A systematic review of herpes zoster incidence and consensus recommendations on vaccination in adult patients on systemic therapy for psoriasis or psoriatic arthritis: From the Medical Board of the National Psoriasis Foundation

Emily Baumrin, MD,[a,b] Abby Van Voorhees, MD,[c] Amit Garg, MD,[d] Steven R. Feldman, MD, PhD,[e] and Joseph F. Merola, MD, MMSc[a,b,f]

Boston, Massachusetts; Norfolk, Virginia; Hempstead, New York; and Winston-Salem, North Carolina

Background: Herpes zoster (HZ) incidence is linked to immunosuppression. Patients with psoriasis or psoriatic arthritis (PsA) on systemic therapy might be at an increased risk for HZ.

Objective: To assess HZ risk in patients with psoriasis and PsA by systemic treatment and provide recommendations regarding HZ vaccination.

Methods: A systematic literature search was performed for HZ in patients with psoriasis and PsA. HZ vaccination guidelines were reviewed, and the medical board of the National Psoriasis Foundation made consensus recommendations in psoriasis and PsA patients using graded evidence.

Results: In total, 41 studies met inclusion criteria. Systemic corticosteroids (strong, 1), tofacitinib (strong, 1), and combination therapy with biologic and conventional synthetic disease-modifying antirheumatic drugs (weak, 2a) carry increased HZ risk while monotherapy does not. There is insufficient evidence to determine risk with interleukin 12/23, 17, and 23 inhibitors or apremilast (weak, 2a). Recombinant zoster vaccine is recommended for all psoriasis and PsA patients >50 years old and patients <50 years old on tofacitinib, systemic steroids, or combination systemic treatment. Vaccination of patients <50 years old on other systemic therapies may be considered on a case-by-case basis.

Limitations: There was significant heterogeneity between studies.

From the Department of Dermatology, Brigham and Women's Hospital, Boston[a]; Harvard Medical School, Boston[b]; Department of Dermatology, Eastern Virginia Medical School, Norfolk[c]; Department of Dermatology, Zucker School of Medicine at Hofstra/Northwell, Hempstead[d]; Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem[e]; and Department of Medicine, Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital, Boston.[f]

Funding sources: None.

Conflicts of interest: Dr Van Voorhees is an advisor, consultant, and/or investigator for Celgene, Corrona, Dermira, Novartis, Allergan, AbbVie, DermTech, Pfizer, Astra Zeneca and Valeant. Dr Garg is an advisor and/or researcher for AbbVie, Pfizer, Asana, National Psoriasis Foundation, and UCB. Dr Feldman is an advisor, consultant, speaker, or researcher for AbbVie, Celgene, Janssen, Lilly, Novartis, Ortho, Merck, Samsung, Almirall, Leo Pharma, and Boehringer Ingelheim. Dr Merola is a consultant and/or investigator for Merck Research Laboratories, Abbvie, Dermavant, Eli Lilly and Company, Novartis, Janssen, UCB, Samumed, Celgene, Sanofi Regeneron, GSK, Almirall, Sun Pharma, Biogen, Pfizer, Incyte, Aclaris, and Leo Pharma, and Dr Baumrin has no conflicts of interest to disclose.

Accepted for publication March 8, 2019.

Correspondence to: Emily Baumrin, MD, Department of Dermatology, Brigham and Women's Hospital, 41 Avenue Louis Pasteur, EC 313, Boston, MA 02115. E-mail: ebaumrin@partners.org.

Published online March 15, 2019.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.03.017

Conclusion: HZ risk depends on disease severity and treatment class. Recombinant zoster vaccine should be given to all psoriasis and PsA patients >50 years old and younger patients at increased risk. (J Am Acad Dermatol 2019;81:102-10.)

Key words: herpes zoster; psoriasis; psoriatic arthritis; recombinant; shingles; Shingrix; vaccination.

CAPSULE SUMMARY

- Treatment of psoriasis and psoriatic arthritis with systemic corticosteroids, tofacitinib, and combination systemic therapy increases risk of herpes zoster.
- The recombinant zoster vaccine should be administered to all psoriasis and psoriatic arthritis patients >50 years old and to those <50 years old at increased risk.

In the United States, herpes zoster (HZ) occurs in 2-4 healthy adults per 1000 person-years, with a lifetime incidence of 10%-20%.[1-7] HZ has increased >4-fold in the past 6 decades despite childhood varicella vaccination and antiviral medications.[1,3] Age and immunosuppression are known risk factors for HZ, and there is high incidence and severity in patients with HIV, bone marrow or organ transplants, and hematologic malignancy.[8-10]

Immune-mediated inflammatory disease has been linked to HZ, with an incidence ratio (IR) of 5.6-14.5 cases/1000 person-years in rheumatoid arthritis (RA) and up to 16-91.5 cases/1000 person-years in systemic lupus erythematosus.[8,11] Hazard ratios (HRs) are even higher for patients using corticosteroids and those using biologics and conventional synthetic disease-modifying antirheumatic drugs (DMARDs) concurrently.[11] However, psoriasis and psoriatic arthritis (PsA) carry lower overall infection risk compared with RA, and HZ rates might not be comparable.[12]

Vaccination guidelines for HZ have recently changed with the release of the recombinant zoster vaccine (RZV), which is indicated in immunocompetent individuals >50 years old.[13] However, administration in younger or immunosuppressed populations is not standardized because of the lack of research focused on these groups.

In the following update, a systematic literature review was conducted to assess HZ incidence in psoriasis and PsA by treatment modality and to assess current HZ vaccination guidelines for psoriasis and PsA patients from key organizations. The National Psoriasis Foundation (NPF) Medical Board provides a consensus statement for HZ vaccination in patients with psoriasis and PsA.

METHODS

A systematic literature review of the PubMed database was performed for articles published during January 1, 1957-June 1, 2018, by using the following search terms: "zoster," "herpes zoster," "varicella," "varicella zoster virus," and "shingles." Each of these terms were searched in combination with search terms "psoriasis" and "psoriatic arthritis." Randomized control trials (RCTs), cohort studies, case—control studies, systematic reviews, and meta-analyses were included. Case reports, case series, literature reviews, and guidelines were excluded. After reading the primary literature, we included additional studies that were not identified through the initial PubMed term search. These additional studies included primary RCT data for guselkumab, tildrakizumab, risankizumab, ixekizumab, secukinumab, brodalumab, and apremilast, which did not yield results in the initial systematic search.

Two authors (Dr Baumrin and Dr Merola) read reference abstracts to select studies that met inclusion and exclusion criteria. Publications were excluded on the basis of the content extracted from independent review of the title, abstract, and manuscript when applicable. Quality assessment was performed by using the Newcastle-Ottawa scale for observational studies and the Cochrane Risk of Bias Tool for interventional studies. Points were awarded for control of age and concomitant medication use. Recommendations were developed, and the strength and level of the supporting evidence for these recommendations were graded according to published guidelines (Table I).[14] The results of the systematic review and proposed recommendations were sent to the NPF Medical Board for review and voting. Member stakeholders (n = 31) were polled, and the response rate was 42% (n = 13). Recommendations underwent an iterative process of revisions until agreed upon by 100% of voting members.

RESULTS

In total, 29 studies met inclusion criteria from systematic search, and 41 studies were included.

Abbreviations used:

CI:	confidence interval
DMARD:	disease-modifying antirheumatic drug
HR:	hazard ratio
IL:	interleukin
HZ:	herpes zoster
IR:	incidence ratio
NPF:	National Psoriasis Foundation
OR:	odds ratio
PHN:	postherpetic neuralgia
PsA:	psoriatic arthritis
RCT:	randomized control trials
RZV:	recombinant zoster vaccine
RA:	rheumatoid arthritis
TNF-α:	tumor necrosis factor-α
VZV:	varicella zoster virus

Overall HZ incidence

When controlling for treatment-related immunosuppression, psoriasis and PsA patients have a lower HZ risk than RA patients, who carry an adjusted HR of 1.65 (95% confidence interval [CI] 1.57-1.75) to 1.91 (95% CI 1.8-2.03), but a higher risk than that of the general population.[11] Psoriasis imparts an increased risk of viral infections with exanthema, with an adjusted HR of 3.63 (95% CI 2.08-6.34) compared with healthy controls, independent of systemic medications dispensed within 90 days of infection.[15] Patients with psoriasis and PsA have higher rates of HZ (13.3 and 15.9 cases/1000 person-years, respectively) compared with healthy controls (8.5 cases/1000 person-years) when adjusted for age, sex, and systemic medications.[9] In a large cohort study (n = 190,055), psoriasis patients (excluding those who were immunosuppressed) had a small but increased HZ risk (odds ratio [OR] 1.08, 95% CI 1.05-1.11).[16] When stratified by disease severity, moderate-severe psoriasis carries most of this risk; mild psoriasis has been shown to have a similar incidence as healthy controls.[15,17]

Conclusion. Psoriasis and PsA patients with high disease severity have a mild increase in HZ risk compared with the general population when controlling for immunosuppressive effects of systemic therapy (weak [strength 2A] conclusion based on limited-quality evidence [level B]).

Biologic DMARDs

Tumor necrosis factor α (TNF-α). TNF-α expression is a key immune response against viral infections, including varicella zoster virus (VZV) infection, and has been shown to inhibit VZV replication and antigen expression in fibroblasts.[18,19] In RA, TNF-α inhibitors are associated with VZV infection, with an OR of 1.54 (95% CI 1.04-2.29) to 1.82 (95% CI 1.05-3.15) compared with standard conventional synthetic DMARDs[20,21]; infliximab carries the highest risk.[22,23] HZ cases associated with TNF-α inhibitors are more severe, with higher rates of hospitalizations, multidermatomal zoster, and postherpetic neuralgia (PHN).[20,22,24]

In contrast with RA, data on psoriasis and PsA do not show a clear association between TNF-α inhibitors and HZ infection. In an Israeli cohort (n = 95,941), psoriasis patients on etanercept, adalimumab, or infliximab had similar HZ rate ratios to those on no systemic therapy after adjusting for age, sex, psoriasis severity, Charlson Comorbidity Index, corticosteroid use, and socioeconomic status.[25] However, combination treatment with biologic DMARDs and methotrexate increased risk, with an incidence rate ratio of 1.66 (CI 1.08-2.57).[25] The incidence rate of HZ among patients taking TNF-α inhibitors was similar to that seen among patients on reference therapies (phototherapy, systemic steroids, topical therapy, and immunomodulators other than methotrexate) in the multicenter Psoriasis Longitudinal Assessment and Registry.[26]

The IR of HZ with etanercept (13.9 [95% CI 0.3-27.4] cases/1000 person-years) infliximab (19.3 [95% CI 0-45.8] cases/1000 person-years), and adalimumab (0 cases/1000 person-years) were not statistically different from those with methotrexate (17.0 [95% CI 10.6-23.4] cases/1000 person-years) and no systemic therapy (4.6 [95% CI 4.3-5.0] cases/1000 person-years) in psoriasis patients (n = 22,300).[27] In a smaller study (n = 5889), there was no difference in the adjusted IR between psoriasis patients treated with biologic DMARDs and those treated with conventional synthetic DMARDs, combination biologic and conventional synthetic DMARDs, or no systemic therapy.[28]

PsA patients (n = 3128) had an increased risk of HZ (HR 2.37, 95% CI 1.32-4.22) in the setting of combination conventional synthetic DMARD and TNF-α inhibitor use compared with no systemic therapy but had no increased risk in the setting of either agent used alone.[29] The time to an HZ event was shorter for TNF-α inhibitors than conventional synthetic DMARDs.[29]

Conclusion. TNF-α inhibitor monotherapy has comparable HZ risk as that of conventional synthetic DMARD monotherapy and no systemic therapy in psoriasis and PsA. Combination therapy with TNF-α inhibitors and conventional synthetic DMARDs increases risk of HZ compared with either agent used alone in psoriasis and PsA (weak [strength 2A] conclusion based on limited-quality evidence [levels A and B]).

Interleukin (IL) 12/23 inhibitor (ustekinumab). Ustekinumab blocks IL-12 and

Table I. Quality of evidence to support recommendations*

Strength of recommendation	Risk, benefit, and cost	Quality level of evidence
1) Strong recommendation: high-quality, patient-oriented evidence	Benefit outweighs risks and costs	A) Systematic reviews and meta-analyses, randomized control trials with consistent findings, all-or-none observational studies
2A) Weak recommendation: limited-quality, patient-oriented evidence	Benefits balanced with risks and costs	B) Systematic reviews and meta-analyses with lower quality studies or inconsistent findings, lower quality clinical trials, cohort studies, case-controlled studies
2B) Weak recommendation: low-quality evidence	Uncertainty in benefits, risks, and costs	C) Consensus guidelines, expert opinion, case series

*Table adapted from Robinson et al.[14]

the downstream activation of T-cell helper 1 and natural killer cell antiviral capabilities.[30] In a pooled RCT of ustekinumab for the treatment of psoriasis, there was a single case of multidermatomal HZ out of 3117 patients followed for 3 years.[31]

In retrospective studies, ustekinumab use had an HZ IR of 53.5 cases (95% CI 0-125.6)/1000 person-years compared with an IR of 5.1-7.1 cases/1000 person-years with TNF-α inhibitor use; however, the sample size for ustekinumab use in this study was small (37 person-years).[32] Likewise, in 63 patients who underwent treatment with ustekinumab, there was an IR of 32.3 (95% CI 3.9-116.8) cases/1000 person-years and an increased risk of HZ in those treated with a rate ratio of 2.67 (95% CI 0.69-10.30), which was higher than those for all other systemic therapies but did not reach statistical significance.[25] More recently, patients treated with ustekinumab in the Psoriasis Longitudinal Assessment and Registry had an elevated HR of 2.73 (95% CI 0.98-7.58) compared with the reference population, but again, the difference was not statistically significant.[26]

Conclusion. The HZ risk in psoriasis patients treated with ustekinumab is not clear due to insufficient evidence; however, there was a trend toward increased incidence in 3 studies (weak [strength 2A] conclusion based on limited-quality evidence [level B]).

IL-17 inhibitors. Data from 7 clinical trials of ixekizumab for the treatment of psoriasis show no cases of HZ in the intervention arms and 2 cases in the placebo arms.[33] Long-term safety of 11 trials (n = 5689) with follow-up for 12,061.5 person-years also reported no cases.[34] In 3 clinical trials of ixekizumab for PsA, dermatomal HZ was noted in 0.4% of patients.[35] Secukinumab use had similarly low rates of HZ (0.1%), compared with etanercept (0.3%) and placebo (0.1%) use in 11 long-term safety trials.[36] There were no reported HZ cases in 6 clinical trials for brodalumab for psoriasis and PsA.[37]

IL-23 (p19 subunit) inhibitors. In clinical trials of guselkumab (VOYAGE 1 and 2), tildrakizumab (reSURFACE 1 and 2), and risankizumab (UltIMMa 1 and 2) for the treatment of psoriasis, there were no significant differences in the rates of HZ between the drug groups and placebo or control groups.[38-41] There was 1 case of HZ in the tildrakizumab group (928 person-years) compared with 1 in the etanercept group (153 person-years) and 0 in the placebo group (219 person-years).[40] Long-term safety data for IL-23 (p19 subunit) inhibitors are not yet available.

Conclusion. Clinical trials do not show evidence of an increased risk of HZ in patients treated with IL-17 or IL-23 inhibitors; however, long-term safety data is limited (weak [strength 2A] conclusion based on limited-quality evidence [level B]).

Targeted synthetic DMARDs

Tofacitinib. Tofacitinib is a selective Janus kinase 1/3 inhibitor of the Janus kinase—signal transducers and activators of transcription pathway, which mediates cell growth, death, and immunity. Through inhibition of interferon signaling and T-cell function, tofacitinib reduces host immunity against viral infections.[42]

Tofacitinib increases the risk of HZ in patients with RA (n = 6192); patients on monotherapy have an IR of 2.2 (95% CI 3.7-4.4) cases/100 person-years, and those on combination therapy with conventional synthetic DMARDs (4.4 cases/100 person-years) or corticosteroids (5.4 cases/100 person-years) have higher rates.[43] This risk is dose dependent, with a pooled OR of 2.10 (95% CI 0.83-5.34) for tofacitinib 5 mg twice a day and 3.01 (95% CI 1.15-7.87) for 10 mg twice a day compared with placebo-control.[32]

Tofacitinib use carries a similar HZ risk in psoriasis and PsA. RCT data of tofacitinib treatment for psoriasis indicate higher numbers of HZ cases in the

intervention group (n = 12) than the placebo group (n = 0), with 3 patients discontinuing the drug due to VZV infection.[44] A noninferiority trial with tofacitinib (n = 3), etanercept (n = 2), and placebo (n = 0) showed similar numbers of HZ cases.[45]

In a pooled analysis of psoriasis patients from the tofacitinib working group (n = 3623), the HZ IR was 2.55 (95% CI 2.13-3.03) cases/100 person-years with tofacitinib monotherapy and 0 cases/100 person-years with placebo.[42] In a Cox proportional-hazards analysis, tofacitinib dose (HR 1.72, 95% CI 1.01-2.94), prior biologic use (HR 1.72, 95% CI 1.15-2.59), and Asian ethnicity (HR 2.92, 95% CI 1.73-4.92) were associated with HZ.[42]

RCT data of tofacitinib treatment for PsA are similar, with more HZ cases in the intervention arms (n = 7) than the placebo arms (n = 0).[46,47] Unlike psoriasis patients, all PsA patients were on background conventional synthetic DMARD therapy (69%-88% methotrexate) at the time of tofacitinib treatment.

Conclusion. Tofacitinib increases HZ risk in psoriasis and PsA. Patients on tofacitinib have an IR 2-3 fold higher than patients on TNF-α inhibitors or conventional synthetic DMARDs (strong [strength 1] conclusion based on good-quality evidence [levels A and B]).

Phosphodiesterase 4 inhibitors (apremilast). There were no reported HZ cases in the long-term safety data on the use of apremilast for the treatment of psoriasis (ESTEEM 1 and 2 trials).[48] Although, long-term safety data are not yet published for PsA (PALACE 1, 2, and 3), no cases were reported in phase 3 trials.[49-51]

Conventional synthetic DMARDs

Conventional synthetic DMARDs are standard systemic medications that suppress the immune system more broadly than biologic or targeted synthetic DMARDs. When used in RA, methotrexate is not associated with HZ,[52] while corticosteroids have reproducible and a dose-dependent risk of HZ.[21,23] Similar findings have been demonstrated in other autoimmune diseases.[19,53]

Psoriasis and PsA patients have a lower HZ risk (IR 6.9 cases/1000 person-years) than RA patients (12.7 cases/1000 person-years) on the same conventional synthetic DMARDs.[19] The incidence of HZ in psoriasis and PsA patients using methotrexate, cyclosporine, or acitretin monotherapy is not significantly different than the incidence in those using no systemic therapy in multivariate Cox regression analysis.[25-27] Corticosteroids are associated with HZ, with an HR of 2.4 (95% CI 2.10-2.73) to 3.32 (95% CI 0.98-11.16)[19,27] and rate ratio of 1.09 (95% CI 1.08-2.57).[25]

In patients with PsA, use of conventional synthetic DMARDs have an equivalent HZ risk as using no systemic therapy, although combination therapy with TNF-α inhibitors (HR 2.37, 95% CI 1.32-4.22) or corticosteroids (HR 1.08, 95% CI 1.04-1.13) increases risk.[29]

Conclusions. Compared with using no systemic therapies, using conventional synthetic DMARDs does not increase HZ risk for psoriasis and PsA patients. Corticosteroid use (both alone and in combination with conventional synthetic or biologic DMARDs) increases HZ risk in psoriasis and PsA (weak [strength 2A] conclusion based on limited-quality evidence [levels B and C]).

Herpes zoster vaccination

Prevention of HZ infection is primarily achieved through oral antiviral prophylaxis or vaccination. Until recently, the only HZ vaccine available was the live-attenuated VZV vaccine, Zostavax. In healthy adults, the live-attenuated vaccine reduces the risk of developing HZ by 51.3% and PHN by 66.5%.[2] Efficacy declines with age, with 18% efficacy in adults >80 years old.

The Advisory Committee on Immunization Practice, Infectious Disease Society of America, American College of Rheumatology, European League Against Rheumatism, and the NPF recommend the VZV vaccine in immunocompetent patients and in those on low-dose immunosuppression (prednisone <20 mg/day, methotrexate <0.4 mg/kg/week).[13,54-57] These recommendations are based on expert opinion supported by small observational studies of the live-attenuated vaccine in patients with rheumatologic disease.[58-61] Although this vaccine is currently contraindicated during active biologic DMARD treatment, no cases of HZ were observed among the 633 patients in a cohort of rheumatologic patients (n = 463,541) who received the live-attenuated vaccine while on biologic DMARDs.[62]

In October 2017, the US Food and Drug Administration approved the nonlive recombinant zoster vaccine (RZV), Shingrix, which utilizes the VZV glycoprotein E and a novel adjuvant liposomal delivery system.[13] The Advisory Committee on Immunization Practice published new guidelines in 2018 recommending the RZV in healthy adults >50 years old and adults on low-dose immunosuppression (prednisone <20 mg/day).[13] The RZV outperforms the live-attenuated vaccine in healthy adults, with 96.6% efficacy in adults aged 50-60 years, 97.4% efficacy in those aged 60-70 years, and 91.3%

Table II. Herpes zoster risk and vaccination recommendations by treatment modality

Systemic treatment	Disease	Herpes zoster risk compared with no systemic therapy	Grade of conclusion	Quality of evidence	RZV vaccination
Tumor necrosis factor α inhibitors	PsO, PsA	=	Weak, 2A	A and B	+
Ustekinumab	PsO	Between = and ⇑	Weak, 2A	B	+
Interleukin 17 inhibitors*	PsO, PsA	=	Weak, 2A	B	+
Interleukin 23 inhibitors†	PsO	=	Weak, 2A	B	+
Tofacitinib	PsO, PsA	⇑	Strong, 1	A and B	++
Apremilast	PsO, PsA	=	Weak, 2A	B	+
Conventional synthetic DMARDs	PsO, PsA	=	Weak, 2A	B and C	+
Corticosteroid	PsO, PsA	⇑	Weak, 2A	B and C	++
Combination therapy‡	PsO, PsA	⇑	Weak, 2A	A and B	++

DMARD, Disease-modifying antirheumatic drug; *PsA*, psoriatic arthritis; *PsO*, psoriasis; *RZV*, recombinant zoster vaccine; +, recommended; ++, strongly recommended.
*Ixekizumab, secukinumab, and brodalumab.
†Guselkumab, tildrakizumab, and risankizumab.
‡Conventional synthetic and biologic DMARDs.

efficacy in those aged >70 years, and the RZV remains 84.7% efficacious at 3 years.[63,64] In the prevention of PHN, RZV is 91.2% efficacious in adults aged >50 years and 88.8% in those aged >70 years.

Although immunocompromised patients were excluded from the initial RZV studies,[63,64] data are emerging in special populations. RZV was safe and immunogenic in 123 HIV patients with CD4 counts ranging from 50 to >500 cells/mm^3, with no vaccine-related serious adverse events.[65] In autologous hematopoietic cell transplantation, vaccination with the RZV reduced HZ by 68.1% (95% CI 55.6%-77.5%) and PHN by 89.3% (95% CI 22.5%-99.8%), with no difference in serious adverse events compared with the placebo group despite significant immunosuppression.[66,67]

There are trials of RZV safety and efficacy in renal transplant recipients on immunosuppression (NCT02058589), solid tumor malignancy patients on chemotherapy (NCT01798056), and lung transplantation recipients (NCT03493776) that are ongoing.

Recommendations. *Live-attenuated VZV vaccine (Zostavax).* The live-attenuated vaccine may be given to psoriasis and PsA patients >50 years old on no systemic therapy or on low-level immunosuppression (methotrexate <0.4 mg/kg/week or prednisone <20 mg/day). The live-attenuated vaccine should not be given to psoriasis or PsA patients on a moderate-high level of conventional synthetic DMARDs, biologic DMARDs, or targeted synthetic DMARDs. If an interruption in these medications is feasible, the live-attenuated VZV vaccine may be administered (weak [strength 2A] recommendation based on limited-quality evidence [levels A, B, and C]).

RZV (Shingrix). The RZV is preferred to the live-attenuated VZV vaccine in patients with psoriasis and PsA. RZV should be administered to psoriasis and PsA patients before initiation of systemic therapy when possible but may be administered safely with concurrent use of biologic DMARDs, targeted synthetic DMARDs, and conventional synthetic DMARDs.

The RZV should be given to all psoriasis and PsA patients >50 years old and to patients <50 years old on tofacitinib, systemic corticosteroids, or combination systemic therapy because these patients have an increased HZ risk. The RZV may be considered in psoriasis and PsA patients <50 years old on other systemic therapies on a case-by-case basis after individualized risk assessment (weak [strength 2A] recommendation based on limited-quality evidence [levels A, B, and C]).

Conclusion

Depending on their disease severity and type of systemic therapy, patients with psoriasis or PsA have variable HZ risks (Table II). Patients with mild psoriasis on no systemic therapy have a similar risk as the general population; psoriasis and PsA patients on tofacitinib, systemic corticosteroids, or biologic and conventional synthetic DMARD combination therapy have a 1.5−3-fold increased likelihood of HZ. The quality of evidence is overall limited due to the heterogeneity of studies with conflicting results. Despite this variability, the RZV is safe, effective, and should be administered to all psoriasis and PsA

patients >50 years old, regardless of systemic therapy, and those <50 years old on tofacitinib, systemic corticosteroids, or combination systemic therapy.

We would like to acknowledge all members of the Medical Board of the National Psoriasis Foundation for voting to establish consensus recommendations.

REFERENCES

1. Kawai K, Yawn BP, Wollan P, Harpaz R. Increasing incidence of herpes zoster over a 60-year period from a population-based study. *Clin Infect Dis*. 2016;63(2):221-226.
2. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity Mortality Weekly Rep Recommendations Rep*. 2008;57(Rr-5):1-30. quiz CE2-4.
3. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med*. 2002;347(5):340-346.
4. Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. *BMC Infect Dis*. 2015;15:502.
5. Pinchinat S, Cebrian-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. *BMC Infect Dis*. 2013;13:170.
6. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med*. 2005;20(8):748-753.
7. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open*. 2014;4(6):e004833.
8. Hata A, Kuniyoshi M, Ohkusa Y. Risk of herpes zoster in patients with underlying diseases: a retrospective hospital-based cohort study. *Infection*. 2011;39(6):537-544.
9. Yun H, Yang S, Chen L, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. *Arthritis Rheumatol*. 2016;68(9):2328-2337.
10. Yenikomshian MA, Guignard AP, Haguinet F, et al. The epidemiology of herpes zoster and its complications in Medicare cancer patients. *BMC Infect Dis*. 2015;15:106.
11. van Assen S, Elkayam O, Agmon-Levin N, et al. Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheumatic diseases. *Autoimmun Rev*. 2011;10(6):341-352.
12. Garcia-Doval I, Hernandez MV, Vanaclocha F, Sellas A, de la Cueva P, Montero D. Should tumour necrosis factor antagonist safety information be applied from patients with rheumatoid arthritis to psoriasis? Rates of serious adverse events in the prospective rheumatoid arthritis BIOBADASER and psoriasis BIOBADADERM cohorts. *Br J Dermatol*. 2017;176(3):643-649.
13. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103-108.
14. Robinson JK, Dellavalle RP, Bigby M, Callen JP. Systematic reviews: grading recommendations and evidence quality. *Arch Dermatol*. 2008;144(1):97-99.
15. Wakkee M, de Vries E, van den Haak P, Nijsten T. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. *J Am Acad Dermatol*. 2011;65(6):1135-1144.
16. Takeshita J, Shin DB, Ogdie A, Gelfand JM. Risk of serious infection, opportunistic infection, and herpes zoster among patients with psoriasis in the United Kingdom. *J Invest Dermatol*. 2018;138(8):1726-1735.
17. Tsai SY, Chen HJ, Lio CF, et al. Increased risk of herpes zoster in patients with psoriasis: a population-based retrospective cohort study. *PLoS One*. 2017;12(8):e0179447.
18. Arvin AM, Moffat JF, Sommer M, et al. Varicella-zoster virus T cell tropism and the pathogenesis of skin infection. *Curr Top Microbiol Immunol*. 2010;342:189-209.
19. Winthrop KL, Baddley JW, Chen L, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. *JAMA*. 2013;309(9):887-895.
20. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-α agents. *JAMA*. 2009;301(7):737-744.
21. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. *Arthritis Rheum*. 2007;57(8):1431-1438.
22. Galloway JB, Mercer LK, Moseley A, et al. Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2013;72(2):229-234.
23. Wolfe F, Michaud K, Chakravarty EF. Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. *Rheumatology (Oxford)*. 2006;45(11):1370-1375.
24. Garcia-Doval I, Perez-Zafrilla B, Descalzo MA, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. *Ann Rheum Dis*. 2010;69(10):1751-1755.
25. Shalom G, Zisman D, Bitterman H, et al. Systemic therapy for psoriasis and the risk of herpes zoster: a 500,000 person-year study. *JAMA Dermatol*. 2015;151(5):533-538.
26. Shalom G, Naldi L, Lebwohl M, et al. Biological treatment for psoriasis and the risk of herpes zoster: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Dermatolog Treat*. 2018:1-20.
27. Dreiher J, Kresch FS, Comaneshter D, Cohen AD. Risk of herpes zoster in patients with psoriasis treated with biologic drugs. *J Eur Acad Dermatol Venereol*. 2012;26(9):1127-1132.
28. Levandoski KA, Quesenberry CP, Tsai AL, Asgari MM. Herpes zoster rates in a large cohort of patients with systemically treated psoriasis. *JAMA Dermatol*. 2018;154(2):218-219.
29. Zisman D, Bitterman H, Shalom G, et al. Psoriatic arthritis treatment and the risk of herpes zoster. *Ann Rheum Dis*. 2016;75(1):131-135.
30. Failla V, Nikkels AF. Ustekinumab and herpes zoster. *Dermatology*. 2011;222(2):119-122.
31. Gordon KB, Papp KA, Langley RG, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. *J Am Acad Dermatol*. 2012;66(5):742-751.
32. Failla V, Jacques J, Castronovo C, Nikkels AF. Herpes zoster in patients treated with biologicals. *Dermatology*. 2012;224(3):251-256.
33. Papp KA, Bachelez H, Blauvelt A, et al. Infections from seven clinical trials of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriasis. *Br J Dermatol*. 2017;177(6):1537-1551.
34. Langley RG, Kimball AB, Nakagawa H, et al. Long-term safety profile of ixekizumab in patients with moderate-to-severe

plaque psoriasis: an integrated analysis from 11 clinical trials. *J Eur Acad Dermatol Venereol*. 2019;33(2):333-339.
35. Mease P, Roussou E, Burmester GR, et al. Safety of ixekizumab in patients with psoriatic arthritis: results from a pooled analysis of three clinical trials. *Arthritis Care Res*. 2019;71(3):367-378.
36. van de Kerkhof PC, Griffiths CE, Reich K, et al. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. *J Am Acad Dermatol*. 2016;75(1):83-98.e4.
37. Attia A, Abushouk AI, Ahmed H, et al. Safety and efficacy of brodalumab for moderate-to-severe plaque psoriasis: a systematic review and meta-analysis. *Clin Drug Invest*. 2017;37(5):439-451.
38. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405-417.
39. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418-431.
40. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288.
41. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661.
42. Winthrop KL, Lebwohl M, Cohen AD, et al. Herpes zoster in psoriasis patients treated with tofacitinib. *J Am Acad Dermatol*. 2017;77(2):302-309.
43. Winthrop KL, Curtis JR, Lindsey S, et al. Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. *Arthritis Rheumatol*. 2017;69(10):1960-1968.
44. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. *Br J Dermatol*. 2015;173(4):949-961.
45. Bachelez H, van de Kerkhof PC, Strohal R, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet*. 2015;386(9993):552-561.
46. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med*. 2017;377(16):1537-1550.
47. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med*. 2017;377(16):1525-1536.
48. Crowley J, Thaci D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: pooled safety analysis for >156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol*. 2017;77(2):310-317.e1.
49. Cutolo M, Myerson GE, Fleischmann RM, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol*. 2016;43(9):1724-1734.
50. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis*. 2016;75(6):1065-1073.
51. Schafer PH, Chen P, Fang L, Wang A, Chopra R. The pharmacodynamic impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers in patients with psoriatic arthritis: substudy results from a phase III, randomized, placebo-controlled trial (PALACE 1). *J Immunol Res*. 2015;2015:906349.
52. Zhang N, Wilkinson S, Riaz M, Ostor AJ, Nisar MK. Does methotrexate increase the risk of varicella or herpes zoster infection in patients with rheumatoid arthritis? A systematic literature review. *Clin Exp Rheumatol*. 2012;30(6):962-971.
53. Marra F, Lo E, Kalashnikov V, Richardson K. Risk of herpes zoster in individuals on biologics, disease-modifying antirheumatic drugs, and/or corticosteroids for autoimmune diseases: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2016;3(4):ofw205.
54. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):309-318.
55. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2016;68(1):1-25.
56. van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2011;70(3):414-422.
57. Wine-Lee L, Keller SC, Wilck MB, Gluckman SJ, Van Voorhees AS. From the medical board of the National Psoriasis Foundation: vaccination in adult patients on systemic therapy for psoriasis. *J Am Acad Dermatol*. 2013;69(6):1003-1013.
58. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. *Arthritis Care Res*. 2010;62(7):1034-1039.
59. Zhang J, Delzell E, Xie F, et al. The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. *Arthritis Res Ther*. 2011;13(5):R174.
60. Yun H, Xie F, Baddley JW, Winthrop K, Saag KG, Curtis JR. Longterm effectiveness of herpes zoster vaccine among patients with autoimmune and inflammatory diseases. *J Rheumatol*. 2017;44(7):1083-1087.
61. Guthridge JM, Cogman A, Merrill JT, et al. Herpes zoster vaccination in SLE: a pilot study of immunogenicity. *J Rheumatol*. 2013;40(11):1875-1880.
62. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA*. 2012;308(1):43-49.
63. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372(22):2087-2096.
64. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med*. 2016;375(11):1019-1032.
65. Berkowitz EM, Moyle G, Stellbrink HJ, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a

randomized, placebo-controlled study. *J Infect Dis*. 2015; 211(8):1279-1287.

66. Stadtmauer EA, Sullivan KM, Marty FM, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. *Blood*. 2014;124(19):2921-2929.

67. Sullivan K, Abhyankar S, Campora L, et al. *Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine in adult autologous hematopoietic stem cell transplant recipients: phase 3, randomized, placebo-controlled, ZOE-HSCT clinical trial*. Lisbon, Portugal: Communication presented at the European Society for Blood and Marrow Transplantation; 2018.