International Journal of Research in Dermatology
Wahyuningtyas LPI et al. Int J Res Dermatol. 2026 Sep;12(5):471-480
https://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20262846

Systematic Review

Neurological complications of herpes zoster in adult patients receiving Janus kinase inhibitors: a systematic review

Luh Putu Indah Wahyuningtyas[1]*, Tjokorde Istri Amrita Rosvanti[2], Anak Agung Ari Agung Kayika Silayukti[2], Anak Agung Istri Saraswati Dewi[2], Made Hermina Laksmi[2]

[1]Mangusada Regional Hospital, Badung, Bali
[2]Department of Dermatology and Venerology, Mangusada Regional Hospital, Badung, Bali

Received: 23 June 2026
Revised: 15 July 2026
Accepted: 03 August 2026

***Correspondence:**
Dr. Luh Putu Indah Wahyuningtyas,
E-mail: putuindah8994@yahoo.com

ABSTRACT

Herpes zoster (HZ) is a recognized infectious adverse event among adult patients receiving Janus kinase (JAK) inhibitors. Although most cases are cutaneous, neurological complications such as post-herpetic neuralgia (PHN), meningitis, and encephalitis may cause substantial morbidity. This systematic review was conducted at the Dermatology and Venereology Department, Mangusada Regional Hospital, Badung, Bali, Indonesia. PubMed, Cochrane Library, and ScienceDirect were searched from 1 May to 15 May 2026 using terms related to HZ, neurological complications, and JAK inhibitors. Eligible studies included clinical trial safety analyses, observational studies, pharmacovigilance studies, and case reports. Seven studies were included and synthesized narratively because of clinical and methodological heterogeneity. Seven studies were included. Evidence consisted of one matched cohort study, one case report, three tofacitinib clinical safety analyses, one ruxolitinib cream safety analysis, and one pharmacovigilance study. Tofacitinib accounted for most systemic JAK inhibitor evidence. In ulcerative colitis studies, HZ occurred in 5.6-8.2% of tofacitinib-treated patients, with PHN reported in 0.3% and one case of HZ encephalitis/meningitis. In rheumatoid arthritis, PHN occurred after first HZ events in 6.9% of patients. A case report described severe HZ meningitis after tofacitinib, with residual visual loss and facial nerve paralysis. Ruxolitinib cream was associated with rare HZ and isolated PHN. Pharmacovigilance data detected PHN signals for tofacitinib, ruxolitinib, and baricitinib. Clinicians should anticipate HZ risk during JAK inhibitor therapy and promptly evaluate neurological symptoms.

Keywords: Herpes zoster, Janus kinase inhibitor, Tofacitinib, Post-herpetic neuralgia, Neurological complications

INTRODUCTION

Herpes zoster (HZ), or shingles, results from reactivation of latent varicella-zoster virus when VZV-specific cell-mediated immunity declines. It is often recognized as an acute vesicular eruption with dermatomal pain, but its clinical impact may extend beyond the skin. Neurological involvement can include PHN, cranial or peripheral nerve palsy, Ramsay Hunt syndrome, meningitis, encephalitis, myelitis, vasculopathy, and stroke.

A large matched cohort study in England showed that immunocompetent adults with HZ had increased neurological complication risk within three months of diagnosis, indicating that neurological disease is clinically meaningful even outside severe immunosuppression.[1,2]

Adults with immune-mediated inflammatory diseases may be particularly vulnerable because of immune dysregulation and exposure to immunomodulatory treatment. JAK inhibitors are now used in several inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and selected dermatologic diseases. These agents interfere with JAK-STAT signaling, a pathway involved in antiviral immune defense and interferon-mediated responses. Clinical trials and long-term safety analyses have repeatedly reported increased HZ risk, particularly with systemic tofacitinib, upadacitinib, and baricitinib, although most cases are described as mild or moderate cutaneous events.[3-7,16-18]

Despite this growing safety signal, the neurological complications of HZ during JAK inhibitor therapy remain insufficiently characterized. Many safety reports record HZ as a general infectious adverse event without separating uncomplicated rash from PHN, meningitis, encephalitis, cranial neuropathy, or other neurological outcomes. Case-level and pharmacovigilance evidence suggests that severe neurological manifestations can occur, but the overall pattern remains unclear.[8-10] This review therefore aimed to synthesize available evidence on neurological complications of HZ in adult patients receiving JAK inhibitors, with attention to clinical manifestations, implicated agents, risk factors, management, and outcomes.

METHODS

Study design

This systematic review evaluated evidence on neurological complications of HZ among adult patients receiving JAK inhibitors. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. Because the included studies differed in design, population, JAK inhibitor exposure, and neurological outcome reporting, the evidence was synthesized qualitatively rather than by meta-analysis.

Study setting, period, and sample size

This review was conducted at the Dermatology and Venereology Department, Mangusada Regional Hospital, Badung, Bali, Indonesia. The literature search, study selection, and data extraction were undertaken from 1 May to 15 May 2026. No a priori sample-size calculation was performed because all studies meeting the predefined eligibility criteria were included. The final review sample comprised seven studies.

Literature search strategy

A systematic search was performed in PubMed, Cochrane Library, and ScienceDirect from 1 May to 15 May 2026 to identify reports of HZ, PHN, meningitis, encephalitis, or other neurological complications related to JAK inhibitor exposure. The final database search was completed on 15 May 2026 and covered records available from database inception through that date. The search combined HZ-related terms with JAK inhibitor terms, including tofacitinib, ruxolitinib, baricitinib, and upadacitinib. The PubMed strategy was: ("herpes zoster" OR shingles OR "postherpetic neuralgia" OR "post-herpetic neuralgia" OR meningitis OR encephalitis) AND (tofacitinib OR ruxolitinib OR baricitinib OR upadacitinib OR "JAK inhibitor"). Similar search concepts were applied in Cochrane Library and ScienceDirect.

Eligibility criteria

Eligible studies reported adult patients with HZ or HZ-related complications in the context of JAK inhibitor exposure, or provided relevant background comparative evidence on neurological complications of HZ. Outcomes of interest included PHN, HZ meningitis, encephalitis, meningoencephalitis, Ramsay Hunt syndrome, cranial or peripheral nerve palsy, myelitis, vasculopathy, stroke, and broader neurological adverse events related to HZ. Eligible designs included clinical trial safety analyses, cohort studies, post hoc pooled analyses, pharmacovigilance studies, case series, and case reports. Studies were excluded if they involved only pediatric populations, reported varicella or herpes simplex without HZ, lacked JAK inhibitor exposure or relevant neurological outcomes, or did not provide sufficient clinical data. Reviews, editorials, commentaries, conference abstracts without full data, animal studies, and in vitro studies were also excluded.

Study selection and data extraction

All identified records were first screened by title and abstract. Records that were clearly unrelated to HZ, JAK inhibitor exposure, or neurological complications were excluded at this stage. Duplicate records were then removed. Full-text articles were assessed for eligibility when the title or abstract suggested relevance to the review question.

Disagreements or uncertainties during eligibility assessment were resolved through re-evaluation of the full-text article against the predefined inclusion and exclusion criteria.

Data were extracted using a structured extraction table developed specifically for this review. Data extraction was performed systematically using a standardized data extraction form to ensure consistency across all included studies.

The extracted information was organized into main tables. Any discrepancies during data extraction were reviewed and resolved through discussion among authors to improve accuracy and minimize extraction bias.

Risk of bias assessment

Risk of bias was assessed using appraisal tools appropriate to each study design. Randomized controlled trials and randomized clinical trial safety analyses were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool. Non-randomized interventional studies and post hoc interventional safety analyses were assessed using ROBINS-I. Observational cohort studies were evaluated using the Newcastle-Ottawa Scale (NOS). Diagnostic accuracy studies, if identified, were planned to be assessed using QUADAS. Case reports and case series were appraised using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports or case series, as appropriate. Pharmacovigilance studies were assessed using a design-specific appraisal approach focusing on database coverage, case definition, adverse-event coding, signal detection method, and reporting transparency.

RESULTS

Study selection

The database search identified 2,914 records, consisting of 456 records from PubMed, 319 from the Cochrane Library, and 2,139 from ScienceDirect. After title and abstract screening, 2,905 records were excluded because they were not relevant to the review question, did not address HZ -related neurological complications, or did not involve JAK inhibitor exposure or relevant comparator populations. This left 9 records for retrieval, among which 1 report not retrieved. Therefore, 8 full-text articles were assessed for eligibility. One full-text article was excluded because of inappropriate participant characteristics and study design. Finally, 7 studies were included in the qualitative synthesis. The study selection process is summarized in Figure 1.

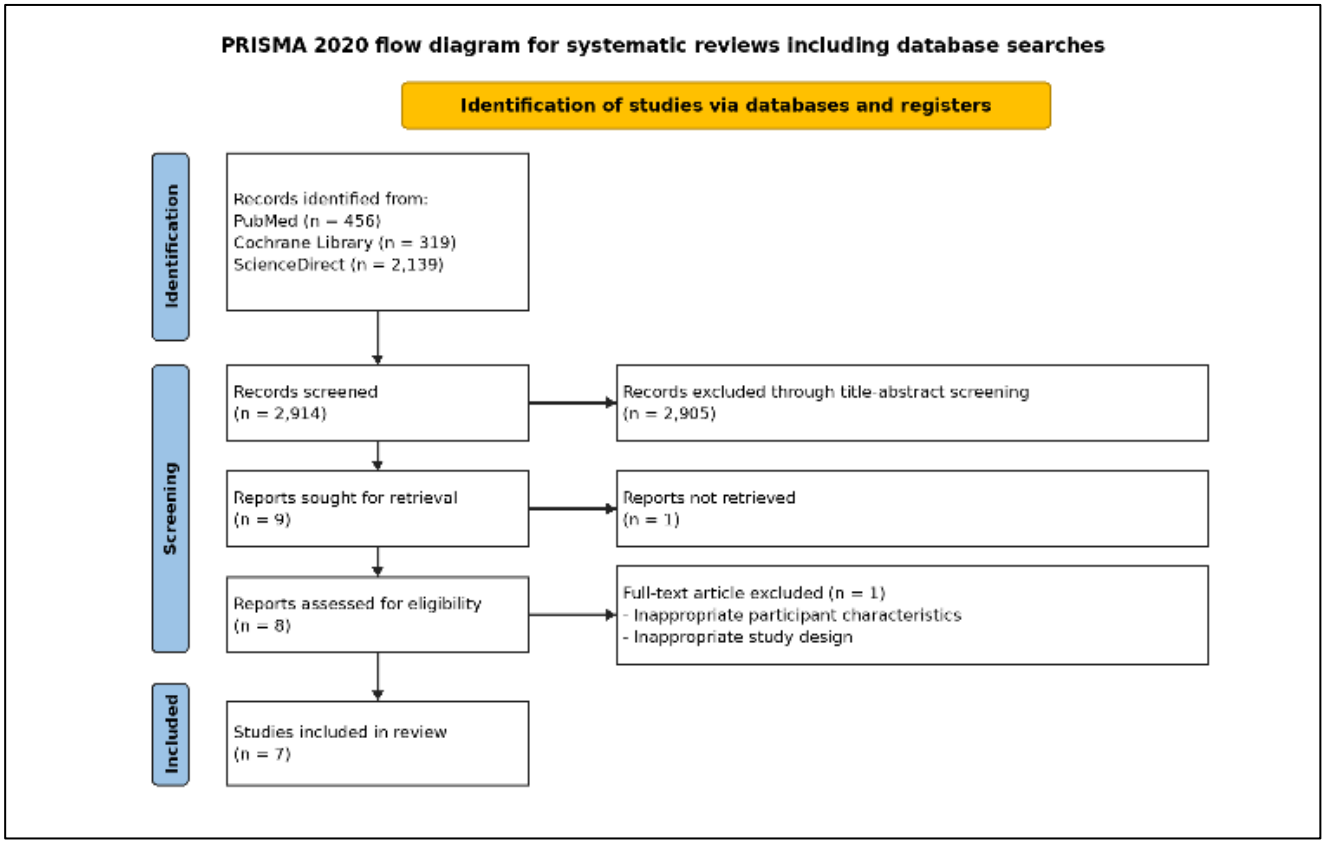

Figure 1: PRISMA 2020 flow diagram for systematic reviews which included searches of databases and registers only.

Study characteristics

The studies were published between 2018 and 2025 and used different designs, including matched cohort studies, case reports, integrated safety analyses of clinical trials, pharmacovigilance disproportionality studies, retrospective safety analyses, and post hoc pooled safety analyses. The sample sizes varied widely, ranging from a single case report to very large population or database-based studies involving tens of thousands to millions of participants or reports. This variation shows that the evidence was drawn from both individual clinical observations and large-scale safety or epidemiological datasets.

The underlying diseases varied across studies. Three studies focused on patients with ulcerative colitis receiving tofacitinib, one study involved patients with rheumatoid arthritis and psoriatic arthritis, one case report described an elderly patient with rheumatoid arthritis

treated with tofacitinib, one clinical trial safety analysis involved patients with nonsegmental vitiligo receiving ruxolitinib cream, and one large cohort study included immunocompetent adults with incident HZ. The pharmacovigilance study included adverse-event reports from multiple indications, with rheumatoid arthritis being common for tofacitinib and baricitinib, and myelofibrosis or polycythaemia vera being common for ruxolitinib. The baseline characteristics of the included studies are summarized in Table 1.

Table 1: Baseline characteristics of the included studies.

Authors	Publication year	Study design	Sample size	Age and sex of participants
Forbes et al[1]	2021	Matched cohort study	178,964 incident HZ cases and 1,799,380 age-, sex-, and practice-matched controls	Median age 62.1 years in HZ group and 61.5 years in controls; female sex 58.8% in HZ group and 58.4% in controls
Nakamura et al[8]	2022	Case report	1 patient	Male; in his 70s
Rosmarin et al[10]	2025	Integrated long-term safety analysis of phase 3 clinical trials	673 total patients; 637 exposed to ruxolitinib cream, contributing 867.9 person-years; 270 exposed to vehicle, contributing 131.1 person-years	Mean age 39.5±15.1 years; 72 patients aged 12-17 years; 358 female patients (53.2%)
Park et al[9]	2025	Pharmacovigilance disproportionality study	30,051,159 total drug reports analyzed; 105,798 tofacitinib reports, 43,661 ruxolitinib reports, and 11,963 baricitinib reports	For neurological AE reports: tofacitinib mostly female 82.7%, commonest age group 45-64 years; ruxolitinib had high missing age/sex data, with 51.9% unknown sex and 65.4% unknown age; baricitinib neurological AE reports were mostly female 83.0%
Winthrop et al[5]	2023	Post hoc integrated safety analysis of clinical trial program	1,157 patients receiving tofacitinib; total exposure 2,814.4 PY in the Overall Cohort and 2,999.7 PY in the Overall plus phase 3b/4 Cohort	Mean age 41.3 years; 6.7% aged ≥65 years; male 58.7%; most patients were White; 45.2% used corticosteroids at baseline; 51.9% had prior TNFi failure
Winthrop et al[6]	2018	Retrospective/post hoc integrated safety analysis of clinical trial data	1,157 tofacitinib-treated patients; total exposure 1,612.8 patient-years in the Overall Cohort	Mean age 41.3 years in Overall Cohort; female 41.3%; baseline corticosteroid use 45.2%; prior TNFi failure 51.9%
Winthrop et al[7]	2022	Post hoc pooled safety and clinical management analysis	RA: 7,061 patients, 22,875 PY exposure; PsA: 783 patients, 2,046 PY exposure	RA: patients with HZ had mean age 55.4 years for single HZ event and 56.0 years for ≥2 HZ events; female 83.3% and 90.5%, respectively. PsA: patients with HZ had mean age 49.0 years; female 61.1%

HZ burden among patients receiving JAK inhibitors

Across clinical trial and pooled safety datasets, HZ was consistently observed during JAK inhibitor therapy, particularly tofacitinib. In ulcerative colitis, Winthrop et al reported HZ in 65 of 1,157 patients (5.6%) in 2018 analysis, corresponding to 4.07 per 100 patient-years. In longer 2023 analysis, HZ occurred in 95 of 1,157 patients (8.2%), with incidence rate of 3.30 per 100 patient-years. Most events were nonserious, mild/ moderate, and resolved without permanent tofacitinib discontinuation.[5,6]

In rheumatoid arthritis and psoriatic arthritis, HZ burden differed by disease population. Among rheumatoid arthritis patients receiving tofacitinib, 783 of 7,061 patients (11.1%) had at least one HZ event, and 63 of those with HZ (8.0%) had recurrent events. Among psoriatic arthritis patients, 36 of 783 (4.6%) developed HZ, and only one patient had a second event.[7] This suggests that age, disease type, background immunosuppression, corticosteroid exposure, cumulative treatment history, and regional or ethnic factors may modify HZ risk. For ruxolitinib cream, HZ was rare, with two reported cases and one PHN event in the integrated vitiligo safety analysis.[10]

Neurological complications of HZ

The neurological complications identified across studies included PHN, HZ meningitis, HZ encephalitis or meningitis/encephalitis, and broader composite outcomes such as cranial or peripheral nerve palsy, transverse myelitis, Guillain-Barre syndrome, and stroke. PHN was

the most consistently reported neurological outcome in JAK inhibitor-specific evidence. In ulcerative colitis, PHN occurred in 3 of 69 HZ events in the 2018 tofacitinib analysis and in 4 of 1,157 patients (0.3%) in the longer 2023 analysis.[5,6] In rheumatoid arthritis and psoriatic arthritis, PHN occurred after first HZ events in 54 of 783 rheumatoid arthritis patients (6.9%) and 1 of 36 psoriatic arthritis patients (2.8%).[7]

Central nervous system involvement was uncommon but clinically important. Nakamura et al. described an elderly man with rheumatoid arthritis who developed HZ meningitis two months after starting tofacitinib 10 mg/day. He presented with seizure and coma, had cerebrospinal fluid findings consistent with meningitis, and improved after tofacitinib discontinuation and intravenous acyclovir; however, severe visual loss and facial nerve paralysis persisted.[8] In the ulcerative colitis tofacitinib program, one invasive HZ encephalitis case resolved after intravenous acyclovir and oral valacyclovir, and the later extended analysis reported one disseminated HZ meningitis/encephalitis event with noncutaneous organ involvement.[5,6]

The matched cohort study by Forbes et al. did not evaluate JAK inhibitor exposure but provided important baseline context. Among immunocompetent adults, HZ was associated with increased neurological complication risk within three months of diagnosis, with an adjusted hazard ratio of 3.63 compared with matched controls.[1] This supports the clinical relevance of neurological monitoring after HZ and strengthens concern when HZ occurs in immunomodulated patients. Summary of findings of the included studies as shown in Table 2.

Risk factors for HZ

Several risk factors for HZ were identified across the included tofacitinib studies. In ulcerative colitis, Winthrop et al found higher HZ incidence among older patients, Asian patients, patients with prior TNF inhibitor failure, patients using corticosteroids at baseline, and patients receiving tofacitinib 10 mg twice daily. Multivariable analysis identified older age and prior TNF inhibitor failure as independent risk factors. The extended Winthrop et al study similarly identified older age, lower weight, geographic region, and prior TNF inhibitor failure as significant risk factors. In the rheumatoid arthritis and psoriatic arthritis pooled analysis, HZ was more frequent among rheumatoid arthritis patients than psoriatic arthritis patients, and recurrence was also more common in rheumatoid arthritis. These findings indicate that HZ risk during JAK inhibitor therapy is not uniform across populations. Age, underlying disease, geographic or ethnic background, prior biologic treatment failure, corticosteroid exposure, and possibly dose intensity may influence the likelihood of HZ occurrence and recurrence.

Risk of bias assessment

Overall, the included evidence had low to moderate risk of bias. Three studies were judged low risk, including the large matched cohort study, the ruxolitinib cream safety analysis, and the 2018 tofacitinib ulcerative colitis analysis. Four studies were considered moderate risk because of post hoc design, spontaneous reporting, absence of direct comparator groups, few neurological events, overlap between earlier and later ulcerative colitis datasets, and limited capacity to infer causality. No study was judged high risk as shown in Figure 2.

Figure 2: Risk of bias assessment result.

Table 2: Summary of findings of the included studies.

Author, publication year	Population	HZ characteristics	Exposure	Comparison	Neurological complication reported
Forbes et al 2021[1]	Unvaccinated immunocompetent adults aged ≥18 years with incident HZ; patients with moderate/severe immunosuppression were excluded	Incident HZ identified from CPRD and HES records; complications assessed within 3 months after HZ diagnosis; antiviral prescription within 7 days of diagnosis was also evaluated	Not applicable; this study did not evaluate JAK inhibitor exposure and specifically focused on immune-competent adults	Matched adults without HZ; additional comparison among HZ cases according to antiviral prescription status	Composite neurological complications included cranial/peripheral nerve palsies excluding Ramsay Hunt syndrome, encephalitis, transverse myelitis, meningitis, GB syndrome, and stroke; Ramsay Hunt syndrome analyzed separately as zoster-specific complication
Nakamura et al 2022[8]	Adult man in his 70s with long standing rheumatoid arthritis for 30 years; previously treated with etanercept, abatacept, tocilizumab and golimumab, all of which had failed; methotrexate was discontinued because of pancytopenia	HZ diagnosed clinically based on rash with blister on the forehead, around the eye, and nose; patient was not vaccinated against HZ and had no previous history of chickenpox or shingles; treated with intravenous acyclovir 10 mg/kg every 8 hours for 2 weeks	Tofacitinib 10 mg/day started 2 months before admission, in combination with salazosulfapyridine 1000 mg/day; tofacitinib was discontinued during acute infection and restarted 6 weeks after admission with oral valaciclovir prophylaxis	None	HZ meningitis presenting with seizure and coma; CSF showed pleocytosis and elevated protein; brain MRI showed no abnormality. Additional sequelae included severe right-eye vision loss attributed to iridocyclitis with secondary glaucoma and right facial nerve paralysis
Rosmarin et al 2025[10]	Adults and adolescents aged ≥12 years with nonsegmental vitiligo involving ≤10% total body surface area, including facial and nonfacial depigmented areas	HZ was reported in 2 patients receiving ruxolitinib cream; both cases resolved with concomitant medication. 1 event occurred on treated area, but neither considered treatment-related by investigators Varicella reported in 1 additional patient receiving ruxolitinib cream	Topical ruxolitinib cream 1.5% twice daily; exposure assessed over up to 104 weeks. Vehicle cream was used during randomized phases/ withdrawal/ maintenance phases depending on study period	Vehicle cream exposure group	Postherpetic neuralgia was reported in 1 patient receiving ruxolitinib cream and was not considered treatment-related. No HZ meningitis, encephalitis, Ramsay Hunt syndrome, myelitis, vasculopathy/ stroke, or cranial/peripheral nerve palsy was reported
Park et al 2025[9]	Patients with adverse-event reports involving JAK inhibitors; major indications included rheumatoid arthritis for tofacitinib and baricitinib, and myelofibrosis/polycythaemia vera for ruxolitinib	HZ infection itself was not the primary exposure/outcome of this study. However, PHN was identified as a neurological adverse-event signal for all three JAK inhibitors: tofacitinib, ruxolitinib, and baricitinib	Tofacitinib, ruxolitinib, and baricitinib; dose, duration, route, and treatment indication were not consistently available in the pharmacovigilance dataset	All other drugs in VigiBase served as the disproportionality comparison background	PHN was detected as a neurological AE signal: tofacitinib, 35 reports, PRR 4.31, ROR 4.32, IC 2.03; ruxolitinib, 36 reports, PRR 10.78, ROR 10.79, IC 3.23; baricitinib, 10 reports, PRR 10.82, ROR 10.83, IC 2.88. Other neurological AE signals included memory impairment, dementia, peripheral neuropathies, sciatica, leukoencephalopathy, metabolic encephalopathy, vocal cord paralysis, and central nervous system vascular disorders depending on the drug

Continued.

Author, publication year	Population	HZ characteristics	Exposure	Comparison	Neurological complication reported
Winthrop et al 2023[5]	Adult patients aged ≥18 years with moderately to severely active ulcerative colitis receiving tofacitinib across induction, maintenance, long-term extension, and dose-reduction settings	HZ events were identified using MedDRA terms and externally adjudicated when involving >1 dermatome or serious events. In the Overall plus phase 3b/4 Cohort, 95/1,157 patients (8.2%) had HZ; >90% were nonserious, >90% mild/moderate, and >90% resolved without discontinuing tofacitinib. Seven patients (0.6%) had serious HZ, 12 patients (1.0%) had multidermatomal HZ, and 7 patients (0.6%) had disseminated HZ.	Oral tofacitinib 5 mg BID or 10 mg BID; induction mainly 10 mg BID; maintenance 5 mg or 10 mg BID; long-term exposure categorized by predominant dose 5 mg BID or 10 mg BID	Placebo in induction and maintenance cohorts; dose comparison between tofacitinib 5 mg BID and 10 mg BID in maintenance/long-term analyses	HZ meningitis/encephalitis was reported in 1 patient as a disseminated HZ event with noncutaneous organ involvement; PHN occurred in 4/1,157 patients (0.3%). Other disseminated noncutaneous events included keratitis and ophthalmic HZ, but no new noncutaneous disseminated HZ cases emerged with longer follow-up to 7.8 years.
Winthrop et al 2018[6]	Adult patients with moderate-to-severe ulcerative colitis receiving tofacitinib in induction, maintenance, or open-label extension trials	Overall, 65/1,157 patients (5.6%) developed HZ during tofacitinib exposure; 69 total HZ events occurred. Most events involved 1-2 adjacent dermatomes. Eleven patients had multidermatomal involvement, and 6 patients had disseminated HZ events. Five patients discontinued the study because of HZ, and 16 temporarily withheld tofacitinib. Antiviral therapy was given in 58/69 events	Oral tofacitinib 5 mg BID or 10 mg BID; 10 mg BID used in induction; 5 mg BID and 10 mg BID used in maintenance and OLE. Patients in the Overall Cohort were categorized by predominant dose	Placebo in induction and maintenance cohorts; dose comparison between tofacitinib 5 mg BID and 10 mg BID, especially in the fixed-dose Maintenance Cohort	One invasive case of HZ encephalitis occurred and resolved after intravenous acyclovir and oral valacyclovir. Postherpetic neuralgia was reported in 3/69 HZ events. No HZ-related deaths were reported
Winthrop et al 2022[7]	Adult patients with rheumatoid arthritis or psoriatic arthritis receiving tofacitinib in clinical studies	RA: 783/7,061 patients (11.1%) had ≥1 HZ event, and 63/783 (8.0%) had ≥2 HZ events. PsA: 36/783 patients (4.6%) had ≥1 HZ event, and 1/36 (2.8%) had a second HZ event. Most HZ events were non-serious, mild/moderate, and resolved. Most patients received antiviral therapy, commonly within 3 days of onset	Oral tofacitinib, mostly 5 mg BID or 10 mg BID; RA patients received tofacitinib as monotherapy or with csDMARDs; PsA patients received tofacitinib with csDMARDs	No direct non-JAK comparator; descriptive analysis across pooled tofacitinib-treated RA and PsA trial populations	PHN occurred after first HZ events in 54/783 RA patients (6.9%) and after second HZ events in 2/63 RA patients (3.2%). In PsA, PHN occurred in 1/36 patients (2.8%) after the first HZ event. No HZ-related deaths were reported. No CNS HZ complication such as meningitis, encephalitis, myelitis, or cranial nerve palsy was reported in the extracted results

DISCUSSION

Principal findings and interpretation

This review shows that HZ is a clinically relevant infectious adverse event in adults receiving JAK inhibitors, particularly systemic tofacitinib. Across the seven included studies, most HZ episodes were cutaneous, localized, nonserious, and resolved with antiviral treatment or temporary treatment interruption. However, HZ in this population should not be viewed as a minor complication. Neurological outcomes were less frequent than uncomplicated skin disease, but they were important because they can lead to persistent pain, ocular damage, functional impairment, or long-term neurological morbidity. PHN was the most consistently reported neurological complication, whereas meningitis, encephalitis, meningitis/encephalitis, facial nerve paralysis, multidermatomal disease, disseminated HZ, and ocular involvement were rare but clinically serious events.[5-8]

Biological plausibility

The link between JAK inhibitors and HZ is biologically plausible. Varicella-zoster virus remains latent in sensory ganglia after primary infection, and reactivation is mainly controlled by cell-mediated immunity. JAK inhibitors suppress signaling through the JAK-STAT pathway, including interferon-related antiviral defense. This may weaken immune surveillance against latent VZV and allow viral reactivation, especially in older or immunologically vulnerable patients. Neurological complications may develop when VZV spreads from sensory ganglia to the meninges, brain parenchyma, cranial nerves, spinal cord, peripheral nerves, or cerebral arteries. PHN is different because it is usually related to nerve injury and persistent neuroinflammation after reactivation, without requiring central nervous system invasion. This may explain why PHN appears more often than meningitis or encephalitis in available trial data.[4,9,11,12]

Comparison with previous evidence

These findings are consistent with broader evidence that autoimmune and inflammatory diseases increase HZ risk, and that immunosuppressive therapy can further increase this vulnerability. Therefore, HZ during JAK inhibitor therapy is probably caused by several overlapping factors rather than by the drug alone. Important contributors include older age, disease-related immune dysfunction, corticosteroid use, previous biologic failure, cumulative immunosuppression, higher JAK inhibitor dose, and possibly geographic or ethnic background.[3,7,13]

In ulcerative colitis studies, HZ occurred more often in older patients, patients with previous TNF inhibitor failure, corticosteroid exposure, Asian or certain geographic backgrounds, lower body weight, and higher dose intensity. Differences between rheumatoid arthritis and psoriatic arthritis may also reflect variation in age, concomitant therapy, disease biology, and prior immunosuppressive exposure.[5,6]

Additional evidence from other JAK inhibitors broadens the safety context. In pooled phase III trials, upadacitinib was associated with HZ incidence rates of 3.0 and 5.3 per 100 patient-years at doses of 15 mg and 30 mg, respectively, compared with 0.8 for methotrexate and 1.1 for adalimumab plus methotrexate.[16] Integrated baricitinib data similarly showed higher HZ incidence with baricitinib than placebo, while long-term tofacitinib data confirmed that HZ remained one of the most prominent infectious safety events during extended exposure.[17,18] A Taiwanese real-world cohort also identified previous HZ as an important clinical risk marker among patients receiving tofacitinib.[20] Collectively, these studies support HZ as a class-wide safety concern, although direct comparisons of neurological complication rates between individual JAK inhibitors remain limited.

Clinical implications

Early antiviral treatment appears important for improving outcomes. In rheumatoid arthritis and psoriatic arthritis analyses, most patients with HZ received systemic antivirals, commonly within three days of symptom onset, and most cases resolved. Evidence from immunocompetent adults also suggests that antiviral prescription is associated with a lower risk of neurological complications, supporting prompt treatment in patients receiving immunomodulatory drugs. Decisions about interrupting JAK inhibitor therapy should be individualized. Mild localized HZ may not require permanent discontinuation, but temporary interruption should be considered for serious, disseminated, ophthalmic, or neurological HZ.[1,7]

Vaccination is a major preventive consideration. Recombinant zoster vaccine is non-live and highly effective in older adults, making it more suitable than live-attenuated vaccine for many immunocompromised or immunomodulated patients. Current Advisory Committee on Immunization Practices recommendations support a two-dose recombinant zoster vaccine series for adults aged 19 years or older who are or will be immunodeficient or immunosuppressed because of disease or therapy.[19]

Ideally, vaccination status should be reviewed before elective JAK inhibitor initiation, especially in older adults, patients with prior HZ, corticosteroid users, patients with prior biologic failure, and those planned for systemic JAK inhibitor therapy. More evidence is still needed on vaccine timing, immunogenicity, durability, and its ability to prevent PHN or central nervous system complications in the JAK inhibitor-treated populations.[13-15,19]

Strengths

A key strength of this review is its specific focus on neurological HZ complications rather than treating HZ as a single undifferentiated adverse event. It integrates clinical trial safety data, real-world epidemiology, pharmacovigilance signals, and case-level evidence. The use of design-specific critical appraisal tools also allowed the methodological limitations of different evidence types to be considered systematically.

Limitations

The evidence base was heterogeneous in study design, population, JAK inhibitor exposure, outcome definition, and follow-up duration. Several included reports were post hoc analyses, and neurological outcomes were frequently reported with limited clinical detail. Severe central nervous system events were rare, some ulcerative colitis datasets overlapped, and one large comparator study did not involve JAK inhibitor exposure. Pharmacovigilance data were additionally affected by underreporting, stimulated reporting, missing clinical variables, and absence of denominator exposure data. These limitations prevented meta-analysis and precluded firm agent-specific incidence estimates or causal conclusions.

CONCLUSION

HZ is a clinically relevant safety concern among adults receiving JAK inhibitors, particularly systemic tofacitinib. Neurological complications were less frequent than uncomplicated cutaneous HZ but were meaningful when present. PHN was the most consistently reported neurological outcome, while HZ meningitis and encephalitis were rare but potentially severe. Most HZ events in trial datasets were mild or moderate, nonserious, and resolved with antiviral therapy and/or temporary treatment adjustment, yet isolated cases had persistent visual impairment and facial nerve paralysis.

Because available evidence remains heterogeneous and relies largely on post hoc safety analyses, pharmacovigilance data, and limited case reports, firm incidence estimates cannot yet be established. Nevertheless, clinicians should conduct proactive risk assessment, consider recombinant zoster vaccination before JAK inhibitor initiation, start antiviral treatment promptly when HZ is suspected, and monitor carefully for neurological symptoms in high-risk adults, especially older patients, corticosteroid users, patients with prior biologic failure, recurrent HZ, or systemic JAK inhibitor exposure.

Recommendations

Future prospective studies and safety registries should distinguish uncomplicated HZ from PHN, meningitis, encephalitis, myelitis, Ramsay Hunt syndrome, vasculopathy, stroke, cranial neuropathy, and ophthalmic-neurological involvement. Event-level reporting should include JAK inhibitor type, dose, route, duration, indication, vaccination status, previous HZ, concomitant immunosuppressive therapy, antiviral timing, treatment interruption, diagnostic confirmation, and long-term outcomes. Clinically, vaccination status should be reviewed before JAK inhibitor initiation, patients should be educated to report dermatomal pain or neurological symptoms promptly, and suspected HZ should receive early antiviral assessment and treatment.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Forbes HJ, Bhaskaran K, Grint D, Hu VH, Langan SM, McDonald HI, et al. Incidence of acute complications of herpes zoster among immunocompetent adults in England: a matched cohort study using routine health data. Br J Dermatol. 2021;184(6):1077-84.
2. Nagel MA, Niemeyer CS, Bubak AN. Central nervous system infections produced by varicella zoster virus. Curr Opin Infect Dis. 2020;33(3):273-8.
3. Yun H, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, et al. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases: Implications for Vaccination. Arthrit Rheumatol. 2016;68(9):2328–37.
4. Nash P, Kerschbaumer A, Dörner T, Dougados M, Fleischmann RM, Geissler K, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. Ann Rheumatic Dis. 2021;80(1):71-87.
5. Winthrop KL, Vermeire S, Long MD, Panés J, Ng SC, Kulisek N, et al. Long-term Risk of Herpes Zoster Infection in Patients With Ulcerative Colitis Receiving Tofacitinib. Inflammatory Bowel Diseases. 2023;29(1):85-96.
6. Winthrop KL, Melmed GY, Vermeire S, Long MD, Chan G, Pedersen RD, et al. Herpes Zoster Infection in Patients with Ulcerative Colitis Receiving Tofacitinib. Inflammatory Bowel Diseases. 2018;24(10):2258-65.
7. Winthrop KL, Curtis JR, Yamaoka K, Lee EB, Hirose T, Rivas JL, et al. Clinical Management of Herpes Zoster in Patients with Rheumatoid Arthritis or Psoriatic Arthritis Receiving Tofacitinib Treatment. Rheumatol Ther. 2022;9(1):243-63.
8. Nakamura Y, Honda D, Takizawa N, Fujita Y. Herpes zoster meningitis in a rheumatoid arthritis patient treated with tofacitinib. BMJ Case Rep. 2022;15(3):e247276.
9. Park S, Kim MK, Park SB, Kim DH, Byun YJ, Choi SA. Neurological Adverse Events Associated with the Use of Janus Kinase Inhibitors: A

Pharmacovigilance Study Based on Vigibase. Pharmaceuticals. 2025;18(3):394.
10. Rosmarin D, Pandya AG, Passeron T, Forman SB, Zdybski J, Amster M, et al. Long-Term Integrated Safety Summary of Ruxolitinib Cream in Phase 3 Clinical Trials of Patients with Vitiligo. Dermatol Ther (Heidelb). 2025;15(12):3703-16.
11. Moens U, Macdonald A. Effect of the Large and Small T-Antigens of Human Polyomaviruses on Signaling Pathways. IJMS. 2019;20(16):3914.
12. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. The Lancet Neurol. 2009;8(8):731-40.
13. 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.
14. Dooling KL, Guo A, Patel M, Lee GM, Moore K, Belongia EA, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. Am J Transplant. 2018;18(3):756-62.
15. 15. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. N Engl J Med. 2015;372(22):2087-96.
16. Winthrop KL, Nash P, Yamaoka K, Mysler E, Khan N, Camp HS, et al. Incidence and risk factors for herpes zoster in patients with rheumatoid arthritis receiving upadacitinib: a pooled analysis of six phase III clinical trials. Ann Rheum Dis. 2022;81(2):206-13.
17. Genovese MC, Smolen JS, Takeuchi T, Burmester G, Brinker D, Rooney TP, et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated integrated safety analysis. Lancet Rheumatol. 2020;2(6):e347-57.
18. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open. 2020;6(3):e001395.
19. Anderson TC, Masters NB, Guo A, Shepersky L, Leidner AJ, Lee GM, et al. Use of recombinant zoster vaccine in immunocompromised adults aged 19 years or older: recommendations of the Advisory Committee on Immunization Practices-United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(3):80-4.
20. Chen YJ, Chen YM, Huang WN, Chen HH, Liao TL, Chen JP, et al. Herpes zoster in rheumatoid arthritis patients receiving tofacitinib: a single-center experience from Taiwan. Medicine (Baltimore). 2020;99(41):e22504.

Cite this article as: Wahyuningtyas LPI, Rosvanti TIA, Kayika Silayukti AAA, Saraswati Dewi AAI, Laksmi MH. Neurological complications of herpes zoster in adult patients receiving Janus kinase inhibitors: a systematic review. Int J Res Dermatol 2026;12:471-80.