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

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

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

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

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

Biological Products

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

Live Vaccines

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

Cytochrome P450 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

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

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

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

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

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

Juvenile Idiopathic Arthritis

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

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

Pediatric Crohn's Disease

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

Pediatric Uveitis

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

Hidradenitis Suppurativa

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

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

Geriatric Use

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

PATIENT COUNSELING INFORMATION

Patient Counseling

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

Advise patients of the potential benefits and risks of HUMIRA.

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

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Survey finds psoriasis patients seek relief with alternative therapies

BY JILL D. PIVOVAROV
FROM THE JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

Treatment failure and the adverse effects of psoriasis therapies may drive patients to complementary and alternative medicines (CAMs), despite limited evidence of their efficacy, reported Emily C. Murphy and her associates, in the department of dermatology, George Washington University, Washington.

They performed a survey-based statistical analysis to identify specific types of commonly used CAMs, and to explore reasons why patients increasingly turn to alternative therapies. The survey was distributed in the National Psoriasis Foundation's (NPF) October 2018 newsletter to its 100,927 members.

Of the 6,101 NPF members who opened the newsletter, 324 clicked on the survey link. Of the 219 who completed the survey, almost 70% were women. The majority were white (84.1%), compared with Hispanic (6.2%), Asian (3.1%), and black (2.6%) participants. Most respondents had a dermatologist diagnosis of psoriasis, as well as access to health insurance to cover any prescribed medicines.

Of the 41% of respondents who reported using alternative therapies, use was high among those who considered their psoriasis as severe (50% vs. 33.6% of those with nonsevere disease). Women were more likely than were men to use CAMs (45.6% vs. 26.5%, $P = .002$).

Only 4% cited access to care as a reason for choosing alternative therapies. Most used CAMs because "medications did not help or had side effects."

While men were more likely than were women to use vitamins (24% vs. 18.9%, respectively), Dead Sea bath salts (17% vs. 7.8%), and cupping (3% vs. 0.8%), women were more likely to use herbals/botanicals (17% vs. 14%) and yoga (9.6% vs. 2%).

Patients with moderate psoriasis were more likely than were those with mild or severe disease to recommend CAMs, regardless of insurance status (52.4% vs. 35% among those with mild disease and 40.4% for those with severe disease).

For some of the commonly used treatments, such as vitamins D and B_{12}, there is insufficient evidence of their efficacy. Dead Sea treatments have been shown to have therapeutic effects. And while there is efficacy evidence for indigo naturalis and meditation, these were not commonly reported by respondents.

Just 43% of patients said they would recommend a CAM to other people with psoriasis. "Educational initiatives that enable physicians to discuss evidence-based CAMs may improve patient satisfaction and outcomes," the researchers wrote.

Previous studies have cited rates as high as 62% for CAM use in psoriasis, but have not examined the motivations for their use. Not surprisingly, patients often misunderstand the benefits of CAM.

"The onus is on us as physicians to not only ask our patients if they are using nonallopathic therapies for their psoriasis, but also to create an accepting environment that enables further discussion regarding said treatments to ensure patient safety and ultimately good outcomes," senior author Adam Friedman, MD, professor and interim chair of dermatology at George Washington University, said in an interview.

The authors had no financial conflicts of interest; there was no funding source.

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SOURCE: Murphy EC et al. J Am Acad Dermatol. 2019 Mar 29. pii: S0190-9622(19)30503-1. doi: 10.1016/j.jaad.2019.03.059.

Commentary by Dr. Gelfand:

Psoriasis is a common, chronic, incurable disease. Even our best treatments fail to achieve complete remission in about half of patients, and patients often lose response to treatment over time. How frustrating! As a further complication, about 10% of patients with psoriasis (roughly 800,000 people in the United States alone) will have a spontaneous remission in their disease at some point, and thus many are convinced that they have stumbled upon a cure. Has your patient asked you about going on a gluten-free diet? I don't know a dermatologist who hasn't been asked this question. We know from prior work that a large percentage of psoriasis patients attempt alternative medicines ranging from supplements to herbs, special diets, and other approaches. Notable, in this study of psoriasis patients who are engaged with the National Psoriasis Foundation, of the 41% of respondents who reported using alternative therapies, usage was especially high among those who considered their psoriasis as severe (50% vs. 33.6% of those with nonsevere disease). Among the respondents, women were more likely than were men to use CAMs (45.6% vs. 26.5%, $P = .002$). Dermatologists should be aware of CAM use by their patients and recognize that some thought to be effective were found to be potent steroids. The only CAM I recommend is mindfulness meditation as it has been shown in a RCT to have some benefit in psoriasis patients undergoing phototherapy, is essentially free, is harmless, and has been shown to have other health benefits such as reducing stress. Full disclosure, I am terrible at meditating, but I am an avid practitioner of yoga, which is supposed to prepare the mind for meditation, so perhaps there is still hope for me yet!

Systemic psoriasis treatments less often prescribed in elderly with psoriasis, despite comparable response rates

BY ANDREW D. BOWSER
REPORTING FROM WCD2019

MILAN – Biologics are underprescribed in the elderly, despite evidence that the efficacy of biologics is comparable among older and younger patients over time, an analysis of German and Swiss registry data shows.

There was an "imbalance" in the types of medications prescribed for older and younger patients in the registry, with biologics used more frequently in younger patients, according to investigator Matthias Augustin, MD, director of the Institute for Health Services Research in Dermatology and Nursing in Hamburg, Germany.

However, the efficacy of systemic treatments, including nonbiologic therapies, was comparable between older and younger patients, other than a few differences in response rates early in treatment that disappeared with longer follow-up, Dr. Augustin said at the World Congress of Dermatology. Coupled with evidence from the literature, this data analysis suggests there are "very few reasons" to avoid use of systemic drugs in elderly patients.

"I think we should create awareness and discuss possible reasons that deter dermatologists from prescribing systemic antipsoriatics in elderly patients," he said.

Concerns about safety and drug interactions in the elderly may be one barrier to prescribing systemic therapy. More data are needed, since the elderly are taking more medications than younger patients and have more contraindications, Dr. Augustin said.

"I think this is a job for all registries for the future," he said. Older individuals have typically been excluded from psoriasis clinical trials, making it difficult to extrapolate existing safety and efficacy data to those patients.

The researchers evaluated prospectively collected data for patients with moderate to severe psoriasis who were included in either the German Psoriasis Registry (PsoBest) or the Swiss Dermatology Network for Targeted Therapies (SDNTT). They split the cohort into those younger than 65 years (about 4,600 individuals) and those 65 years or older (about 740 individuals).

A few systemic drugs were used more frequently in the elderly, including apremilast and methotrexate, while most other drugs, including biologics, were used more frequently in younger patients. There were a few differences between the elderly and controls related to weight, smoking, and other factors, but not so pronounced that they would explain differences in the use of systemic therapy.

Response rates to systemic therapies were generally comparable between those over age 65 and those younger, as measured by Psoriasis Area Severity Index (PASI) 75 responses, PASI scores of 3 or less, and Dermatology Life Quality Index scores of 1 or less.

One exception was methotrexate, which was more effective in the elderly after 3 and 6 months of treatment, but that difference was no longer apparent after 12 months of treatment, he said. Likewise, cyclosporine showed a higher response rate in younger patients at 3 months, but not at 6 or 12 months.

The PsoBest registry is sponsored by CVderm, DDG, and BVDD, and "has been established and is operated in close cooperation with the involved pharmaceutical companies whose statutory pharmacovigilance requirements are taken into account," according to a statement on the PsoBest website. The Swiss registry is supported by Janssen, AbbVie, Pfizer, Celgene, Lilly, and Novartis. The investigators did not report any disclosures.

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Commentary by Dr. Gelfand:

It is well known that there is widespread undertreatment of chronic immune-mediated diseases, which include not only psoriasis but also psoriatic arthritis and rheumatoid arthritis. This European registry study found that a few systemic drugs were used more frequently in the elderly, including apremilast and methotrexate, while most other drugs, including biologics, were used more frequently in younger patients. This finding is especially concerning given that elderly patients are at greater risk of side effects from methotrexate (because of a lower glomerular filtration rate that comes with age) and apremilast (because of a greater sensitivity to dehydration if there is diarrhea). The reasons behind these differences in treatment patterns are not well understood. In my own practice, I find it especially gratifying to treat psoriasis in the older population. Many of these patients have lived with psoriasis for decades and have tried and failed many treatments over the years. To be able to achieve psoriasis remission with some of our more targeted therapies often feels like a miracle to long-suffering patients and their families. Getting to see the joy and relief that finally obtaining control of their psoriasis brings to the patient and their loved ones is one of the best parts of being a physician!

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Infections linked with transition to psoriatic arthritis

BY MITCHEL L. ZOLER
REPORTING FROM THE EULAR 2019 CONGRESS

MADRID – Several novel risk associations with psoriasis progression were found to differ by sex, and collectively appeared to implicate infections and the "stress response" as a trigger of psoriatic arthritis.

The findings come from a risk factor analysis of a U.S. claims database of more than 200,000 adults with psoriasis including more than 4,000 patients who progressed to psoriatic arthritis during nearly 6 years of follow-up.

The new analysis confirmed several previously described risk associations linked with progression to psoriatic arthritis (PsA) that have roughly equal impact on both women and men: fatigue, obesity, and depression, Alexis Ogdie, MD, said at the European Congress of Rheumatology. The new findings also showed several novel, sex-specific associations. In women, these associations included salmonella infection, sepsis, and uveitis; in men, they included gangrene, encephalitis, and hidradenitis suppurativa.

The links with various infections were generally rare; they showed strong nominal associations in multivariate analyses but with wide confidence limits. The findings suggest that events that induce major stress responses, such as infections, often preceded the progression of psoriasis to a diagnosis of PsA, said Dr. Ogdie, director of the psoriatic arthritis clinic at the University of Pennsylvania in Philadelphia. Other, noninfectious clinical features that significantly linked with PsA development but at a lower magnitude included anemia and diabetes in women, and irritable bowel syndrome and venous thromboembolism in men.


DR. OGDIE

Dr. Ogdie cautioned that the findings were preliminary and need confirmation in different data sets, as well as in additional subgroup analyses of the data used in the current analysis, taken from the electronic medical records of 215,386 U.S. residents diagnosed with psoriasis in the Optum medical-claims database for 2006-2017.

The analysis focused on patients who received a second diagnostic code in their EMR for psoriasis during the 12 months after the index psoriasis entry. The identified group averaged 50 years old; 55% of the psoriasis patients were women, and 86% were white.

During the year after their first diagnostic-code entry for psoriasis, 4.6% of the patients received a biological drug and 4.2% received an oral drug for their psoriasis. During 5.6 years of follow-up, 4,288 patients (2%) developed PsA, a rate of 3.5 cases/1,000 patient-years. Dr. Ogdie noted that prior studies have documented the challenge of diagnosing PsA in patients with psoriasis, so this may be a conservative estimate of the progression rate.

The researchers assessed possible linkage with PsA progression for more than 250 different entries in the EMR, but the analysis was limited by the absence of measures of rheumatoid susceptibility, such as immunologic markers, which were not included in the EMR. In multivariate analysis of the full cohort, fatigue at baseline

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Continued from previous page

was linked with a 77% higher rate of progression to PsA, obesity was linked with a 48% higher rate, and depression with a 29% higher rate of progression when compared with psoriasis patients without each of these factors. All three differences were statistically significant. Dr. Ogdie cited an article she recently coauthored that detailed the background to this approach in studying the etiology of PsA (Nat Rev Rheumatol. 2019 Mar;15:153-66).

This is the first study to report sex-linked differences in clinical measures that link with progression to PsA, Dr. Ogdie noted. In women, salmonella infection linked with a 9-fold higher rate of PsA development compared with women with psoriasis without salmonella infection, women with uveitis had a 2.9-fold higher rate of PsA development, and those with sepsis had a 2.4-fold increased rate of PsA. Among men, those with gangrene, encephalitis, or hidradenitis suppurativa each had a greater than 4-fold higher rate of developing PsA, and men with osteomyelitis had a 2.7-fold increase.

All these between-group differences were statistically significant. But because each of these was a relatively rare event, the confidence intervals around these point estimates were wide. For example, in women with salmonella infection from a statistical standpoint the possible range of increased risk could be anywhere from 1.3 to 66. The analysis identified among women and men several additional sex-specific risk associations that were statistically significant but with smaller point estimates.

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SOURCE: Ogdie A et al. Ann Rheum Dis. Jun 2019;78(Suppl 2):131-2, Abstract OP0115. doi: 10.1136/annrheumdis-2019-eular.4390.

Commentary by Dr. Gelfand:

Why do some people with psoriasis develop psoriatic arthritis when the majority do not? This is a key question for researchers, physicians, and patients. This study was led by Alexis Ogdie, MD, a rheumatologist and epidemiologist who specializes in psoriatic arthritis (full disclosure, I am an author on this abstract and also serve as Dr. Ogdie's mentor on a number of grants, and she is a key collaborator of mine in the clinic and in research). In this study, Dr. Ogdie leveraged the OptumInsights EHR Database (United States) between 2006-2017. Among 215,386 patients with psoriasis, mean age was 50 and 55% were female. At 1 year after date of first psoriasis code, 4.6% and 4.2% of patients had been prescribed a biologic therapy or oral therapy in the past year. Mean follow-up time was 5.6 years and 4,288 patients developed incident PsA (incidence 3.5 cases/1,000 person-years). Previously identified predictors were confirmed (depression, fatigue, inflammatory bowel disease, uveitis, hyperlipidemia, fracture – think Koebner for the joints!) but several new predictors were also identified (diabetes, hidradenitis suppurativa, celiac disease, irritable bowel syndrome, sepsis, posttraumatic stress disorder, anxiety, and anemia). The study could not evaluate the impact of genetics or what is one of the strongest risk factors for developing PsA, namely body surface area affected by psoriasis (but Dr. Ogdie and I plan to address this question in the ongoing iHOPE [Incident Health Outcomes and Psoriasis Events] study of 9,000 patients with psoriasis in which we obtained data on body surface area affected prospectively). The use of medical informatics, bolstered by emerging machine learning and artificial intelligence technologies offers the hope that one day, all the clicking we do in our EMRs will yield useful prognostic information so we can let our patients accurately know their risk of developing PsA.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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INDICATIONS AND USAGE

BRYHALI™ (halobetasol propionate) Lotion, 0.01% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

BRYHALI has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment with the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with BRYHALI was evaluated in a study of 19 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area (BSA). HPA axis suppression was reported for 1 (5.6%) subject at Week 4 and for 3 (15.8%) subjects at Week 8. All 3 subjects had normal HPA axis suppression test with discontinuation of treatment [see *Clinical Pharmacology* in full Prescribing Information].

Because of the potential for systemic absorption, use of topical corticosteroids, including BRYHALI, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios *[see Use in Specific Populations]*.

Local Adverse Reactions

Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. These may be more likely with occlusive use, prolonged use, or use of higher potency corticosteroids, including BRYHALI. Some local adverse reactions may be irreversible.

Concomitant Skin Infections

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of BRYHALI until the infection has been adequately treated.

Allergic Contact Dermatitis

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue BRYHALI if allergic contact dermatitis occurs.

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.

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 426 adults with plaque psoriasis were treated with BRYHALI and had post-baseline safety data. Subjects applied BRYHALI once daily for up to eight weeks. Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with BRYHALI and more frequently than in vehicle-treated patients.

Table 1: Adverse Reactions Occurring in ≥1% of the Subjects Treated with BRYHALI through Week 8

	BRYHALI (N=284)	Vehicle (N=142)
Adverse Reaction	**%**	**%**
Upper Respiratory Tract Infection	2%	1%
Application Site Dermatitis	1%	0
Hyperglycemia	1%	0

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on BRYHALI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI.

The 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

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

Lactation

Risk Summary

There are no data on the presence of halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with BRYHALI.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

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

Clinical Considerations

Advise breastfeeding women not to apply BRYHALI directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use

Safety and effectiveness of BRYHALI in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children *[see Warnings and Precautions]*.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema *[see Warnings and Precautions]*.

Geriatric Use

Of 284 subjects exposed to BRYHALI in clinical trials, 61 subjects were 65 years or older. Clinical trials of BRYHALI did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, or in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured for:
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Bridgewater, NJ 08807 USA

By:
Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada
U.S. Patent Numbers: 6,517,847 and 8,809,307

Based on 9652102 November 2018 BRY.0032.USA.18

BRYHALI™
(halobetasol propionate) Lotion, 0.01%

FOR ADULTS WITH PLAQUE PSORIASIS

CHART A COURSE TO SYMPTOMATIC RELIEF

The efficacy of Class 1 halobetasol with safety proven for up to 8 weeks of dosing[1,2]

A NEW POTENCY CLASS OF STEROID LOTION

2 PIVOTAL PHASE 3 TRIALS

POTENT TO SUPERPOTENT CLEARANCE[1]:

Continued results 4 weeks post treatment[1]

Significant symptomatic relief as early as week 2[2]

No increased epidermal atrophy
observed through 8 weeks of treatment[2]

Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, hypopigmentation and allergic contact dermatitis. Some local adverse reactions may be irreversible.

STUDY RESULTS: 36.5% of patients in trial 1 and 38.4% in trial 2 achieved treatment success* at week 8 (primary endpoint) vs 8.1% and 12.0% of patients with vehicle, respectively ($P<0.001$ in both trials).[2]

STUDY DESIGN: The safety and efficacy of BRYHALI Lotion were assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in 430 adult patients with moderate-to-severe plaque psoriasis. Patients were treated with BRYHALI Lotion or vehicle lotion, applied once daily. Primary efficacy endpoint was treatment success evaluated at week 8. Secondary efficacy endpoint was treatment success evaluated at weeks 2, 4, 6, and 12 (4 weeks post treatment). Tertiary efficacy endpoint was a 2-grade improvement from baseline at each time point for the individual signs of psoriasis (erythema, plaque elevation, and scaling).[2]

*Treatment success was defined as at least a 2-grade improvement from baseline in the Investigator's Global Assessment score, and a score of "clear" or "almost clear" (primary endpoint at week 8).[2]

References: 1. BRYHALI Lotion [prescribing information]. Bridgewater, NJ. Valeant Pharmaceuticals North America LLC. **2.** Data on file.

Indication

BRYHALI™ (halobetasol propionate) Lotion, 0.01% is a corticosteroid indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information

Warnings and Precautions

- BRYHALI Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during treatment or upon cessation of treatment; periodic evaluation may be required.
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria.
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids.
- Local adverse reactions may include atrophy, striae, telangiectasias, hypopigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible.
- Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist.
- Use an appropriate antimicrobial agent if a skin infection is present or occurs, and if prompt response is not seen, discontinue use until infection has been adequately treated.
- Discontinue BRYHALI Lotion if allergic contact dermatitis occurs.

Adverse Reactions

- The most common adverse reactions (≥1%) were upper respiratory tract infection, application site dermatitis, and hyperglycemia.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or FDA at 1-800-FDA-1088.

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

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