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Risk of herpes zoster and postherpetic neuralgia in patients with psoriasis treated with biologics: a nationwide study using a target trial emulation framework

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Abstract

Background Patients with psoriasis have a higher baseline risk of herpes zoster (HZ) than the general population. This has raised concerns that tumour necrosis factor (TNF)-α inhibitor use may be associated with an increased risk of HZ. However, the risk profiles for newer biologics, including interleukin (IL)-17, IL-12/23 and IL-23 inhibitors, remain uncertain.

Objectives To compare the risks of HZ and postherpetic neuralgia (PHN) in patients with psoriasis using different biologics (ustekinumab, secukinumab, ixekizumab, guselkumab, etanercept and adalimumab) vs. traditional systemic treatments (TSTs).

Methods We conducted a retrospective cohort study using data from Taiwan's National Health Insurance Research Database (2011–2021). We included patients with psoriasis or psoriatic arthritis aged ≥ 20 years who had been treated with biologics or TSTs for at least 6 months. We classified patients by individual biologics or TST and followed them for up to 2.5 years from drug initiation until the occurrence of outcome events or death. The primary outcome was a diagnosis of HZ. We used inverse probability of treatment weighting to adjust for covariates, including patient age, sex, comorbidities and comedications. We used Cox proportional hazards models to evaluate the risk of HZ with different biologics.

Results We identified 815, 1870, 1095, 2327, 261, 303 and 98 patients with psoriasis who were taking etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab and guselkumab, respectively. Compared with patients receiving TSTs, for those receiving ustekinumab and guselkumab the risk of HZ trended lower [ustekinumab: weighted hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.61–1.11; guselkumab: weighted HR 0.48, 95% CI 0.22–1.02], while for those receiving adalimumab it was statistically significantly higher (weighted HR 1.63, 95% CI 1.22–2.18). Additionally, ustekinumab was associated with a reduced risk of PHN (HR 0.22, 95% CI 0.08–0.64). There were no statistically significant differences in the risk of HZ between TSTs and either etanercept, secukinumab, ixekizumab or brodalumab.

Conclusions Our findings suggest that ustekinumab and guselkumab may be associated with a reduced risk of HZ and PHN vs. TSTs in patients with psoriasis. This study could have significance for real-world practice.

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Lay summary

Psoriasis is an inflammatory skin condition. It affects around 2% to 3% of people globally. People with psoriasis can have itchy and painful raised patches on their skin. The development of drugs called 'biologics' has changed how we treat psoriasis. Some people taking biologics experience complete clearance of their psoriasis.

Biologics work by suppressing the immune system. There are concerns about infections like 'herpes zoster' when taking biologics. Herpes zoster is also known as 'shingles'. Shingles results when the virus that causes chickenpox reactivates. As well as skin infections, shingles can cause nerve pain. Other complications include specific eye and brain infections. Giving patients the shingles vaccine before they take biologics is important.

We investigated the link between shingles and biologics in people with psoriasis. The biologics studied were ustekinumab, secukinumab, ixekizumab, guselkumab, etanercept and adalimumab. We used a national database in Taiwan to compare patients with psoriasis taking biologics to those on other treatment. The database covers 99% of Taiwan's population (approximately 23 million people). Patients on adalimumab were at higher risk of shingles than people on other treatment. People on ustekinumab or guselkumab were at less risk of shingles and nerve pain.

Some biologics may lower the risk of shingles and nerve pain versus other treatments. This could be important for treating people with psoriasis.

What is already known about this topic?

- There are concerns that tumour necrosis factor-α inhibitors may increase the risk of herpes zoster.
- Evidence regarding the association of interleukin (IL)-17, IL-12/23 or IL-23 inhibitors with herpes zoster and postherpetic neuralgia in psoriasis is scarce.

What does this study add?

- Compared with patients receiving traditional systemic treatments, patients with psoriasis receiving ustekinumab and guselkumab had a reduced risk of developing herpes zoster and postherpetic neuralgia.
- Patients with psoriasis taking secukinumab, ixekizumab or brodalumab were not at increased risk of developing herpes zoster.

What are the clinical implications of this work?

- Patients with moderate-to-severe psoriasis who are at risk of herpes zoster might consider using ustekinumab or guselkumab.

Herpes zoster (HZ) is the reactivation of the varicella zoster virus (VZV) that causes chickenpox in childhood. HZ is characterized by multiple grouped vesicles along one or more adjacent dermatomes. Usually self-limited, HZ often causes acute neurological pain, which may become chronic in some patients, causing intolerably painful postherpetic neuralgia (PHN). Complications can include herpetic keratitis or herpetic meningoencephalitis. Patients with psoriasis have higher rates of HZ [13.3 cases/1000 person-years (PYs)] compared with the general population (8.5 cases/1000 PYs), after adjustment.[1,2] Tsai *et al*. have reported that there is a high risk of HZ in patients with severe psoriasis.[3]

Psoriasis is an immune-mediated chronic inflammatory disease characterized by erythematous plaques with thick silvery white scales on the trunk and extensor sides of the extremities. The development of biologics has dramatically changed psoriasis treatment, with many patients with moderate-to-severe psoriasis becoming almost 100% lesion-free.[4,5] However, concerns remain about HZ being associated with tumour necrosis factor (TNF)-α inhibitors (TNF-αi). Ting *et al*. found that patients with psoriasis treated with etanercept and adalimumab had an increased risk of HZ,[6] possibly through downregulation of interferon (IFN)-γ via blockage of the TNF-α signalling pathway or other proinflammatory cytokines from TNF-α inhibition. One meta-analysis yielded conflicting results, with an increased risk of HZ found only with combinations of biologics and conventional synthetic disease-modifying antirheumatic drugs but not with biologics alone.[7,8] Moreover, current evidence predominantly concerns TNF-αi, while evidence regarding the risk of HZ with new biologics like interleukin (IL)-17, IL-12/23 and IL-23 inhibitors (IL-17i, IL-12/23i and IL-23i, respectively) remains scant. One randomized controlled trial of limited sample size found that IL-17i was not associated with an increased risk of HZ.[9]

Our study aimed to evaluate the association between biologics and HZ risk, and to compare this association with traditional systemic immunosuppressants in patients with psoriasis, using a population-based claims database to achieve sufficient sample size. We evaluated specific risk profiles of different biologics to extend the current knowledge, and used a target trial emulation framework to enhance causal inference.

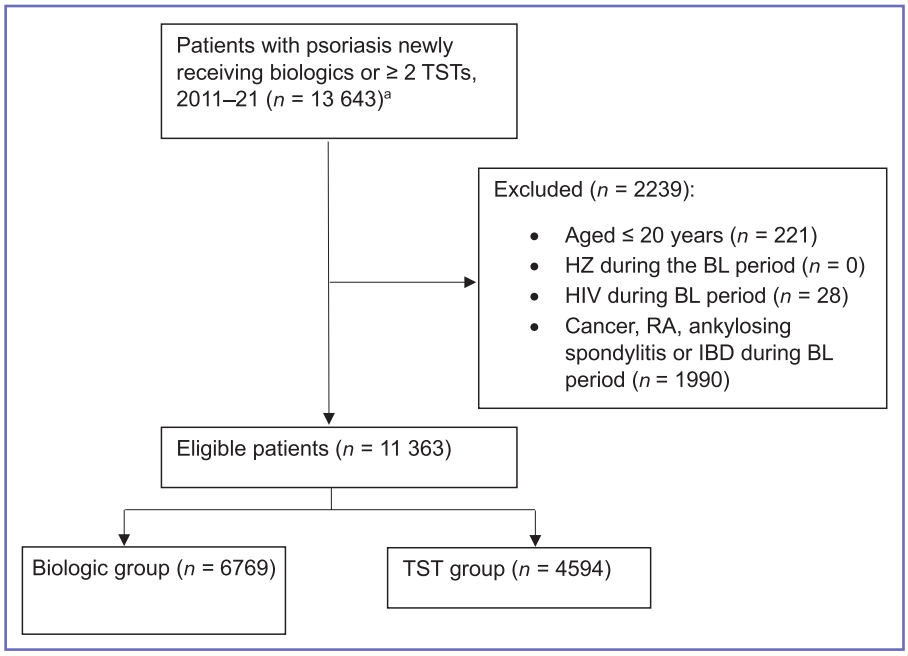

Figure 1 Flowchart of the study cohort selection. BL, baseline; HZ, herpes zoster; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; TST, traditional systemic treatment. [a]Excludes 41 patients who died before the index date or the index date surpassed 31 December 2021.

Patients and methods

Data source

This study used data from Taiwan's National Health Insurance Research Database (NHIRD) covering the period from 2011 to 2021. The NHIRD, operated in conjunction with the national health insurance programme and covering 99% of Taiwan's population (23 million people), includes records of outpatient and inpatient clinical visits and claims, pharmacy prescriptions, procedures and diagnoses [using the codes from International Classification of Diseases (ICD), Ninth Revision (ICD-9) and ICD, Tenth Revision (ICD-10)].[10] We linked the NHIRD to the National Death Registry to obtain precise death records. Complete capture of almost all biologics use can be assumed, as patients are likely to have sought National Health Insurance (NHI) reimbursement for the high costs.

Study participants

We used a target trial design to emulate a randomized controlled pragmatic clinical trial with retrospective data (Table S1; see Supporting Information).[11] We included patients aged ≥ 20 years, diagnosed between 2011 and 2021 with psoriasis with or without psoriatic arthritis (PsA). Figure 1 shows patients who were excluded from the cohort. In Taiwan, patients with moderate-to-severe chronic plaque psoriasis are reimbursed for biologics by the NHI, with each reimbursement period lasting for 2 years. Patients for whom the treatment was unsuccessful or who were drug intolerant after receiving ≥ 2 traditional systemic treatments (TSTs; methotrexate, ciclosporin or acitretin) and regular phototherapy, each administered for > 3 months, were eligible for NHI reimbursement for biologic agents, including TNF-αi (etanercept, adalimumab), IL-12/23i (ustekinumab), IL-17i (secukinumab, ixekizumab, brodalumab) and IL-23i (guselkumab). Patients taking any of these agents were included in the biologics group. On the basis of these unique reimbursement criteria, patients received regular and long-term doses of biologics. For the control group, and to improve the comparability of patients between the different study groups,[12] we selected patients who had received two TSTs (methotrexate, ciclosporin or acitretin) for at least 6 months and then continued with TSTs. In the biologics group, the index date was the date of first prescription of biologics; in the TST group it was 6 months after the initiation of systemic treatment. Patients taking TNF-αi, including etanercept and adalimumab, were enrolled for sensitivity analyses. The single control group included patients on methotrexate, ciclosporin or acitretin. Owing to low cohort numbers, risankizumab, infliximab and certolizumab were not included. We also excluded patients with a history of cancer, HIV/AIDS or pregnancy, and patients with recent HZ (i.e. within 180 days before the study entry date, defined as the first date of new treatment). We only enrolled patients who were new users of biologics.

Outcome definitions

The primary outcome was HZ infection; the secondary outcome was subsequent PHN. PHN was defined based on a history of HZ and ≥ 1 session of low-level laser treatment, or at least 6 weeks' exposure to analgesic drugs such as tramadol plus acetaminophen or pregabalin (Table S2; see Supporting Information).

Follow-up and censoring

Our on-treatment analysis, an analogue of the per-protocol effect, followed patients for 2.5 years from the day after the index date until outcome occurrence, treatment

discontinuation, death or the end of the study (31 December 2021), whichever came first. We defined the grace period as discontinuation of regular dosing for an additional 30 days. For example, in the TST group, discontinuation meant > 30 days without treatment. For ustekinumab, the grace period was set at 3 months plus 30 days. The aim was to evaluate the treatment strategies at baseline and throughout the study. On-treatment analysis is more suitable for evaluating safety issues than as-started analysis, an analogue of the intention-to-treat effect (ITT). This represented the effect of initial assignment to TST vs. biologics, regardless of subsequent treatment changes; patients were censored upon discontinuation or biologic switching.

Covariates and statistical analyses

We selected baseline covariates based on the literature and expert opinion.[12,13] Covariates included patient demographics (sex, age at study entry), and comorbidities/comedications captured in the 1-year baseline period before study entry. To adjust for the effect of time on disease and treatment patterns, we incorporated cohort entry year as a covariate in the regression model. Detailed definitions are provided in Table S3 (see Supporting Information).

Descriptive analysis used counts with proportions and mean (SD) for categorical and continuous variables, respectively. We used the standardized mean difference (SMD) to describe differences between groups, and calculated incidence rates as events/follow-up years (events per 1000 PYs). We used multivariable Cox proportional hazards models to derive hazard ratios (HRs) and 95% confidence intervals (95% CIs) to compare HZ risks, and SMD to characterize heterogeneity levels between the drug and comparator groups, with statistical significance set at SMD > 10%.[14]

We used propensity scoring with inverse probability of treatment weighting (IPTW) to compare the risks of HZ and PHN for each biologic individually against the TST reference group.[15] The models were adjusted for patient age, sex, comorbidities, immunosuppressant exposure and comedications. IPTW uses propensity scores to balance baseline traits between patients receiving and not receiving treatment, by assigning weights based on the inverse probability of their actual treatment. Each weight is determined as 1/propensity score for exposed patients, or 1/(1 – propensity score) for unexposed patients. The resulting pseudopopulation has measured confounders distributed equally across groups, effectively reducing confounding bias. Notably, through IPTW, the differences in prior duration of TST for psoriasis between the biologics and TST groups were mitigated.[15,16] Pairwise propensity score weighting was used to compare each individual biologic with TST. To account for residual confounding, any covariates with absolute value of SMD > 0.1 after IPTW were further adjusted using regression modelling. Statistical analyses were performed with SAS version 7.1 (SAS Institute, Cary, NC, USA).

Sensitivity analyses

We conducted several sensitivity analyses. Firstly, we additionally performed as-started analysis, an analogue of ITT. Secondly, we stratified patients based on the presence or absence of a PsA diagnosis, to assess its impact on infection risk. Finally, to account for intercurrent events[17] – including treatment-modifying events (e.g. drug switching, add-on or combination treatments, and drug discontinuation) and truncating events (e.g. competing risks like death) – we applied various methodological approaches. The treatment policy strategy (ITT analysis) evaluated outcomes based on the initially assigned treatment, while the while-on-treatment strategy, akin to a per-protocol analysis in a target trial, assessed the effect of receiving the assigned treatment throughout follow-up. Treatment deviations were determined after a 1-month grace period from the index date to account for the typical duration of bridge treatment with conventional immunosuppressants. Additionally, we used a subdistribution model to account for competing risks and a time-dependent Cox model to incorporate time-varying intercurrent events as covariates.[18]

Results

Baseline characteristics

We identified 6769 and 4594 patients with psoriasis receiving biologics and TST, respectively. Figure 1 shows the study cohort selection flowchart. Most patients were men. Comorbidities and comedications in the biologics and TST groups (SMD cutoff < 0.1) before and after IPTW are presented in Figure S1 (see Supporting Information). Prior to IPTW, the most significant differences between the two groups were found regarding history of TST, phototherapy and vitamin D use.[14] Other baseline information is presented in Table 1 and Table S4 (see Supporting Information). Overall, of the 11 363 patients included, 40.4% ($n = 4594$) received TST and 59.6% ($n = 6769$) received biologics, with 9.6% ($n = 1095$), 20.5% ($n = 2327$), 16.5% ($n = 1870$), 7.2% ($n = 815$), 2.3% ($n = 261$), 0.9% ($n = 98$) and 2.7% ($n = 303$) receiving etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab and guselkumab (before IPTW), respectively. Around 70% of biologics users were concurrently receiving conventional synthetic disease-modifying antirheumatic drugs on the index day.

Primary outcomes

The adjusted HR was calculated after IPTW and further adjustment. Table 2 shows the incidence rates (IRs) and HRs for the primary outcome of HZ and the secondary outcome of PHN in patients with psoriasis. The IR of HZ was highest for adalimumab (IR 27.2) and lowest for guselkumab (IR 6.6). In descending order, the IRs after IPTW for the remaining biologics were as follows: secukinumab 17.7, etanercept 16.6, ixekizumab 16.1, brodalumab 16.0 and ustekinumab 14.0 (Table 2). Using the IPTW approach, the HRs for the HZ IRs for ustekinumab and guselkumab vs. TST were associated with a lower but not statistically significant risk (ustekinumab: weighted HR 0.82, 95% CI 0.61–1.11; guselkumab weighted HR 0.48, 95% CI 0.22–1.02), while patients in the adalimumab group had a statistically significantly higher risk of HZ (weighted HR 1.63, 95% CI 1.22–2.18). Detailed cumulative incidence function plots are provided in Figure 2. Cumulative HZ incidences were lower for ustekinumab and

Table 1 Baseline characteristics of interleukin (IL)-17, IL-12/23 and IL-23 inhibitor and control cohorts after inverse probability of treatment weighting (IPTW) adjustment

Characteristic	Etanercept (*n* = 1861)[a]	Adalimumab (*n* = 4359)[a]	Ustekinumab (*n* = 3895)[a]	Secukinumab (*n* = 1946)[a]	Ixekizumab (*n* = 822)[a]	Brodalumab (*n* = 349)[a]	Guselkumab (*n* = 987)[a]
Male sex	1315 (70.7)	3060 (70.2)	2964 (76.1)	1376 (70.7)	622 (75.7)	248 (71.2)	742 (75.5)
Age at study entry date (years), mean (SD)	48.2 (16.9)	47.4 (17.6)	48.3 (20.3)	48.0 (21.2)	47.5 (23.6)	48.9 (29.0)	46.5 (24.5)
Age group (years)							
20–29	134 (7.2)	344 (7.9)	373 (9.6)	210 (10.8)	67 (8.2)	51 (14.6)	90 (9.1)
30–39	415 (22.3)	949 (21.8)	818 (21.0)	356 (18.3)	181 (22.0)	46 (13.2)	242 (24.5)
40–49	422 (22.7)	1170 (26.8)	869 (22.3)	483 (24.8)	216 (26.3)	76 (21.8)	278 (28.1)
50–59	537 (28.9)	1083 (24.8)	903 (23.2)	440 (22.6)	198 (24.1)	75 (21.5)	198 (20.1)
60–69	256 (13.8)	600 (13.8)	698 (17.9)	361 (18.6)	116 (14.1)	77 (22.1)	125 (12.6)
≥ 70	98 (5.3)	213 (4.9)	234 (6.0)	96 (4.9)	44 (5.4)	24 (6.9)	54 (5.5)
Duration of follow-up (months), mean (SD)	289.3 (326.2)	375.1 (377.6)	607.3 (370.9)	503.9 (424.3)	375.6 (393.8)	261.6 (314.3)	448.1 (452.2)
Calendar year							
2011	297 (16.0)	101 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2012	255 (13.7)	179 (4.1)	42 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)
2013	187 (10.0)	274 (6.3)	283 (7.3)	0 (0)	0 (0)	0 (0)	0 (0)
2014	190 (10.2)	324 (7.4)	489 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)
2015	226 (12.1)	456 (10.5)	553 (14.2)	0 (0)	0 (0)	0 (0)	0 (0)
2016	151 (8.1)	590 (13.5)	627 (16.1)	23 (1.2)	0 (0)	0 (0)	0 (0)
2017	198 (10.6)	638 (14.6)	723 (18.6)	334 (17.2)	0 (0)	0 (0)	0 (0)
2018	104 (5.6)	428 (9.8)	615 (15.8)	670 (34.4)	4 (0.5)	0 (0)	0 (0)
2019	93 (5.0)	422 (9.7)	265 (6.8)	546 (28.1)	160 (19.5)	0 (0)	277 (28.1)
2020	77 (4.1)	599 (13.7)	206 (5.3)	164 (8.4)	387 (47.1)	152 (43.6)	400 (40.5)
2021	83 (4.5)	348 (8.0)	93 (2.4)	209 (10.7)	271 (33.0)	197 (56.4)	310 (31.4)
History of medication							
Methotrexate	1577 (84.7)	3733 (85.6)	2886 (74.1)	1455 (74.8)	606 (73.7)	251 (71.9)	672 (68.1)
Cyclosporine	502 (27.0)	1928 (44.2)	1809 (46.4)	1112 (57.1)	465 (56.6)	204 (58.5)	584 (59.5)
Acitretin	754 (40.5)	1656 (38.0)	2747 (70.5)	1077 (55.3)	516 (62.8)	239 (68.5)	698 (70.7)
Calcipotriol	853 (45.8)	1262 (29.0)	1494 (38.4)	269 (13.8)	60 (7.3)	16 (4.6)	125 (12.7)
Calcipotriol combinations	541 (29.1)	2529 (58.0)	2430 (62.4)	1523 (78.3)	689 (83.8)	288 (82.5)	868 (87.9)
Tazarotene	135 (7.3)	190 (4.4)	212 (5.4)	74 (3.8)	17 (2.1)	8 (2.3)	32 (3.2)
Phototherapy	864 (46.4)	1759 (40.4)	2738 (70.3)	1028 (52.8)	143 (17.4)	0 (0)	208 (21.1)
History of systemic steroid use	462 (24.8)	965 (22.1)	472 (12.1)	308 (15.8)	109 (13.3)	46 (13.2)	72 (7.3)
Prior TST use[b]	1704 (91.6)	4087 (93.8)	3179 (81.6)	1726 (88.7)	719 (87.5)	311 (89.1)	848 (85.9)
Concurrent use of csDMARD[c]	1258 (67.6)	3166 (72.6)	2730 (70.19)	1447 (74.4)	678 (82.5)	298 (85.4)	761 (77.1)
Psoriatic arthritis	1246 (67.0)	2991 (68.6)	1107 (28.4)	993 (51.0)	339 (41.2)	63 (18.1)	205 (20.8)
Concurrent diagnosis							
Diabetes	306 (16.4)	658 (15.1)	630 (16.2)	297 (15.3)	144 (17.5)	72 (20.6)	153 (15.5)
Hypertension	544 (29.2)	1224 (28.1)	1160 (29.8)	532 (27.3)	230 (28.0)	97 (27.8)	278 (28.2)
Hyperlipidaemia	354 (19.0)	890 (20.4)	826 (21.2)	410 (21.1)	190 (23.1)	69 (19.8)	219 (22.2)
CHD	97 (5.2)	267 (6.1)	245 (6.3)	122 (6.3)	53 (6.4)	25 (7.2)	37 (3.7)
MI	7 (0.4)	21 (0.5)	21 (0.5)	13 (0.7)	8 (1.0)	4 (1.1)	2 (0.2)
Stable or unstable angina	33 (1.8)	108 (2.5)	98 (2.5)	60 (3.1)	28 (3.4)	17 (4.9)	17 (1.7)
Stroke	30 (1.6)	50 (1.1)	76 (2.0)	28 (1.4)	23 (2.8)	4 (1.1)	12 (1.2)
TIA	9 (0.5)	25 (0.6)	27 (0.7)	12 (0.6)	8 (1.0)	0 (0)	4 (0.4)
CKD	57 (3.1)	114 (2.6)	143 (3.7)	71 (3.6)	39 (4.7)	19 (5.4)	42 (4.3)
COPD	44 (2.4)	112 (2.6)	122 (3.1)	17 (0.9)	4 (0.5)	16 (4.6)	12 (1.2)
Asthma	56 (3.0)	171 (3.9)	141 (3.6)	52 (2.7)	18 (2.2)	16 (4.6)	24 (2.4)
Hyperthyroidism	13 (0.7)	47 (1.1)	48 (1.2)	18 (0.9)	8 (1.0)	0 (0)	9 (0.9)
Hypothyroidism	9 (0.5)	41 (0.9)	20 (0.5)	10 (0.5)	3 (0.4)	0 (0)	4 (0.4)
Heart failure	44 (2.4)	77 (1.8)	89 (2.3)	60 (3.1)	10 (1.2)	4 (1.2)	10 (1.0)
Vasculitis	0 (0)	2 (< 0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Connective tissue disease	29 (1.6)	103 (2.4)	11 (0.3)	16 (0.8)	1 (0.1)	0 (0)	9 (0.9)
Glaucoma	30 (1.6)	94 (2.2)	64 (1.6)	37 (1. 9)	16 (1.9)	16 (4.6)	23 (2.3)
Cataract	110 (5.9)	278 (6.4)	249 (6.4)	102 (5.2)	40 (4.9)	25 (7.2)	49 (5.0)
Comedication							
Aspirin	32 (1.7)	118 (2.7)	103 (2.6)	46 (2.4)	16 (1.9)	8 (2.3)	11 (1.1)
Antiplatelet medication other than aspirin	62 (3.3)	139 (3.2)	113 (2.9)	63 (3.2)	27 (3.3)	20 (5.7)	14 (1.4)
Statin	231 (12.4)	655 (15.0)	516 (13.2)	282 (14.5)	139 (16.9)	69 (19.8)	136 (13.8)
Fibrate	74 (4.0)	146 (3.3)	150 (3.9)	78 (4.0)	43 (5.2)	13 (3.7)	53 (5.4)
Beta blockers	331 (17.8)	724 (16.6)	628 (16.1)	309 (15.9)	127 (15.5)	50 (14.3)	116 (11.8)
ACE inhibitors/ARBs	250 (13.4)	539 (12.4)	562 (14.4)	257 (13.2)	107 (13.0)	59 (16.9)	137 (13.9)
Calcium channel blockers	380 (20.4)	771 (17.7)	697 (17.9)	308 (15.8)	152 (18.5)	44 (12.6)	151 (15.3)
Diuretics	200 (10.7)	416 (9.5)	426 (10.9)	185 (9.5)	81 (9.9)	42 (12.0)	58 (5.9)
Sulfonylurea	132 (7.1)	231 (5.3)	213 (5.5)	111 (5.7)	44 (5.4)	23 (6.6)	34 (3.4)
DPP-4 inhibitors	58 (3.1)	140 (3.2)	170 (4.4)	60 (3.1)	19 (2.3)	18 (5.2)	26 (2.6)
Glinides	24 (1.3)	31 (0.7)	62 (1.6)	25 (1.3)	9 (1.1)	4 (1.1)	7 (0.7)
Thiazolidinediones	19 (1.0)	75 (1.7)	52 (1.3)	16 (0.8)	18 (2.2)	6 (1.7)	14 (1.4)
Insulins	46 (2.5)	79 (1.8)	107 (2.7)	39 (2.0)	9 (1.1)	12 (3.4)	14 (1.4)
Systemic steroids	822 (44.2)	1844 (42.3)	1168 (30.0)	702 (36.1)	253 (30.8)	111 (31.8)	269 (27.3)
PPIs	165 (8.9)	388 (8.9)	280 (7.2)	166 (8.5)	64 (7.8)	32 (9.2)	58 (5.9)

Data are presented as *n* (%) unless otherwise stated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; DPP-4, dipeptidyl peptidase-4; MI, myocardial infarction; PPI, proton pump inhibitor; TIA, transient ischaemic attack; TST, traditional systemic treatments. [a]Data reflects the cohort after applying IPTW. [b]TST was used in the 6 months prior to the index date. [c]On index date.

guselkumab than for TST, and higher for adalimumab than for TST.

Secondary outcomes

The IRs for PHN were 0.2, 2.8, 1.0 and 2.1 per 1000 PYs for etanercept, adalimumab, ustekinumab and secukinumab, respectively. Events with other biologics were too few to analyse. Using the IPTW approach, the HR for the IR of PHN for ustekinumab vs. TST was 0.22 (95% CI 0.08–0.64), which was statistically significantly different, while it was 0.69 (95% CI 0.19–2.48) for etanercept, 1.11 (95% CI 0.47–2.62) for adalimumab and 0.67 (95% CI 0.25–1.81) for secukinumab (Table 2).

Sensitivity analysis

The results of the sensitivity analyses were consistent with those of the primary analysis. Details are provided in Appendix S1 and Tables S5–S9 (see Supporting Information).

Discussion

This population-based study found that ustekinumab and guselkumab were associated with a reduced risk of HZ and PHN vs. TSTs. However, in those receiving IL-17i, the effects did not reach statistical significance. Additionally, our findings were consistent with a previous study which indicated that adalimumab was associated with an increased risk of HZ, strengthening causality in our analysis. These findings suggest considering ustekinumab or guselkumab for clinical use in patients at potential risk of HZ.

We designed a target trial to emulate a randomized controlled pragmatic clinical trial to investigate associations between HZ risk and IL-17i, IL-12/23i and IL-23i. Previous studies on the association of HZ with these newer biologics are limited. Two retrospective studies included in a systematic review reported a slightly higher (not statistically significant) incidence of HZ in patients with psoriasis using IL-12/23i.[7,8,19] Davidson *et al.* claim that only ustekinumab and infliximab are associated with HZ in patients with psoriasis,[20] based on a global database of spontaneous adverse drug reaction reports maintained by the World Health Organization. In contrast, in real-world data, HZ risks with IL-12/23i and IL-17i appear reduced vs. TNF-αi.[21,22] Another systematic review found a higher risk of HZ with biologic vs. nonbiologic systemic therapies,[23] but it did not find an association with ustekinumab.[23] A review of three randomized controlled trials concluded that there is not a higher risk of HZ in patients with psoriasis treated with IL-17i.[24] Notably, one study found secukinumab to be associated with a lower risk of HZ, but this did not reach statistical significance [odds ratio (OR) 0.87, 95% CI 0.62–1.22].[20] In a study of 4399 guselkumab-treated patients with psoriasis followed for 10 787 PYs, only 1 patient developed HZ.[25] Based on these studies, IL-17i, IL-12/23i and IL-23i, potentially, do not pose the same risk of HZ as TNF-αi.

Our TNF-αi analysis yielded results consistent with previous studies, whereby adalimumab was associated with an increased risk of HZ,[6] strengthening the quality of our analysis. Furthermore, Shalom *et al.* reported that combinations of biologics with methotrexate are associated with a significantly increased incidence of HZ,[2] possibly because combination therapy might enhance the immunosuppressive effects of the treatment.[7] However, etanercept is not associated with a higher incidence of HZ.[26] The incidence of HZ may vary, depending on the TNF-αi used,[27] with HZ incidence and severity higher in patients receiving monoclonal TNF-αi (adalimumab: OR 3.25; infliximab: OR 3.94) than in those receiving a soluble TNF receptor (etanercept: OR 1).[28] This may be explained by their different mechanisms of action.[28,29] Guidelines recommend the HZ vaccine for patients with psoriasis receiving TNF-αi, especially when combined with methotrexate.[7,30] Our research found an elevated incidence of HZ with adalimumab, similarly to a previous study.[6]

The lower risk of HZ found with ustekinumab and guselkumab vs. adalimumab may reflect biologic-specific

Table 2 Incidence rates (IRs) and hazard ratios (HRs) for herpes zoster (HZ) and postherpetic neuralgia (PHN) in patients with psoriasis treated with different biologics vs. traditional systemic treatments

Group	No. (events)	IR per 1000 PY (95% CI)	IRR	Crude HR (95% CI)	Adjusted HR (95% CI)
HZ					
Etanercept	1095 (24)	16.60 (11.10–24.60)	0.93 (0.60–1.45)	1.03 (0.62–1.72)	0.77 (0.47–1.24)
Adalimumab	2327 (122)	27.20 (22.80–32.50)	1.54 (1.20–1.99)	1.48 (1.07–2.02)	1.63 (1.22–2.18)
Ustekinumab	1870 (90)	14.00 (11.40–17.10)	0.82 (0.63–1.08)	0.97 (0.69–1.37)	0.82 (0.61–1.11)
Secukinumab	815 (48)	17.70 (13.30–23.50)	1.01(0.72–1.426)	1 (0.61–1.64)	1.17 (0.80–1.71)
Ixekizumab	261 (14)	16.10 (9.40–27.30)	0.91 (0.51–1.60)	0.86 (0.31–2.34)	1.03 (0.55–1.92)
Brodalumab	98 (4)	16.00 (6.00–42.70)	0.89 (0.33–2.43)	0.72 (0.10–5.20)	0.95 (0.33–2.70)
Guselkumab	303 (8)	6.60 (3.30–13.20)	0.37 (0.18–0.77)	0.31 (0.08–1.27)	0.48 (0.22–1.02)
TST[a]	4595 (95)	17.90 (14.60–21.80)	1.00	1.00	1.00
PHN					
Etanercept	1095 (3)	0.20 (0.70–6.30)	0.573 (0.172–1.91)	0.86 (0.25–2.91)	0.69 (0.19–2.48)
Adalimumab	2327 (13)	2.80 (1.60–4.90)	0.87 (0.40–1.60)	0.97 (0.44–2.13)	1.11 (0.47–2.62)
Ustekinumab	1870 (7)	1.00 (0.50–2.20)	0.28 (0.12–0.66)	0.35 (0.12–1.02)	0.22 (0.08–0.64)
Secukinumab	815 (6)	2.10 (0.90–4.80)	0.55 (0.22–1.38)	0.47 (0.11–2.02)	0.67 (0.25–1.81)
Ixekizumab	261 (0)	NA	NA	NA	NA
Brodalumab	98 (0)	NA	NA	NA	NA
Guselkumab	303 (0)	NA	NA	NA	NA
TST[a]	4595 (20)	3.70 (2.40–5.80)	1.00	1.00	1.00

CI, confidence interval; IRR, incidence rate ratio; NA, not available; PY, person-years; TST, traditional systemic treatment. [a]Events, IR and IRR were HZ and PHN outcomes, based on the inverse probability of treatment weighting cohort, except for TST, which are provided as crude data.

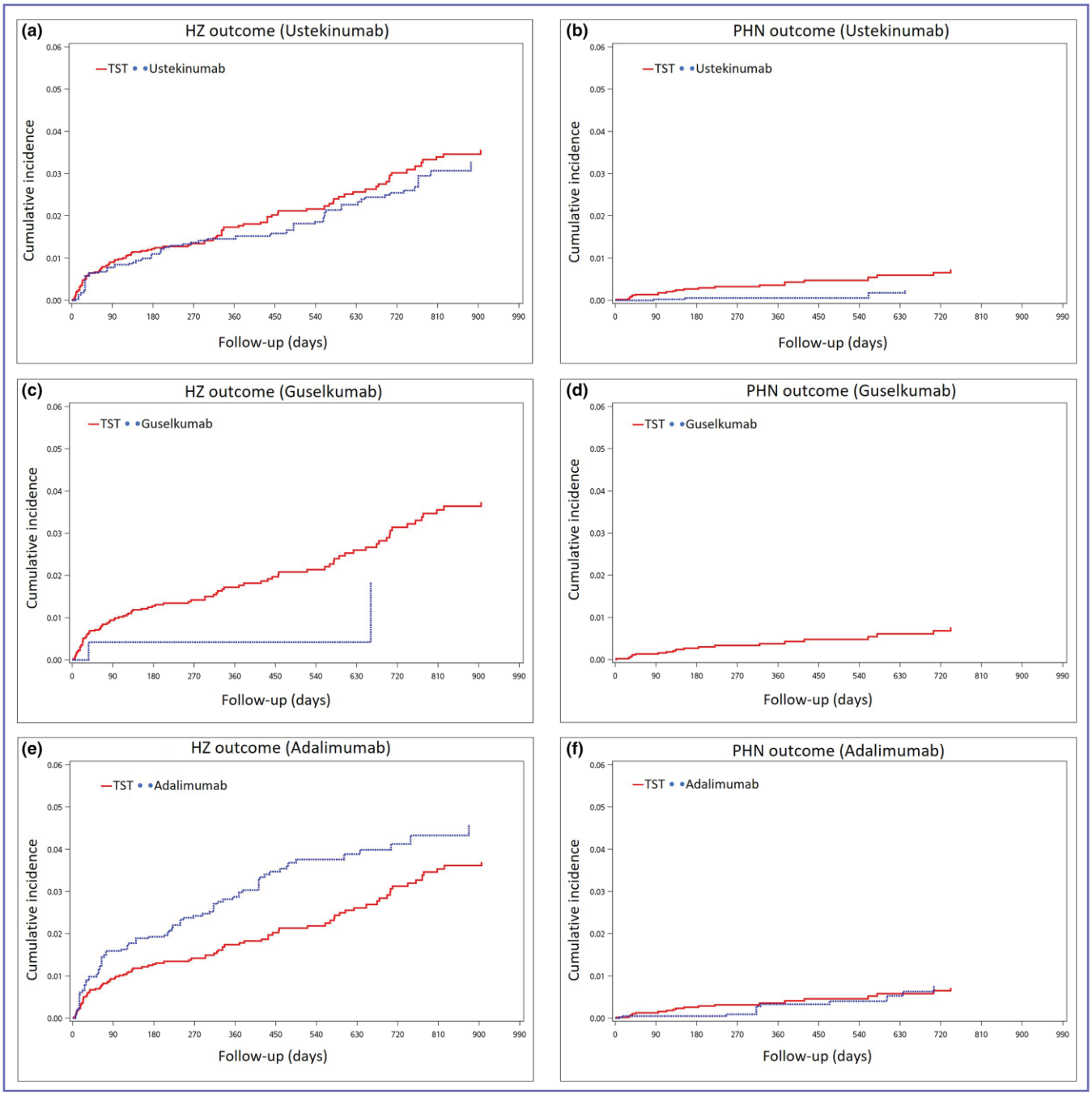

Figure 2 Herpes zoster (HZ) and postherpetic neuralgia (PHN) risks: cumulative incidence curves for patients receiving biologics vs. traditional systemic treatments (TSTs). (a, b) Ustekinumab, (c, d) guselkumab and (e, f) adalimumab. The outcome events for guselumab in (d) were very few; hence rendering the blue-dotted line either not visible or unable to be plotted.

differences in immune response to infection. The blockage of TNF-α signalling, which downregulates interferon (IFN)-γ, could exacerbate VZV dissemination.[31] IL-12/23 inhibition represents a complex interplay of the inflammatory IL-23 and mysterious anti-inflammatory IL-12 effect. One study in mice found that IL-12 primarily supports innate immunity by enhancing natural killer cell activity and promoting IFN-γ production, which is crucial for early defence against infections like herpes simplex virus type 2 (HSV-2), suggesting a protective role of IL-12i,[32] while IL-23 is insignificant in antiviral immunity.[33] However, other studies suggest that ustekinumab, compared with methotrexate, is not associated with an increased risk of infections in psoriasis.[34] IL-17 plays a complex role in viral infections, enhancing T helper (Th)1 immune responses against genital HSV-2 while limiting virus-induced organ pathology. However, it is also linked to promoting viral infections, particularly boosting antiviral Th1 cell immunity.[35,36] Interestingly, IL-17C promotes peripheral neuron growth and branching during HSV-2 infection, potentially explaining the absence of nerve damage in recurrent HSV infections.[37] Th17 cells help HIV replication in humans and IL-17 induces tissue inflammation in many viral infections,

including COVID-19.[33,35] Discussion of guselkumab remains limited. However, as it targets the p19 subunit specific to IL-23, it may avoid interactions between antiviral immunity and IL-12, as seen with ustekinumab.[38] Broader investigation of IL-17i, IL-12/23i and IL-23i is warranted.

Evidence on PHN associated with biologics remains scant. In an older, healthy population, the incidence of PHN is around 2–10% in people with HZ,[39] and ranges from < 1% to 20% in patients with rheumatoid arthritis (RA) or other diseases treated with TNF-αi.[40] Patients with RA receiving TNF-αi have a higher incidence of HZ, disease severity and pain.[41] One study reported that 20% of 1220 patients receiving first-generation biologics developed PHN,[19] while other studies have found that < 3% of 300 patients receiving TNF-αi develop PHN.[27,42] As studies on PHN with novel biologics are limited, the degree of PHN risk posed by biologics in patients with psoriasis remains controversial.[39] In our study, patients with psoriasis using ustekinumab were at lower risk of PHN. The definition of PHN, as proposed by Dworkin and Portenoy,[43] is neuropathic pain or any pain occurring more than 3 months after HZ. Another study reported mainly T-lymphocyte infiltration and general cell loss within the dorsal root ganglia innervating the painful area, even years after resolution of HZ.[44] While the actual mechanisms of these associations are not fully understood, they may involve reducing inflammation in the dorsal roots. Given the limited number of patients with PHN, further investigation is warranted. Our sensitivity analyses reinforced confidence in our assessment of the risks of HZ and PHN associated with adalimumab, ustekinumab and guselkumab. We obtained similar results in patients with and without PsA. By using diverse strategies to address intercurrent events through an estimand approach – an analytical framework that aligns methods with clinical objectives for clearer treatment effect interpretation – we strengthened the robustness of our findings. These strategies included ITT and per-protocol follow-up with a grace period extension, incorporation of time-varying covariates and consideration of competing risks such as death. Together, these adjustments enhanced temporal associations, improved consistency and provided strong supporting evidence.

The trends in HZ risk across the treatment groups remained consistent with the primary analysis, even after accounting for concurrent immunosuppressant use and incorporating the estimand analysis. Remarkably, for patients using guselkumab, the adjusted HR of 0.48 (95% CI 0.22–1.02) in the primary analysis indicated a decreasing trend in HZ risk, achieving statistical significance in the while on treatment/while alive strategy analysis (HR 0.27, 95% CI 0.10–0.76). These findings suggest that IL-23i, particularly ustekinumab and guselkumab, may provide protective effects against HZ and represent suitable treatment options for high-risk patients.

The current study has some limitations. Firstly, although the NHIRD covers 99% of Taiwan's population, it lacks data on self-paying patients, who are likely to be few with irregular treatments; thus, excluding them may have eliminated allocation bias. Secondly, the NHIRD does not record the Psoriasis Area and Severity Index (PASI) score; however, the NHI covers biologics only for patients with a PASI > 10, and our comparator group required at least two TSTs for > 6 months, ensuring the inclusion of patients with primarily moderate-to-severe psoriasis, thus minimizing the impact of this limitation. Thirdly, the risk of HZ is higher in patients with moderate-to-severe psoriasis than in those with mild psoriasis.[12] Tsai *et al.* reported the incidence of HZ to be higher in patients with severe psoriasis,[12] defined as patients receiving systemic or biologic treatment or phototherapy. However, their study did not include patients with mild psoriasis, leaving it uncertain whether the incidence of HZ is related to psoriasis severity or systemic treatment, or to the use of biologics. To improve validity, we only included patients with moderate-to-severe psoriasis on TST or biologics. Misclassification by severity was probably uniform between the groups and the bias was eliminated through the active comparator design. Fourthly, NHI policy requires patients with psoriasis to take at least 6 months of two different TST drugs before qualifying for biologics. Therefore, to eliminate immortal time bias, our control group included such patients, minimizing the effect of this bias. Some unmeasured confounding factors remained, such as body weight, smoking, alcohol intake and so on. However, these factors were identical across drug groups and should not have affected our results. Fifthly, owing to data limitations, we could not assess differences in HZ vaccination rates between groups; however, vaccination is rare among Taiwanese patients with psoriasis, primarily due to high out-of-pocket costs and younger patient age than the recommended target population. Consequently, the impact of this limitation is likely to be minimal.

The findings suggest that ustekinumab and guselkumab may be associated with a reduced risk of HZ and PHN vs. TSTs. Although not statistically significant in some comparisons, probably due to sample size, the trends suggest a potential protective effect. These findings could be significant for real-world practice as they underscore the need to prioritize biologics with favourable safety profiles in clinical practice. Further studies are required to confirm these associations.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

The study complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2013. The study was approved by the Institutional Review Board of National Cheng Kung University of Taiwan (HREC-110-310). The study used secondary data sources with encrypted patient identifiers from the National Health Insurance Research Database and no patients were personally identifiable at any time during the entire study period.

Patient consent

The requirement for patient informed consent was waived for this study as all personally identifying information within the National Health Insurance Research Database is encrypted.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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