Prevention and management of herpes zoster in patients with rheumatoid arthritis and psoriatic arthritis: a clinical review

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ABSTRACT

The risk of herpes zoster (HZ) and HZ-related complications is increased in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) relative to the general population; therefore, HZ vaccination is recommended in these patient groups. In this literature-based review, we summarise the available evidence on the use of HZ vaccines in patients with RA and PsA, and discuss strategies for managing breakthrough infection. Currently available data show suboptimal rates of HZ vaccination among these patients and highlight a need for strategies to improve HZ vaccination programmes in clinical practice. Further clinical studies are also required to optimise the use of HZ vaccines in patients with RA and PsA, particularly with regard to determining the impact of different immunosuppressive therapy regimens on vaccine immunogenicity and, ultimately, efficacy, as well as the impact of vaccination on disease activity and safety.

Introduction

Herpes zoster (HZ; known as shingles) is caused by reactivation of latent varicella zoster virus (VZV), the causative agent of chickenpox (1). Approximately 20–30% of the general population will develop HZ during their lifetime (2, 3) with risk increasing with age, which is thought to be due to decreasing cell-mediated immunity against VZV (1, 2). HZ typically presents as a painful monodermatomal vesicular skin rash, although multidermatomal and disseminated disease can also occur (1, 3). Disseminated disease can be limited to the skin, but the central nervous system, lungs and other organs can also be involved (3). Ocular disease can occur and may result in longstanding visual disturbance, while neurological impairment and a short-term increased risk of stroke have also been described (2, 4, 5). Importantly, postherpetic neuralgia occurs in ≤30% of individuals with HZ, causing disability and an impairment in quality of life that can be long-lasting (2, 3, 5).

The risk of HZ in patients with autoimmune conditions, such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA), is generally 1.5–2-fold higher *versus* the general population (6, 7), due to disease-associated immune dysregulation and the use of immunosuppressive therapies (8, 9). The estimated incidence rate (IR) of HZ (data from 2007–2010) in healthy older subjects *versus* patients with RA and PsA, respectively, was 0.6 *versus* 1.5 and 1.3 per 100 person-years (PY) for ages 51–60 years, and 0.9 *versus* 1.7 and 1.6 per 100 PY for ages 61–70 years (6).

The increased HZ incidence and potential complications in patients with autoimmune conditions highlight a need to raise awareness of the risk and optimise prevention and management strategies. This literature-based review provides an overview of data on HZ prevention and management in patients with RA and PsA, including: current vaccination recommendations; vaccination rates and outcomes; barriers to vaccination and strategies to improve coverage; and management strategies for breakthrough HZ.

HZ risk in patients with RA and PsA receiving corticosteroids, csDMARDs, bDMARDs and tsDMARDs

HZ risk in patients with RA is influenced by age, disease therapy, geographical region, comorbidities and concomitant/background medications

(10, 11). Increased risk has been shown in studies involving corticosteroids and Janus kinase (JAK) inhibitors, while the risk associated with biologic disease-modifying antirheumatic drugs (bDMARDs), such as tumour necrosis factor inhibitors (TNFi), has been less consistent across studies.

Prednisone use was identified as an independent risk factor for HZ in a retrospective study of a US cohort with RA (10). Dose-dependent risks of corticosteroid use were identified at prednisone doses ≥7.5 mg/day (12) and ≥10.0 mg/day (13-15) *versus* no use, and with 1 mg/day increments (16), while lower doses did not increase the relative risk in two studies (12, 13). However, a dose-independent risk of prednisone use relative to no use has also been reported (15, 17). Conventional synthetic DMARDs (csDMARDs), including methotrexate, leflunomide, sulfasalazine and hydroxychloroquine, have also been reported to increase HZ risk *versus* no use in patients with RA, in some but not all studies (15, 17-19). However, data on the risk associated with use of methotrexate *versus* no use were inconsistent in meta-analyses (18, 19).

Treatment with certain bDMARDs may increase the likelihood of VZV reactivation due to effects on VZV-specific effector T cells (20), but there are inconsistencies in the available data on risk in patients with autoimmune diseases. In a US claims analysis, HZ IRs for bDMARDs in patients with RA varied from 1.95–2.71 per 100 PY, with the highest IR reported for infliximab, and risk relative to abatacept similar across all bDMARDs (21). In a Japanese RA cohort, crude HZ IR was 0.67 per 100 PY and risk was significantly elevated with TNFi use *versus* no use (odds ratio 2.28; p=0.03) but not with use of the non-TNFi bDMARDs, tocilizumab and abatacept (16). A retrospective study of patients with RA in Korea demonstrated an IR of 2.6 per 100 PY for bDMARDs overall, but found variable risk depending on the bDMARD, with higher HZ IRs for abatacept, rituximab and adalimumab (8.5, 3.9 and 3.7 per 100 PY, respectively) *versus* other bDMARDs (22). TNFi data demonstrated a small risk (hazard ratio 1.63) or no increased risk for TNFi overall *versus* csDMARD use in patients with RA or PsA (13, 14), and were inconsistent regarding relative risks of specific TNFi (13, 14).

HZ risk is reported to be higher for patients with RA treated with targeted synthetic DMARDs (tsDMARDs) in the JAK inhibitor class *versus* bDMARDs (19, 21), with a higher risk among older patients or those enrolled in clinical studies in Asia (23-25). Pooled analyses of data from baricitinib RA clinical studies reported an overall HZ IR of 3.0 per 100 PY for all baricitinib (23) and HZ IRs of 4.3 per 100 PY for baricitinib 4 mg and 1.0 per 100 PY for placebo over the placebo-controlled period (26), and an overall HZ IR of 6.5 per 100 PY for Japanese patients (27). Similarly, for tofacitinib, an increased risk of HZ was reported for patients from Asia, with HZ IRs of 8.0 and 8.4 per 100 PY for patients with RA from Japan and Korea, respectively, *versus* 4.0 per 100 PY across the tofacitinib RA clinical programme (24). Asian ethnicity has been associated with a numerical (non-significant) increase in risk of HZ *versus* white patients with RA (6). However, the underlying reasons why some Asian cultures may be uniquely susceptible to HZ when treated with JAK inhibitor therapy are not clear; genetic predisposition may explain some but not all of this increased risk (28). Concomitant corticosteroids have been shown to increase the risk of HZ *versus* tofacitinib monotherapy particularly when combined with csDMARDs (24, 29), and the risk was tofacitinib dose-dependent (24). The HZ IR was slightly lower in other tofacitinib disease programmes, possibly reflecting differences in study populations and underlying risk: 2.1 per 100 PY across the PsA programme (30) and 2.6 per 100 PY in the psoriasis programme, in which a dose-dependent risk was also observed (31). Phase 3 data for upadacitinib in RA suggested dose-dependent effects, with HZ IRs of 3.7 per 100 PY for the 15 mg dose and 7.0 per 100 PY for the 30 mg dose, *versus* 1.3 per 100 PY for adalimumab and 1.4 per 100 PY for methotrexate (32). Integrated analysis of data from seven Phase 2 and 3 trials of filgotinib reported HZ IRs of 1.1 and 1.7 per 100 PY for filgotinib 100 and 200 mg, respectively, *versus* 1.1 and 0.7 per 100 PY for methotrexate and adalimumab, respectively (33).

HZ vaccination recommendations in patients receiving immunosuppressive therapy for RA and PsA

Two vaccines are available for the prevention of HZ and postherpetic neuralgia in patients aged ≥50 years. An attenuated live zoster vaccine (Zostavax®; referred to as LZV) (34, 35) became available in 2006, and an adjuvant recombinant subunit vaccine (Shingrix®; referred to as HZ/su) (36, 37), administered as two injections 2–6 months apart, became available in 2017. The findings of a recent systematic literature review and network meta-analysis suggest that HZ/su is superior to LZV for HZ prevention in patients aged >50 years, but is associated with a significantly higher risk of injection-site reactions (38). However, the relative efficacy and safety of the vaccines in patients with autoimmune conditions have not been established and LZV is contraindicated in immunosuppressed patients (34, 35).

An overview of the available guidance/recommendations for HZ vaccination in immunocompromised patients and those with RA and PsA is provided in Table I (39-55). There are currently no World Health Organization recommendations on routine HZ vaccination for patients with autoimmune conditions, due to a lack of evidence (56). Recommendations for patients with autoimmune conditions are, however, included in several general guidelines on immunisation and infection, but rheumatologists often follow rheumatology society guidelines. Recommendations generally restrict the use of HZ vaccines in healthy adults to those aged ≥50 (HZ/su) or ≥60 (LZV) years, despite the approved indication. However, for patients receiving immunosuppressive therapies and those with RA or PsA, recommendations for the use of LZV from specialty societies extend to patients aged ≥50 years in recognition of the higher HZ risk.

In patients receiving csDMARDs, including those with RA or PsA, LZV

use is recommended; however, a delay of ≥2–4 weeks post-vaccination is proposed before initiating bDMARDs or tsDMARDs. LZV is not recommended during therapy with medium- to high-dose corticosteroids (*i.e.* >20 mg/day), bDMARDs or tsDMARDs. Despite a lack of evidence, recent guidance for PsA from the National Psoriasis Foundation includes HZ/su as the preferred vaccine, and recommends use for all PsA patients aged >50 years and for patients aged <50 years receiving concomitant with csDMARDs, bDMARDs or tsDMARDs, concurrent with these therapies if necessary (43). Similarly, German guidance recommends HZ/su in patients with RA aged ≥50 years, but does not provide any specific information regarding RA therapies (50). Serologic testing before HZ vaccination (*e.g.* glycoprotein-based enzyme-linked immunosorbent assay [gpELISA]) is not generally recommended, as prior exposure to VZV among those aged ≥50 years is almost ubiquitous, and the positive predictive value of a self-reported history of VZV is quite high (57). In addition, serologic testing is likely to be of limited value in elderly patients, due to the difficulty of interpreting whether a negative result is due to lack of VZV exposure or waning VZV antibody titres associated with accelerated immunosenescence (9). However, some guidelines recommend that serologic testing is considered before LZV use where there is uncertainty about VZV exposure history (45, 46), or for immunocompromised patients (55).

Restrictions on LZV in patients with RA or PsA receiving bDMARDs or tsDMARDs require temporary cessation to allow vaccination (*e.g.* a delay of 2–4 weeks pre-vaccination and another 2–4 weeks before resuming therapy), which could affect disease control. Similarly, the requirement to delay initiation of bDMARDs or tsDMARDs for 2–4 weeks post-vaccination could impact disease progression in patients with inadequate disease control on csDMARDs. Many clinicians and patients may be unwilling to pause or delay initiation of targeted therapy, making this practice problematic for LZV use in patients with autoimmune conditions. Given the paucity of evidence on HZ/su use in patients with autoimmune conditions, guidance from most health authorities is lacking for these populations, and extrapolation from the general population of older, relatively healthy patients may not be appropriate. There is a notable lack of evidence on HZ vaccine use in patients aged <50 years, due to restrictions on the use of available vaccines in this age group. VZV history and serology might be helpful in identifying patients aged <50 years who lack prior exposure to VZV (46), and are important to consider before use of LZV (a booster vaccine which is technically only meant for patients with prior VZV exposure). Such patients might be considered for primary VZV (chickenpox) vaccination prior to initiating immunosuppressive therapy (41). However, the risk of VZV transmission and subsequent reactivation of VZV from the attenuated live VZV vaccine needs to be weighed against the risk of acquiring VZV infection through natural exposure, which will be minimal in some countries, such as the US, where vaccination against VZV is routine and wild-type VZV strains in circulation is rare (58). HZ/su, being a non-live vaccine, could be theoretically used to provide primary immunity against VZV in any patient regardless of prior exposure.

HZ vaccination in patients with RA and PsA

HZ vaccination coverage for immunocompetent adults is below target (59), and vaccination rates in patients with RA and PsA have also been shown to be suboptimal, with rates <10% reported in multiple studies (Table II) (60-68).

A key reason for not vaccinating was lack of recommendation from a healthcare provider. In a cross-sectional study of 136 patients with RA in Canada, a vaccination rate of 5.6% was reported for the third quarter of 2015, with physician recommendation being the strongest predictor of vaccine uptake (61). Low vaccination coverage suggests a lack of awareness of HZ risk in patients with RA and PsA among clinicians and their patients, and uncertainty about vaccine efficacy and safety, despite data demonstrating the positive impact of the vaccine on HZ rates for up to 5 years in patients with autoimmune conditions (69, 70).

Evidence on use of HZ vaccines in patients receiving therapies for RA and PsA: safety, immunogenicity and efficacy

Few clinical studies investigating the safety, immunogenicity and efficacy of HZ vaccines in patients receiving immunosuppressive therapy for RA or PsA were identified (Table III) (71-76). Available data are largely from studies using LZV, and suggest that vaccination is feasible and safe in patients receiving RA therapy and does not increase disease activity; however, larger, controlled clinical studies are required to confirm this.

In a retrospective US claims analysis of data for 463,541 patients aged ≥60 years with immune-mediated diseases (including ~300,000 patients with RA and ~11,000 with PsA), there was one case of primary VZV infection within a 42-day window post-vaccination among the 18,683 (4%) patients who received LZV (70). Additionally, there were no primary VZV infections among 633 vaccinated patients receiving bDMARDs at time of vaccination or during the 42-day post-vaccination period (70). Longer-term follow-up indicated greater protection against HZ in the vaccinated *versus* unvaccinated matched cohort, but showed a decline in efficacy after 5 years (69). In an observational study of patients with RA receiving csDMARDs and/or low-dose corticosteroids, LZV was immunogenic and well-tolerated, and RA disease activity remained generally stable during 12 weeks post-vaccination (71) (Table III). LZV efficacy and safety has also been investigated in the National Institutes of Health-funded randomised, blinded, placebo-controlled VERVE trial of 617 patients, all of whom received TNFi (72) (Table III). During the 6-week post-vaccination period, there were no cases of wild-type or vaccine strain VZV, or viral reactivation (72). A prospective study has shown consistent results with LZV in patients receiving bDMARDs for RA or PsA (73) (Table III). LZV use was also investigated in a

Table I. Overview of recommendations on HZ vaccination for immunocompromised patients and patients with RA or PsA.

	Immunocompromised patients	Patients with RA	Patients with PsA
North America			
Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) (39, 40)	A single dose of LZV can be administered to patients aged ≥60 years (who have not previously received LZV) ≥2 weeks before immunosuppressive therapies, with a delay of 4 weeks after vaccination if possible Two doses of HZ/su can be administered to patients aged ≥50 years with chronic medical conditions taking low-dose immunosuppressants (*i.e.* <20 mg/day prednisone or equivalent) No recommendation yet for use of HZ/su for immunocompromised patients or those on medium- to high-dose immunosuppressants, or patients known to be VZV-negative	NR	NR
Infectious Diseases Society of America (IDSA) (41)	LZV can be administered to patients aged ≥60 years, and those aged 50–59 years with a history of VZV infection (seropositive), ≥4 weeks before immunosuppressive therapies LZV can be administered to patients aged ≥60 years on therapies considered to be low-level immunosuppressants LZV is not recommended for highly immunocompromised patients	NR	NR
American College of Rheumatology (ACR) (42)	NR	LZV can be administered to patients aged ≥50 years 2 weeks before starting bDMARD or tofacitinib therapy LZV should not be given while the patient is receiving bDMARDs	NR
National Psoriasis Foundation (NPF) (43)	NR	NR	LZV can be given to patients aged >50 years who are either not receiving systemic therapy or are on low-dose immunosuppressive therapy (*i.e.* <20 mg/day prednisone or equivalent or <0.4 mg/kg/week MTX) LZV should not be given to patients receiving bDMARDs or tsDMARDs, but may be administered if dose interruption is possible HZ/su is preferred and should be administered before initiation of systemic therapy where possible, but may also be given concurrently with csDMARDs, bDMARDs or tsDMARDs HZ/su should be given to all PsA patients aged >50 years and also to patients aged <50 years on tofacitinib, systemic corticosteroids or combination systemic therapy due to increased risk of HZ infection. Use in patients aged <50 years receiving other systemic therapies should be considered on a case-by-case basis, although this is off-label and may not be reimbursed
Canadian National Advisory Committee on Immunization (NACI) 2018 update (44)	HZ/su may be considered for immunocompromised patients aged ≥50 years on a case-by-case assessment of benefit:risk	NR	NR
Canadian Dermatology Association (CDA) Guidelines for Patients with Immune-Mediated Disorders (45)	LZV should be administered ≥2–4 weeks prior to initiation of immunosuppressive therapy in treatment-naïve patients LZV can be administered safely to patients at risk of HZ while receiving immunosuppressive therapy Serum status should be considered before use of LZV Hz/su is the preferred option for patients on immunosuppressive therapy	NR	NR

	Immunocompromised patients	Patients with RA	Patients with PsA
Europe			
European League Against Rheumatism (EULAR) (46)	NR	LZV can be administered to patients with AIIRD 4 weeks before initiating bDMARDs or tsDMARDs, but not during treatment Serum status should be considered before use of LZV to avoid primary infection No recommendation to-date on HZ/su due to lack of data in patients with AIIRD	
European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (47)	LZV can be administered to patients aged ≥50 years with a history of VZV or HZ infection and should be administered 4 weeks before immunosuppressive therapy LZV is contraindicated in immuno-compromised patients and HZ/su will be the vaccine of choice for these patients	NR	NR
Public Health England (PHE) (48)	Decision to give LZV should be based on clinical risk assessment Patients should receive vaccine ≥2 weeks before starting immunosuppressive therapy Patients with RA or other chronic inflammatory diseases receiving long-term, stable low-dose corticosteroids (prednisone ≤20 mg/day) with or without low-dose csDMARDs (*e.g.* MTX ≤25 mg/week, AZA ≤3 mg/kg/week, 6-MP ≤1.5 mg/kg/day) can receive LZV Patients who have received bDMARDs within 12 months, or short-term, high-dose corticosteroids (prednisone >40 mg/day for >1 week), long-term, low-dose corticosteroids (prednisone >20 mg/day for >14 days), or non-bDMARDs (*e.g.* MTX >25 mg/week, AZA >3 mg/kg/day, 6-MP >1.5 mg/kg/day) within 3 months should not receive LZV		
British Society of Rheumatology (49)	NR	HZ vaccination is recommended for patients with RA or PsA aged >50 years who have not received treatment with prednisone >40 mg/day for >1 week or >20 mg/day for >2 weeks, MTX >25 mg/week, or AZA >3 mg/kg/day within 3 months Patients should receive vaccine >2 weeks before initiating bDMARD	
German Standing Committee on Vaccination (STIKO) (50)	NR	HZ/su recommended for patients aged ≥50 years with RA	NR
Latin America			
Brazilian Society for Rheumatology (51)	NR	LZV recommended for patients aged ≥50 years with RA, and can be given while on standard-dose MTX	
Asia			
Korean Society of Infectious Diseases (52, 53)	LZV is recommended for adults aged ≥60 years without contraindication and for adults aged 50–59 years depending on individual health conditions LZV should not be administered to patients while receiving immunosuppressive therapy, except for low-dose systemic corticosteroids and low-dose MTX (<0.4 mg/kg/week), and should be administered ≥4 weeks before or after bDMARDs	NR	NR
Middle Eastern region			
Rheumatology and infectious disease expert group recommendations for Kuwait and the Arab Gulf region (54)	LZV is recommended for patients aged >50 years with inflammatory rheumatic diseases, including RA, and should be administered 2–4 weeks before initiation of csDMARDs, corticosteroids (>20 mg/day), bDMARDs or tsDMARDs		NR
Australia			
Australian Technical Advisory Group on Immunization (ATAGI) (55)	LZV is recommended for adults aged ≥60 years but should be considered on a case-by-case basis for immunocompromised patients and should be administered ≥4 weeks before initiating high-dose corticosteroids (prednisone >20 mg/day), csDMARDs, bDMARDs or tsDMARDs Serologic testing should be considered before vaccination for patients who anticipate being significantly immuno-compromised due to medical therapy	NR	NR

6-MP: 6-mercaptopurine; AIIRD: autoimmune inflammatory rheumatic diseases; AZA: azathioprine; bDMARD: biologic disease-modifying anti-rheumatic drug; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; HZ: herpes zoster; HZ/su: adjuvant recombinant subunit vaccine; LZV: live zoster vaccine; MTX: methotrexate; NR: not reported; PsA: psoriatic arthritis; RA: rheumatoid arthritis; tsDMARD: targeted synthetic disease-modifying antirheumatic drug; VZV: varicella zoster virus.

Table II. Rates of HZ vaccination among patients with rheumatologic conditions.

Country	Study/setting (year)	Patients (n)	Rates of vaccination	Reported reasons for not being vaccinated/factors associated with vaccination
Canada (60)	Patient survey in rheumatology clinics (2015)	RA (n=183)	3.8%	Lack of physician recommendation (49.1%) Concerns about vaccine efficacy/safety (26.3%) Lack of interest (14%) Age restriction (8.7%) Costs (1.7%)
Canada (61)	Patient survey in rheumatology clinic (2015)	RA (n=136)	5.6%	Physician recommendation was the strongest predictor of vaccine uptake
Canada (62)	Electronic medical records in primary-care setting (to 2015)	RA (n=1405)	13.8%	NR
China (63)	Patient survey in tertiary hospital setting (2017)	235 patients with rheumatic diseases, including 23 with RA	0%*	Unnecessary (8.9%) Troublesome to take (8.5%) Cost (3.0%) No reason (52.8%)
Mexico (64)	Patient survey in rheumatology clinic (2017)	84 patients with rheumatic disease, including 45.3% with RA	0%	Lack of indication from physician (34.5%)
United States (65)	Retrospective claims analysis (2006–2009)	RA (n=19,326) PsA (n=867)	37.4% 2.0%	Patients most likely to be vaccinated: Not using TNFi Aged 60–64 years Fewer comorbidities Fewer hospitalisations
United States (66)	Retrospective claims analysis (2006–2011)	RA patients initiating new bDMARD (n=29,129)	4.1% (2011)	NR
United States (67)	Patient survey in an academic rheumatology clinic (2013)	RA (n=102)	7.8%	Not recommend to them (52.7%) Did not think it was required (28.0%) Dislike/distrust of vaccine (6.5%) Physician/pharmacist recommended against (14.0%)
United States (68)	Electronic medical records of rheumatology outpatient clinics (2012–2013)	RA (n=1823)	10.1%	NR

*3.8% of patients had a physician recommendation for vaccination against influenza, pneumococcus or HZ.
bDMARD: biologic disease-modifying anti-rheumatic drug; HZ: herpes zoster; NR: not reported; PsA: psoriatic arthritis; RA: rheumatoid arthritis; TNFi: tumour necrosis factor inhibitor.

Phase 2 study including 112 patients initiating tofacitinib (with methotrexate) or placebo 2–3 weeks post-vaccination (74) (Table III). Immune responses to LZV were comparable in tofacitinib- and placebo-treated patients. During 12 weeks of tofacitinib treatment, one patient with no primary immunity to VZV experienced disseminated primary VZV, but there were no cases of reactivation (74). This case highlights the importance of considering serology before LZV use for patients with an unknown VZV history. Longer-term follow-up (up to 2 years) of 100 vaccinated patients who received tofacitinib showed a similar HZ IR *versus* the tofacitinib-treated population (HZ IR 3.6 per 100 PY) in the RA clinical programme (77, 78). Similarly, in a *post-hoc* analysis of the 1-year ORAL Strategy study, HZ IRs were comparable for patients who received LZV 4 weeks before initiating tofacitinib (IR 1.5 per 100 PY monotherapy [n=69/384; 18.0%] and 3.0 per 100 PY combination therapy with methotrexate [n=75/376; 19.9%]) and unvaccinated patients (IR 1.0 per 100 PY monotherapy [n=315/384; 82.0%] and 2.2 per 100 PY combination therapy with methotrexate [n=301/376; 80.1%) (79). Collectively, these data suggest LZV may be safe in patients with RA or PsA receiving bDMARDs or tofacitinib; however, it may not provide adequate long-term protection for patients initiating JAK inhibitor therapy, although the numbers of vaccinated patients in these studies was small. These data also need to be interpreted in the context of the limited efficacy (51%) of LZV reported in immunocompetent individuals aged ≥60 years after up to 4.9 years of follow-up (35). An investigational, inactivated VZV vaccine in development as an alternative to LZV for prevention of HZ and HZ-related complications in immunocompromised patients was well-tolerated and immunogenic in a Phase 2 study in patients with autoimmune diseases (including RA) receiving bDMARDs and non-bDMARDs (80).

The impact of HZ/su on RA disease activity and safety was investigated in a retrospective chart review of 403 patients, including 239 patients with RA (75) (Table III). In the 12 weeks post-vaccination, disease flares (6.7%) and side effects (12.7%) were mild and less frequent than in pivotal trials, and there were three HZ cases (75). However, case ascertainment for these outcomes was retrospective and *ad-hoc*; medical record review was performed *post-hoc* to identify whether patients called their rheumatologist with symptoms suggestive of disease flare or other side effects. No formal definition of flare nor longitudinal prospective assessment

Table III. Overview of clinical studies investigating safety and efficacy of licensed HZ vaccines in patients with RA or PsA.

Study	Patients	Therapy	Safety	Immunogenicity	Disease activity
LZV					
Observational study (71)	RA (n=41)	csDMARDs and/or low-dose corticosteroids	No cases of HZ during follow-up (median 1.6 years)	Significant increase in VZV specific ELISPOT SFU and anti-VZV IgG at Week 12 post-vaccination (both p≤0.001)	• DAS28 was stable between baseline and Week 12 • 6 patients (15%) had disease flare* during Weeks 6–12
Randomised, placebo-controlled Phase 2 study (VERVE) (72)	All (n=617) RA (n=368) PsA (n=151)	TNFi	• No wild-type or vaccine strain VZV at Week 6 • No adjudicated cases of HZ by Week 6	NR	NR
Prospective single-centre study (73)	Patients with RA, PsA or AS receiving IV (n=160) or SC (n=142) bDMARDs	bDMARDs (dosing interrupted at next scheduled dose to allow vaccination, and resumed 2 weeks post-vaccination)	• No HZ at 6 weeks post-vaccination • Two patients in the IV cohort had HZ at 16 and 20 months post-vaccination	NR	NR
Randomised, placebo-controlled Phase 2 study (74)	RA (n=112)	Tofacitinib 5 mg BID with background MTX initiated at 2–3 weeks post-vaccination	• One case of disseminated vaccine strain, primary VZV in a patient without prior VZV immunity in the tofacitinib group • No cases of HZ	• Geometric mean-fold increase in anti-VZV IgG at Week 6 post-vaccination was similar in the tofacitinib (2.11) and placebo (1.74) groups • Geometric mean-fold increase in VZV-specific T cell responses at Week 6 post-vaccination was similar in the tofacitinib (1.50) and placebo (1.29) groups	NR
HZ/su					
Single-centre retrospective study (chart review) (75)	RA and systemic rheumatic diseases (n=403)	csDMARDs Corticosteroids bDMARDs Tofacitinib	• 51 (12.7%) patients experienced mild side effects (injection-site soreness, fever, stomach ache, nausea and flu-like symptoms): 43 (10.7%) after the 1st dose and 12 (5.4%) after the 2nd dose • Three cases of HZ (single dermatome): 2 cases were in patients with RA receiving tofacitinib	NR	23 (5.7%) and 5 (2.3%) of patients, respectively, had disease flare[¥] after the 1st and 2nd doses of HZ/su
Retrospective study (chart review) (76)	Rheumatology (n=47) RA (n=36)	csDMARDs bDMARDs	• 6.4% of patients experienced non-severe side effects (fever, myalgia, fatigue, stomach upset) • No cases of HZ in patients with RA	NR	• No significant changes in CRP, RAPID3 score or prednisone dose after vaccination • Four patients with RA had disease flare[‖]

*DAS28 >1.1; [¥]Documented flares occurring up to 12 weeks after each dose, new prednisone prescription or increased dose of prednisone; [‖]Two of the four patients had discontinued csDMARD therapy.
AS: ankylosing spondylitis; bDMARD: biologic disease-modifying anti-rheumatic drug; BID: twice daily; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; DAS28: Disease Activity Score in 28 joints; ELISPOT: enzyme-linked immunospot; HZ: herpes zoster; HZ/su: adjuvanted recombinant subunit vaccine; IgG: immunoglobulin G; IV: intravenous; LZV: live zoster vaccine; MTX: methotrexate; NR: not reported; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RAPID3: Routine Assessment of Patient Index Data 3; SC: subcutaneous; SFU: spot-forming units; TNFi: tumour necrosis factor inhibitor; VZV: varicella zoster virus.

was available, and no data on the incidence or severity of severe *(i.e.* Grade 3) systemic reactogenicity were available. Additional small studies and *post-hoc* analyses of HZ/su have reported consistent safety and vaccine efficacy findings in patients with autoimmune conditions, including RA (76, 81).

Ongoing clinical studies of HZ vaccination in patients with RA include: a sub-study of VERVE, in which the impact of abatacept on LZV immunogenicity and safety will be investigated (NCT03604406); a 6-week open-label study of LZV administered before bDMARD or tofacitinib initiation (NCT03016884); and a Swedish study (VACCIMIL-ZOSTER; NCT03886038) on HZ/su use in patients initiating or already treated with JAK inhibitors.

Vaccination barriers in patients with RA and PsA

A variety of factors impact HZ vaccination uptake. Experience with LZV and HZ/su is relatively short *versus* other vaccines (*e.g.* meningococcus). Even with LZV, which has been available since 2006 (35), questions remain about the duration of protection, optimal vaccination age and booster vaccination strategy (54). The high incidence of Grade 3 or higher reactogenicity reported in trials of HZ/su in healthy older subjects (12%) (82) may influence uptake of the second required dose, making it difficult to determine duration of efficacy.

Access and reimbursement issues also impact vaccine coverage. HZ/su is not yet available in all countries and sup-

plies are limited, while in some areas, LZV is only available in a frozen and lyophilised form that requires thawing and reconstitution. In some regions, including the Middle East, government immunisation programmes do not all include HZ vaccination (54). Reimbursement generally varies for patients aged ≥50 *versus* ≥60 years (83, 84), and financial barriers (*i.e.* lack of reimbursement and out-of-pocket costs) negatively impact vaccination uptake among managed-care populations (84). There is also a lack of clear and consistent guidance on vaccine use in patients receiving immune-modifying therapies, and regarding which patients are a priority for vaccination. Most vaccinations occur in primary-care or community pharmacy settings rather than specialists' offices, and lack of resource and systematic approaches for documenting VZV infection and vaccination history, and lack of follow-up to confirm vaccine uptake, may impact vaccination rates (68, 83, 85). In the primary-care setting, physicians and healthcare providers may not be as familiar as rheumatologists with vaccination guidance for patients receiving immunosuppressants or the importance of considering concomitant therapy (68, 83). In addition, regional population differences, such as high numbers of temporary expatriates, may also contribute to suboptimal vaccination rates (54).

Strategies to improve vaccination coverage among patients with rheumatic diseases

Several approaches to modify prescriber behaviour have been investigated to improve HZ vaccination coverage, including use of vaccine reminders and schedules (68, 86), and decision support tools requiring active choices to determine eligibility for vaccination before bDMARD therapy (87). For example, a significant improvement in LZV vaccination rates from 10.1–51.7% ($p<0.0001$) was reported in a quality improvement project at 13 rheumatology outpatient clinics (n>1000) after implementation of an electronic medical records alert system combined with patient/staff education (68). A systematic literature review reported a statistically significant mean improvement in HZ vaccination rates of 21.8% (from 2.5–10.1%) after introduction of vaccination reminders to physicians and/or patients (86). Use of decision support tools to facilitate screening of patients for eligibility also improved rates of HZ vaccination among eligible patients from 25–42% (87). Scheduling HZ vaccination concurrent with other recommended vaccines for immunosuppressed patients (*e.g.* pneumococcal and influenza) may also improve vaccination coverage.

HZ management in patients receiving therapy for RA or PsA

For patients initiating immunosuppressive therapies, assessment of VZV/HZ history and HZ immunisation status is warranted, and vaccinations may need to be updated in line with current guidelines. For vaccinated patients with autoimmune conditions, reported IRs for HZ ranged from 0.75 per 100 PY in the first year to 1.25 per 100 PY in the seventh year (69). Given the increased risk of HZ complications associated with RA and PsA, it is important that patients receiving immunosuppressive therapy are closely monitored during and post-treatment, and that they receive education on the early signs/symptoms of primary VZV infection or viral reactivation.

Few patients with autoimmune conditions who come into contact with active VZV cases or HZ will need VZV immunoglobulin or antiviral prophylaxis (88). Most patients with autoimmune conditions have latent VZV infection, and such exposure does not present a risk (88); however, exposure should be avoided for those who lack primary immunity.

If a patient has had contact with individuals with VZV, or direct exposure to exposed HZ lesions, VZV immunoglobulin and prophylactic antivirals should be considered as part of a risk-dependent management approach based on VZV history, vaccination and serologic status, and immunosuppressive therapy use (88, 89). For example, the Centers for Disease Control and Prevention recommend administration of VariZIG® as soon as possible and within 10 days of VZV exposure for patients who are at high-risk for severe varicella and complications, including those who are immunocompromised and lack immunity to VZV (89).

Symptoms of vesicular rash (most commonly in the thoracic region), mild-to-moderate pain localised to the rash area, and general malaise are suggestive of VZV or HZ reactivation (90). In a small proportion of cases, HZ can present without skin involvement (*e.g.* symptoms of ocular HZ can include conjunctivitis or uveitis), and molecular or immunologic testing is recommended to confirm the diagnosis in such cases (90). In cases of HZ reactivation, immunosuppressive therapy should be interrupted until infection has resolved; this is a specific recommendation in the prescribing information for rituximab, baricitinib and upadacitinib (91-93). Interruption or avoidance of therapy is also recommended for tofacitinib during active serious infections, including localised infections (94). Experience with a JAK inhibitor demonstrated a rate of HZ of ~4% per year (29), with rare central nervous system or visceral involvement, mostly monodermatomal cases, and no known deaths (24, 25), and has shown that treatment can be resumed post-infection with no impact on the likelihood or severity of a subsequent HZ event (24, 31).

Standard antiviral treatment (*e.g.* oral acyclovir, valacyclovir, famciclovir or brivudine for ≥7 days until lesions have crusted over) started within 48–72 hours will limit rash symptoms and reduce acute pain (88, 90). Intravenous acyclovir can be used for multidermatomal or disseminated HZ (88, 90). Evidence from a claims analysis has also shown an association between prompt antiviral treatment (within 7 days of onset) and a lower risk of stroke (4, 90). However, findings from a UK study suggest that antivirals are often not prescribed for patients with RA presenting with HZ (95), possibly due to presenting too late (*i.e.* >3 days) after symptom onset or physicians not considering antiviral treatment necessary (95). For recurrent HZ, prophylactic treatment with antivirals could be considered, but there are limited data to

support this. Non-steroidal anti-inflammatory and opioid analgesics are also helpful for controlling acute pain (90). There is some evidence that high-dose prednisone with acyclovir can improve pain and quality of life in immunocompetent adults with HZ; however, this has only been demonstrated in a few short-term studies (96, 97).

Longer-term options for pain management will be required for patients who develop postherpetic neuralgia characterised by chronic pain of ≥3 months' duration and abnormal sensations (90, 98). Short-term use of opioids and neuropathic pain medications (*e.g.* pregabalin, gabapentin, tricyclic antidepressants, and capsaicin or lidocaine patches) have been used successfully in the general population (90). Other HZ manifestations may require a multidisciplinary care team, involving neurologists or ophthalmologists, or hospitalisation (90).

Conclusions

There is a need for increasing physician/healthcare provider awareness and education about the risk of HZ and its complications among patients with RA and PsA, particularly as an elevated risk has been demonstrated in studies of patients receiving corticosteroids or JAK inhibitors. Guidelines generally recommend HZ vaccination in patients aged ≥50 years on low-dose immunosuppressants, but advise a delay or treatment interruption when using LZV in patients on higher doses of corticosteroids or DMARDs. HZ/su experience in immunocompromised patients is limited, but initial observational studies suggest use is feasible and well-tolerated, and some guidelines recommend it as the preferred option, despite limited data on the magnitude and duration of benefit, and the risk of disease flare or severe reactions. HZ vaccination rates among patients with RA and PsA are suboptimal and strategies need to be implemented in specialist and primary-care settings to improve vaccination programmes for patients at risk. Ongoing clinical studies will provide further information on which patients are at greatest risk, and how the use of available HZ vaccines can be optimised.

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