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ARTICLE

Biological treatment for psoriasis and the risk of herpes zoster: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR)

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ABSTRACT

Purpose: To describe the risk of herpes zoster (HZ) in patients with psoriasis and its relation to non-biologic systemic therapies or biologic treatment.

Materials and methods: Psoriasis Longitudinal Assessment and Registry (PSOLAR) is an international, prospective, registry that follows adult patients with psoriasis eligible to receive non-biologic systemic therapies or biologic therapies. Mutually exclusive therapy cohorts were defined. HZ incident rates were calculated for each therapy cohort and rates between cohorts were compared using hazard ratios (HR) adjusted for potential confounders, in new users and prevalent-exposure patients.

Results: A total of 55 HZ events were identified in 10,469 patients in PSOLAR. The adjusted hazard ratio in the overall study population (new user and prevalent-exposed patients) was 2.22 (95% CI: 0.82–5.97; $p = .116$) for tumor necrosis factor-α (TNF) inhibitors, 2.73 (0.98–7.58; $p = .054$) for ustekinumab, and 1.04 (0.20–5.41; $p = .966$) for methotrexate versus reference (combined phototherapy, systemic steroids, topical therapy, and immunomodulators other than methotrexate).

Conclusions: Exposure to ustekinumab, TNF-α inhibitors, and methotrexate was not associated with a statistically significant increased risk of HZ. However, HRs were elevated for ustekinumab and TNF-α inhibitors; a larger number of HZ events would be needed to assess the presence or absence of risk.

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Introduction

Herpes zoster (HZ) is a public health concern and is associated with disability and pain, which may become chronic in the form of post-herpetic neuralgia (1,2). In general, HZ incidence rates range between 4 per 1000 patient years (PY) in the fifth decade of life, and 10 per 1000 patient years in the eighth decade, with a predilection for females (3,4). The lifetime risk of HZ is estimated at 10–20% (5).

In rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), data regarding the association of HZ and treatment with tumor necrosis factor (TNF) inhibitors are contradictory (6). Recent observational studies reported that treatment with TNF inhibitors is associated with increased risk for HZ (7–12) and more severe HZ disease (13,14). On the contrary, a study of 407,319 patients with various immune-mediated inflammatory disorders reported no such association, as did other smaller studies (15,16).

Unlike RA or IBD, no association between HZ and TNF inhibitor treatment has been demonstrated for psoriasis. Two sequential studies from Israel (17,18) based on a large group of patients with psoriasis reported that monotherapy with biologic treatments had a higher incidence of HZ compared with the controls; however, the difference did not reach statistical significance (19). However, in the second study, which included more than 500,000 PY of follow-up, patients treated with biologics and methotrexate (MTX) showed a statistically significant greater incidence of HZ compared with patients treated with non-biologic systemic therapies and biologics alone (18).

Given the expanded use of biologics, including mechanisms of action other than TNF inhibition, there is a need for further studies evaluating the association between non-biologic systemic therapy for psoriasis and HZ risk. Prophylactic vaccination for HZ is available, and identification of high-risk populations could lead to meaningful clinical intervention. The objective of this investigation was to evaluate the risk for HZ in a large population with psoriasis exposed to non-biologic systemic therapies or biologic therapies from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) registry (20).

Patients and methods

Patients and study design

This is an observational cohort study of the patients enrolled in PSOLAR. Details of the registry have been previously described (20). PSOLAR is a prospective, international disease-based registry that follows adult patients with psoriasis receiving or eligible to receive conventional non-biologic systemic therapies or biologic agents (20,21). In brief, physicians prescribed treatments for psoriasis based on usual practices of care. Disease activity, psoriasis

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drug utilization patterns, data for comorbidities, and adverse events were captured by the participating physicians at enrollment and at 6-month follow-up visits.

Treatment cohorts

Information pertaining to the use of psoriasis treatments was collected prospectively and exposure was based on person-time. The following mutually exclusive exposure groups were considered: (1) TNF inhibitors (combined adalimumab, etanercept, infliximab, and golimumab), (2) ustekinumab, (3) MTX, and (4) no biologics/no MTX. In the TNF inhibitor and ustekinumab groups, patients may have been exposed in the past to other biologic, non-biologic systemic therapies, and photo/topical therapies. Patients with concomitant use of MTX were excluded. Patients in the MTX cohort may have been exposed in the past to a biologic therapy. The no biologics/no MTX exposure group included patients receiving phototherapy, systemic steroids, topical therapy, and immunomodulators other than MTX, with no biologic therapy exposure on their medical record.

Outcomes

Only the first HZ episode during the registry follow-up for any given patient was included in the analysis, and episodes were based on physician reporting. All HZ adverse events captured in PSOLAR are coded to terms in the "Infections and Infestations" system organ class of the Medical Dictionary for Regulatory Activities (version 16.0). The following events representative of HZ were included: HZ, HZ multi-dermatomal, HZ disseminated, HZ oticus, HZ ophthalmic, HZ iridocyclitis, and HZ neurological. Information about antiviral medication use and prior HZ vaccination was not collected.

Statistical analysis

Demographic and disease characteristics at baseline, as well as medical history and prior treatments, are summarized as means and percentages. The incidence rate of HZ was calculated as the number of new events per 100 PY of follow-up in each treatment group. Person time (PY) corresponds to the number of years exposed to the group defining medication. The start date of exposure (index date) was the first exposure to a medication on/during registry participation and ended at the earlier of the date of first HZ event, reference end date, initiation of another biologic treatment or MTX, 90 days after the last dose of the cohort defining treatment, or the date of the data cutoff (August 23, 2014). The start date of exposure matched the registry enrollment date for patients who were already exposed to a cohort-defining treatment at registry entry (prevalent users). The main analysis (overall population) includes both the new user (incident) population of patients initiating biologic therapy on or after registry entry and the prevalent user population. An additional pre-specified analysis includes only the new user population.

Incidence rates of HZ were compared between treatment cohorts against the no biologics/no MTX reference cohort using Cox proportional hazard ratios (HR) adjusted for potential pre-specified defined confounders (i.e., baseline demographics [i.e., age, gender, ethnicity], baseline disease characteristics [e.g. body mass index, duration of disease], severity of psoriasis, prior treatments, and recent systemic steroid use). Only covariates with a p values $\leq .2$ were retained in the multivariate model. Missing values for covariates were imputed as the mean for continuous variables and the median for categorical covariates. HR are also reported within pre-specified groups (those with diabetes and malignancies) and by age strata.

Results

Baseline demographic and disease characteristics

A total of 10,469 patients (24,025 PY) from PSOLAR contributed to this analysis with a median follow-up time of 3.2 years. Baseline characteristics at the time of enrollment in PSOLAR for the overall population were comparable among treatment groups, with a mean age of 49 years. Most patients were white (83.3%), and more than half of the patients were overweight (57.2%), with a mean body mass index of 30.9 kg/m^2 (Table 1). The mean duration of psoriasis was 17.5 years and mean body surface area involvement was 11.9%.

Overall, 48.5% of patients ($n = 5076$) received TNF inhibitors, 25.8% had received ustekinumab ($n = 2704$), 11.5% had received MTX ($n = 1201$), and 14.2% ($n = 1488$) received no biologics/no MTX during participation in the registry; these groups were not mutually exclusive (Table 1). Prior to entering the registry, most patients (70.4%) in the overall population had received at least one biologic, 96.9% had used topical therapy, 63.3% had used phototherapy, 23.1% had used systemic steroids, and 46.5% had used immunomodulators (Table 1). Overall, 73.3% of patients receiving TNF-inhibitors, 84.6% receiving ustekinumab, 70.3% receiving MTX, and 47.8% receiving no biologics/no MTX remained in the registry at the end of the study follow-up (Figure 1).

Incidence of HZ in the overall population

In the overall population, a total of 55 HZ events through 24,025 PY of follow-up were identified across the treatment cohorts (Table 2). Incidence rates/100 PY for each treatment cohort were 0.25 [0.17–0.36] for TNF inhibitors, 0.29 [0.18–0.46] for ustekinumab, 0.14 [0.02–0.49] for MTX, and 0.11 [0.04–0.27] for the no biologics/no MTX control cohort. The adjusted HR for incidence rates of HZ for each treatment cohort versus the no biologics/no MTX reference cohort were: 2.22 (95% CI: 0.82–5.97; $p = .116$) for TNF inhibitors, 2.73 (95% CI: 0.98–7.58; $p = .054$) for ustekinumab, and 1.04 (95% CI: 0.20–5.41; $p = .966$) for MTX.

Increasing age was associated with HZ (HR = 1.35 [95% CI: 1.08–1.68; $p = .008$]) (Table 3). Other risk factors such as race, obesity, systemic steroid use, psoriasis severity, duration of psoriasis, psoriatic arthritis, and prior history of phototherapy were not found to be predictors of HZ (Table 3).

HZ in the new user population

In the new user population subset, which was based on fewer events ($n = 19$) among 3561 patients, adjusted incident HRs for each treatment cohort compared with the reference cohort were: 3.66 (95% CI: 1.15–11.63; $p = .028$) for TNF inhibitors and 2.69 (95% CI: 0.76–9.58; $p = .126$) for ustekinumab (data not shown). No HZ events were reported in the MTX cohort.

Discussion

We studied a large population-based cohort from the PSOLAR registry comprising 10,469 patients with psoriasis and median follow-up of 3.2 years. It was observed that treatment with TNF inhibitors, ustekinumab, or MTX was not associated with a statistically significant increased risk of HZ, although HRs for

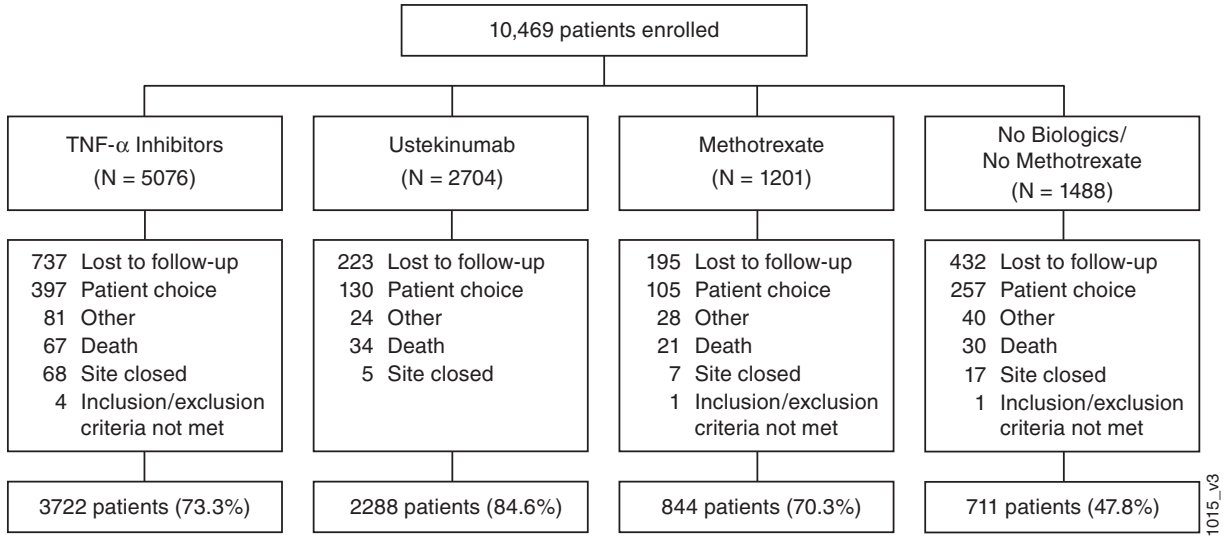
Table 1. Baseline demographics and disease characteristics; overall cohort.

	TNF-α inhibitors[a] (*N* = 5076)	Ustekinumab (*N* = 2704)	Methotrexate (MTX) (*N* = 1201)	No biologics/No MTX (*N* = 1488)	All (*N* = 10,469)
Age (years), *n*	5076	2704	1201	1487	10,468
Mean ± SD	47.9 ± 13.4	47.3 ± 13.0	52.3 ± 13.7	49.9 ± 15.9	48.5 ± 13.8
Men	2881 (56.8)	1601 (59.2)	570 (47.5)	750 (50.4)	5802 (55.4)
White	4123 (81.2)	2357 (87.2)	980 (81.6)	1263 (84.9)	8723 (83.3)
Weight (kg)					
N	4994	2660	1190	1479	10,323
Mean ± SD	90.8 ± 22.9	91.6 ± 22.5	89.7 ± 23.1	86.2 ± 21.3	90.2 ± 22.7
Body mass index (kg/m^2)					
N	4987	2656	1190	1477	10,310
Mean ± SD	31.0 ± 7.1	31.0 ± 7.0	31.2 ± 7.5	29.8 ± 6.8	30.9 ± 7.1
Obesity class	4987	2656	1190	1477	10,310
Underweight/Normal (BMI <25)	952 (19.1)	468 (17.6)	232 (19.5)	346 (23.4)	1998 (19.4)
Overweight/Obesity class I (25.0 ≤ BMI <35)	2826 (56.7)	1566 (59.0)	660 (55.5)	846 (57.3)	5898 (57.2)
Obesity class II–III (BMI ≥35.0)	1209 (24.2)	622 (23.4)	298 (25.0)	285 (19.3)	2414 (23.4)
PGA Score					
N	4874	2606	1147	1392	10,019
Mean ± SD	1.9 (1.20)	2.0 (1.27)	2.1 (1.18)	2.3 (1.05)	2.0 (1.21)
Body Surface Area involvement (%)					
N	5011	2675	1197	1483	10,366
Mean ± SD	11.1 (17.20)	12.3 (17.42)	12.5 (18.59)	13.4 (16.66)	11.9 (17.36)
Duration of psoriasis, years					
N	5024	2679	1186	1481	10,370
Mean ± SD	17.7 ± 13.1	19.4 ± 12.6	17.2 ± 14.4	13.8 ± 14.3	17.5 ± 13.4
Patients with psoriatic arthritis	2177 (42.9)	785 (29.0)	525 (43.7)	207 (13.9)	3694 (35.3)
Medical history					
Cardiovascular[b]	1940 (38.2)	1020 (37.7)	530 (44.1)	534 (35.9)	4024 (38.4)
Pulmonary	741 (14.6)	334 (12.4)	208 (17.3)	206 (13.8)	1489 (14.2)
Psychiatric illness	1042 (20.5)	528 (19.5)	298 (24.8)	277 (18.6)	2145 (20.5)
Hepatic	237 (4.7)	90 (3.3)	47 (3.9)	49 (3.3)	423 (4.0)
Skin cancer	297 (5.9)	115 (4.3)	85 (7.1)	124 (8.3)	621 (5.9)
Malignancies[c]	146 (2.9)	61 (2.3)	75 (6.2)	94 (6.3)	376 (3.6)
Diabetes mellitus type II	541 (10.7)	311 (11.5)	159 (13.2)	165 (11.1)	1176 (11.2)
Serious infections[d]	1308 (25.8)	602 (22.3)	323 (26.9)	312 (21.0)	2545 (24.3)
Alcohol use, current	3299 (65.0)	1973 (73.0)	604 (50.3)	962 (64.7)	6838 (65.3)
Smoking, current	1109 (21.9)	751 (27.8)	265 (22.1)	345 (23.2)	2470 (23.6)
Prior therapy use					
Biologic agents	4413 (86.9)	2349 (86.9)	613 (51.0)	0 (0.0)	7375 (70.4)
Etanercept	2819 (55.5)	946 (35.0)	347 (28.9)	0 (0.0)	4112 (39.3)
Adalimumab	1990 (39.2)	824 (30.5)	269 (22.4)	0 (0.0)	3083 (29.4)
Ustekinumab	113 (2.2)	1856 (68.6)	90 (7.5)	0 (0.0)	2059 (19.7)
Infliximab	1063 (20.9)	341 (12.6)	265 (22.1)	0 (0.0)	1669 (15.9)
Golimumab	16 (0.3)	18 (0.7)	7 (0.6)	0 (0.0)	41 (0.4)
Topical therapy	4950 (97.7)	2596 (96.1)	1170 (97.5)	1412 (95.0)	10,128 (96.9)
Phototherapy					
Psoralens + UVA	928 (18.3)	565 (20.9)	220 (18.3)	95 (6.4)	1808 (17.3)
UVB	2285 (45.1)	1405 (52.0)	494 (41.2)	623 (41.9)	4807 (46.0)
Systemic steroids	1256 (24.8)	518 (19.2)	347 (28.9)	290 (19.5)	2411 (23.1)
Immunomodulators	2312 (45.6)	1486 (55.0)	1012 (84.3)	54 (3.6)	4864 (46.5)
Methotrexate	1910 (37.7)	1205 (44.6)	988 (82.3)	0 (0.0)	4103 (39.3)
Cyclosporine	811 (16.0)	654 (24.2)	172 (14.3)	34 (2.3)	1671 (16.0)
Oral Tacrolimus	4 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	5 (<0.1)
Mycophenolate mofetil	13 (0.3)	17 (0.6)	10 (0.8)	1 (0.1)	41 (0.4)
Other immunomodulators	116 (2.3)	81 (3.0)	36 (3.0)	17 (1.1)	250 (2.4)

Values are *n* (%) unless otherwise indicated.
BMI: body mass index; PGA: Physician's Global Assessment; SD: standard deviation; TNF: tumor necrosis factor; UVA: ultraviolet A; UVB: ultraviolet B.
[a]TNF-α inhibitors represents patients who are on or start any (combined adalimumab, etanercept, infliximab, and golimumab) upon registry entry.
[b]Includes atherosclerotic disease, peripheral arterial disease, coronary artery disease, transient ischemic attack/stroke, angina, congestive heart failure, myocardial infarction, hypertension, and hyperlipidemia.
[c]Includes melanoma and other (solid) malignancies.
[d]Serious infections requiring treatment within the last 3 years.

TNF inhibitors and ustekinumab were elevated. As expected, older age was associated with increased risk of HZ; however, systemic steroid use and disease activity were not found to be associated with the risk of HZ in the overall population studied.

A total of 55 HZ events were identified through 24,025 PY of observation in this large psoriasis cohort, corresponding to an incidence rate of <3 per 1000 PY. In the United States' (US) general population, incidence rates for HZ in patients >18 years of age were approximately 3–5 per 1000 PY (22), and these rates increased with age to 7–11 per 1000 PY for those between 60 and 80 years of age, respectively (23). In another study, incidence rates of HZ were 5.1 and 9.8 per 1000 PY, respectively, among US patients with psoriasis using non-biologic disease-modifying antirheumatic drugs (DMARDs) or those using TNF inhibitors (14). In contrast, the rates of HZ reported in the PSOLAR registry are lower. Of note, HZ was not listed as a protocol-specified safety adverse event of interest in PSOLAR, which may have led, in part, to underreporting by registry investigators and accrual of fewer events than expected.



Note: The TNF-α inhibitors cohort represents patients who are on or start any (combined adalimumab, etanercept, infliximab, golimumab) upon registry entry.

Figure 1. Patient disposition; overall population.

Table 2. Incidence rates and adjusted hazard rates of herpes zoster per 100 patient-years; overall cohort.

	TNF-α inhibitors[a] (*N* = 5076)	Ustekinumab (*N* = 2704)	Methotrexate (MTX) (*N* = 1201)	No biologics/no MTX (*N* = 1488)
Patient years, *N*	11,717	6471	1463	4374
Herpes zoster events, *N*	29	19	2	5
Rates (95% CI)	0.25 (0.17, 0.36)	0.29 (0.18, 0.46)	0.14 (0.02, 0.49)	0.11 (0.04, 0.27)
Adjusted hazard ratio (95% CI)	2.22 (0.82, 5.97)	2.73 (0.98, 7.58)	1.04 (0.20, 5.41)	Reference group

95% CI: 95% confidence interval. The incidence of adverse events is reported as rate of adverse events per 100 patient-years. Number of patient-years is defined as the number of years exposed to the group defining medication. Exposure starts from first exposure to a medication on/during registry participation and ends at the earlier of the date of first HZ event, reference end date, initiating another biologic treatment or MTX, 90 days after the last dose of the cohort defining treatment, or the date of the annual data cutoff (August 23, 2014). Patient-years: number of days of exposure/365.25. Hazard ratio is derived using Cox proportional model with covariates adjusted.

[a]Tumor necrosis factor-alpha (TNF-α) inhibitors represents patients who are on or start any (combined adalimumab, etanercept, infliximab, and golimumab) upon registry entry.

Table 3. Predictors of time to first herpes zoster event; overall cohort.

	Adjusted hazard ratio (95% CI)	*p* value
Age/10 years at baseline	1.35 (1.08, 1.68)	.008
Non-White vs. White	0.51 (0.18, 1.43)	.199
Overweight/Obesity Class I vs. Underweight/normal (25 < BMI <35 vs. <25) at baseline	0.91 (0.41, 2.02)	.821
Obesity Class II, III versus Underweight/normal (BMI ≥35 versus <25) at baseline	1.78 (0.77, 4.10)	.177
PGA 2,3 versus PGA 0,1 at baseline	1.05 (0.60, 1.83)	.866
PGA 4,5 versus PGA 0,1 at baseline	0.24 (0.03, 1.78)	.161
Duration of psoriasis/5 years at baseline	1.03 (0.93, 1.13)	.608
History of phototherapy versus no history	1.31 (0.73, 2.36)	.369
Psoriatic arthritis versus no history	1.16 (0.67, 2.03)	.590
Time-dependent systemic steroid use in the past 6 months versus no use	2.59 (0.93, 7.22)	.070
TNF-α inhibitors versus no biologics/no MTX	2.22 (0.82, 5.97)	.116
Ustekinumab versus no biologics/no MTX	2.73 (0.98, 7.58)	.054
MTX versus no biologics/no MTX	1.04 (0.20, 5.41)	.966

95% CI: 95% confidence interval; TNF: tumor necrosis factor; BMI: body mass index; PGA: Physician's Global Assessment; MTX: methotrexate.
The TNF-α inhibitors cohort represents patients who are on or start any (combined adalimumab, etanercept, infliximab, and golimumab) upon registry entry.
Hazard ratio is derived using Cox proportional model with other covariates adjusted; *p* values are derived from Wald Chi-square test after accounting for other covariates in the Cox model. Only covariates with univariate *p* values ≤.2 were included in this table.
Concomitant topical, phototherapy, or systemic steroid use each represent a time-dependent variable that varies at 6-month intervals prior to the first herpes zoster event and is defined as any use within 183 days of the event date; time-dependent disease activity (PGA) is the non-missing value from the last visit prior to the first herpes zoster event.

There are very few studies that explore the risk of developing HZ among patients with psoriasis in relationship to treatment exposure. Evidence from randomized clinical trials are often underpowered to detect differences. An observational cohort study from a US claims database reported no difference between the risk of HZ in new users of TNF inhibitors and the use of non-biologic DMARDs (reference group) (adjusted HR = 0.63 [95% CI: 0.28–1.43]) (15). Similarly, a study in Israel also reported no difference among patients receiving phototherapy, MTX, cyclosporine or a single biologic agent alone in comparison to patients not

receiving non-biologic systemic therapies (18). Nevertheless, that study did report an increase in HZ incidence with the use of biologics and MTX in combination (HR = 1.66 [95% CI 1.08–2.57]).

Our study was consistent with these previous reports (18). However, unlike these previous reports, the HRs for HZ risk were elevated for biologic therapies (i.e. TNF inhibitors and ustekinumab), albeit not statistically significant findings. Our study design excluded biologic patients receiving concomitant treatment with MTX; therefore, we were unable to confirm the increased risk observed with combined therapy in the Israeli study (18). In a subset of the new-user population, for which we could characterize exposure with more accuracy and adjust for pretreatment variables appropriately, we did observe a significantly increased risk of HZ among patients receiving TNF inhibitors (adjusted HR = 3.66 [95% CI: 1.15–11.63]), but the wide CIs make it difficult to interpret the magnitude of risk. The reference group used was heterogenous to increase power; however, the inclusion of non-biologic systemic therapies in this group could have confounded the results. Also, data for TNF inhibitors were pooled; therefore, we did not estimate the potential risk associated with each individual TNF inhibitor.

In this report, increasing age was the only factor that was associated with higher susceptibility to development of HZ. This finding is expected, as the incidence and severity of HZ are known to increase with age (24). Other known risk factors, such as systemic steroid exposure (HR = 2.59 [95%CI: 0.93–7.22, $p = .070$]), did not reach statistical significance, most likely due to the paucity of HZ events. Disease severity and various comorbidities associated with psoriasis, similarly did not confer an increased risk of HZ.

A strength of our study is that it utilizes the largest disease-based psoriasis registry experienced in enrolling and gathering detailed demographic, clinical, and treatment data from patients with median follow-up of 3.2 years. Some limitations of this study design should be considered when interpreting these findings. Lower than expected incidence rates of HZ may be a result of the low sensitivity to detecting new HZ events in patients enrolled in PSOLAR and recall bias. Also, previous history of HZ and vaccination status prior to therapy exposure was not recorded; therefore, this limited the power of the study and its ability to draw conclusions on the relationship of drug therapy and HZ. Additionally, treatment selection bias may exist to some extent; consequently, baseline demography and disease characteristics varied among treatment cohorts. We addressed this limitation by adjusting results for relevant and identifiable confounding factors; nonetheless residual confounding could exist for unmeasured variables. Finally, data regarding dosing adjustments were not captured; therefore, stratification of the results by dose and dose intervals was not performed.

In conclusion, in this real-world global study in patients with psoriasis, treatment with TNF inhibitors, ustekinumab, and MTX did not demonstrate a significant increase in the risk of HZ; however, continued follow-up will be important as more data and events accrue.

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