Herpes zoster and Janus kinase inhibition in rheumatology and gastroenterology patients: managing risk and vaccination

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ABSTRACT

Patients with chronic inflammatory diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis (UC), have an increased risk of herpes zoster (HZ) infection, compared with the general population. This risk is further increased by the use of immunomodulatory therapies, with a higher incidence of HZ reported in patients receiving Janus kinase (JAK) inhibitors, compared with those receiving other immunomodulatory or biological therapies.

Tofacitinib is an oral JAK inhibitor for the treatment of RA, PsA and UC. In this narrative review, we discuss the effects of tofacitinib and other JAK inhibitors on HZ risk in patients with RA, PsA and UC, and strategies for risk management. We also discuss current UK guidelines for HZ vaccination in healthy individuals and patients with chronic inflammatory diseases, consider selected international guidelines, and review current HZ vaccination strategies.

Introduction

Varicella zoster virus (VZV) infections are prevalent globally (1, 2). Most acquire the virus during childhood, and it has been estimated that >90% of VZV infections occurred before adolescence in temperate, high-income countries in the prevaccination era (3). The age of VZV occurrence varies geographically (3, 4), and ethnicity may affect VZV seropositivity (4). Primary VZV infection results in varicella (chickenpox), and once initial symptoms have resolved, VZV establishes latency in the cranial nerve, autonomic and dorsal root ganglia cells, and can re-emerge many years later, resulting in herpes zoster (HZ) infection (shingles) (1, 2). Approximately half of adults will have ≥1 episode of HZ by the age of 85, and risk increases with age (2, 3), with five cases of HZ per 1000 patient-years (PY) in those aged 50–59 years, increasing to approximately 11 cases per 1000 PY in those aged ≥80 years (5). Furthermore, 68% of HZ cases occur in those aged ≥50 years (2). Immunocompromised patients and those of older age are at higher risk of developing HZ complications (6). One of the most common complications of HZ infection is postherpetic neuralgia, where chronic pain can develop, which can have a detrimental impact on quality of life (6). Dermatomal complications can arise, such as secondary bacterial infections, segmental paresis and ophthalmic complications, although these are less common (6). Disseminated HZ has been described in immunocompromised individuals and, when in in visceral locations, has been shown to lead to pneumonia, encephalitis and hepatitis (6, 7).

Incidences of HZ infection are higher in patients with chronic inflammatory diseases compared with the general population (8), and may be further increased in patients receiving corticosteroids and other immunomodulatory therapies (9-12). A UK HZ vaccination programme was introduced in September 2013 for individuals aged 70–79 years with a functioning immune system (*i.e.* immunocompetent) (13). Adults are eligible for routine HZ vaccination on their 70th birthday, while a catch-up programme exists for those aged >70 years who have not previously been vaccinated; these individuals are eligible for HZ vaccination from their 78th to 80th birthdays (14). The data suggest that 2.8% and 4.1% of individuals invited to receive HZ vaccination in the routine and catch-up cohorts, respectively, were identified as being in clinical risk groups where use of live HZ vaccination is contraindicated (14). Cumulative coverage from the

national immunisation programme is reported as 47.9% for individuals aged 71 years and 76.8% for those aged 76 years (15).

In this narrative review, we summarise the data on HZ risk with Janus kinase (JAK) inhibitors (primarily tofacitinib), risk management strategies, and UK vaccination policy in relation to HZ.

Rheumatoid arthritis, psoriatic arthritis and ulcerative colitis: disease characteristics and treatment options

In the UK, rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis (UC) have an estimated prevalence of 0.67%, 0.19% and 0.24–0.43%, respectively (16-19). RA incidence is approximately two-fold higher in women *versus* men, and increases with age, with onset most common at ≥60 years (16, 20, 21). In contrast, PsA and UC incidence appears similar in men and women, and patients are generally younger than those with RA (PsA: age of onset, 33–60 years; UC: peak age of onset, 15–25 years [a second, smaller peak has been reported in those aged 55–65 years, although this has not been universally confirmed]) (22-24).

For patients with chronic inflammatory diseases, the aim of treatment is to achieve remission or low disease activity through a treat-to-target strategy. Many patients cycle through multiple treatments, including immunomodulatory, biological or targeted synthetic therapies. In addition, background/concomitant steroids continue to be used to manage flares. Patients begin first-line treatments, such as methotrexate (for RA and PsA) or 5-aminosalicylic acid (for UC), and if the response is inadequate, treatment can be advanced to options such as biological therapies, including tumour necrosis factor inhibitors (TNFi) approved for RA, PsA or UC, anti-CD20 inhibitors (for RA), interleukin (IL)-6 inhibitors (for RA), T-cell co-stimulation signal modulators (for RA and PsA), IL-17 inhibitors (for PsA), IL-12/23 inhibitors (for UC), integrin inhibitors (for UC), or targeted synthetic therapies (*e.g.* JAK inhibitors; for RA, PsA and UC) (25-30).

HZ in patients with chronic inflammatory immune diseases

In an analysis of real-world data, age- and gender-standardised HZ incidence rates were approximately 1.3–3.8-fold higher in patients with chronic inflammatory diseases, compared with the general population (8). HZ risk has been shown to further increase in those receiving immunomodulatory treatments (9, 10, 12, 31-33).

While the precise reason for increased HZ risk in patients with chronic inflammatory diseases is unknown, VZV reactivation mechanisms are likely to be multifactorial, and may be influenced by age, ethnicity and/or genetic predisposition (2-4, 34, 35), as well as altered immune status due to disease activity, immunomodulatory therapy, and polypharmacy approaches in patients with comorbidities, which may interact synergistically to influence overall HZ risk.

JAK/signal transducers and activators of transcription pathway

Cytokines can bind to a variety of receptors on immune cells to initiate signalling cascades which activate and regulate immune responses. The JAK/signal transducers and activators of transcription (JAK/STAT) signalling pathway is a key modulator of cytokine signalling during the immune response. Signalling through cytokine receptors requires transactivation of two associated JAK isoforms (JAK1, JAK2, JAK3, tyrosine kinase [Tyk]2), which work as heterodimers (*e.g.* JAK1/JAK3; Fig. 1A) or, in the case of JAK2, a homodimer (JAK2/JAK2) (36-41).

The JAK/STAT pathway plays an important role in viral infection defence. Binding of pathogens to pattern recognition receptors activates factors that induce the transcription of interferons (IFNs), *e.g.* IFNα, IFNβ and IFNγ (38, 40). Binding of IFNs to extracellular receptors activates JAK/STAT signalling via transactivation of JAK homo/heterodimers, with type I IFNs (*e.g.* IFNα and IFNβ) (41) thought to play a more prominent role in antiviral responses than the type II IFN (IFNγ). IFNα and IFNβ signal via JAK1/Tyk2 heterodimers, resulting in the formation of the IFN-stimulated gene factor 3 (ISGF3) complex, which is responsible for transcriptional activation of multiple IFN-stimulated genes (ISGs). ISGs are involved in antiviral responses, via direct mechanisms, such as disruption of virus replication, or indirect mechanisms, such as signalling to innate immune cells *e.g.* natural killer cells (Fig. 1B) (36, 38, 41).

VZV infection results in the disruption of IFN-induced intracellular JAK/STAT signalling via JAK1/Tyk2, through inhibition of both STAT1 and IFN regulatory factor 9 (IRF9), integral to the expression of ISGs (Fig. 1C) (42, 43). Thus, VZV can disrupt innate antiviral immune responses, leading to viral reactivation (36, 44, 45). Therefore, inhibition of JAK1 may mimic VZV inhibition of IFN-induced antiviral activity, influencing the risk of VZV reactivation.

Current clinical experience and observed HZ rates with tofacitinib and other JAK inhibitors

Tofacitinib is an oral JAK inhibitor for the treatment of RA, PsA and UC (46, 47). Tofacitinib preferentially inhibits downstream signalling of common γ-chain receptors that associate with JAK1 and/or JAK3. Tofacitinib-mediated inhibition attenuates signalling of several cytokines, including IL-2, IL-4, IL-6, IL-7, IL-9, IL-15 and IL-21, as well as type I/II IFNs, resulting in modulation of immune and inflammatory responses (48-51). The efficacy and safety of tofacitinib and biological therapies have been shown to be generally similar (52-54), although increased risk of HZ and venous thromboembolism has been reported with tofacitinib *versus* biological therapies (9, 55, 56). Details of approved posology in clinical use in the UK and incidence rates (IRs; number of unique patients with events per 100 PY) for HZ, are shown in Table I.

In patients with RA, data pooled from phase I, II, III, IIIb/IV and long-term extension (LTE) tofacitinib studies found that HZ IR was 3.5–3.7, 92.7% of patients had non-serious HZ (*i.e.* did not require in-patient hospitalisation or prolonging of existing hospitalisation; did not result in persistent/significant disability/incapacity, congenital anom-

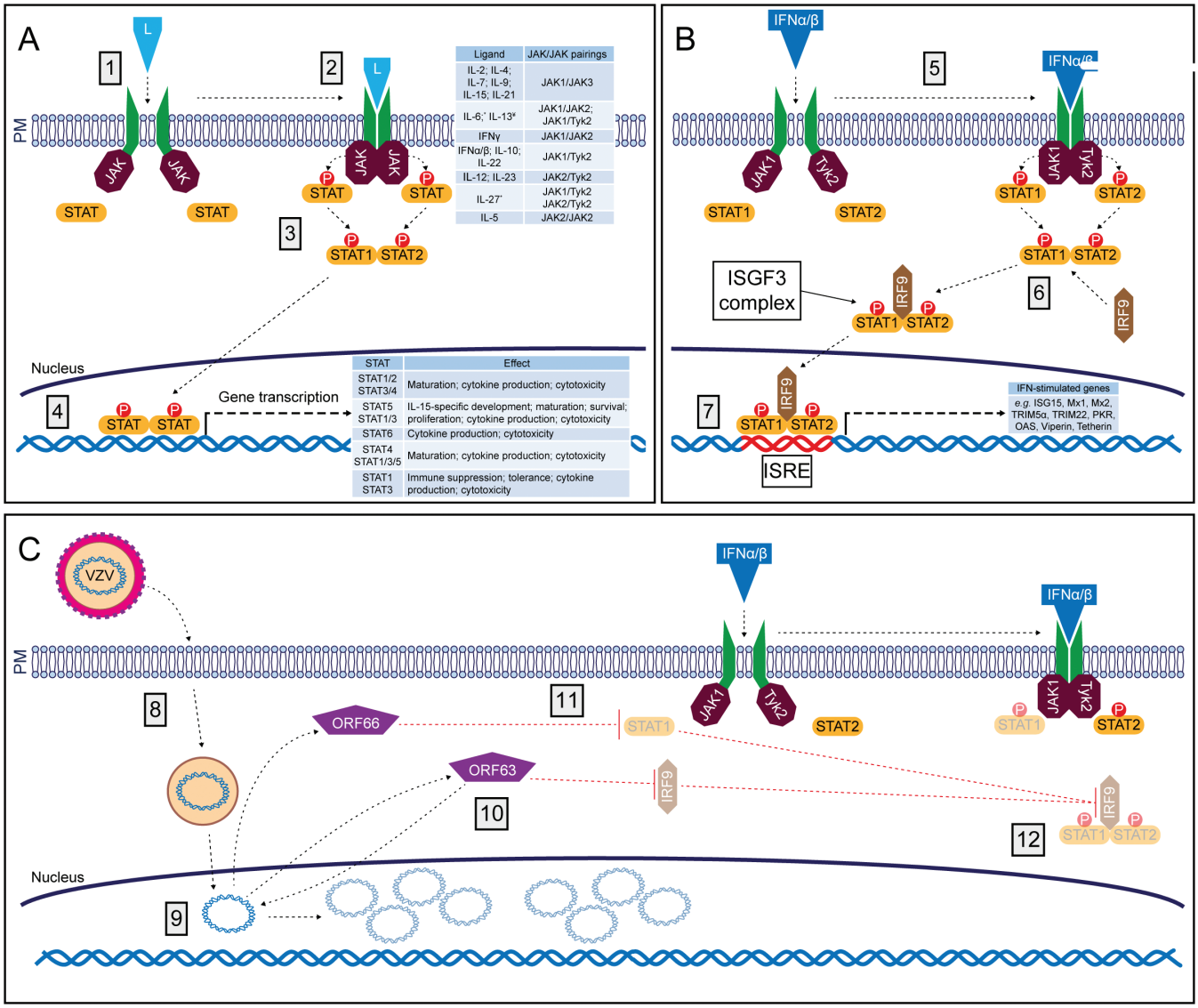

Fig. 1. A. JAK/STAT signalling pathway; **B**. Activation of JAK/STAT signalling by IFNα/β; and **C**. VZV-induced inhibition of JAK/STAT signalling.
A: 1. Ligands (*e.g.* cytokines or growth factors) bind to transmembrane receptors; 2. Binding induces conformational changes which bring two receptor-bound JAKs into close proximity, resulting in JAK transactivation; 3. Activated JAKs phosphorylate STAT monomers, leading to the formation of STAT dimers; 4. STAT dimers translocate to the nucleus and bind to specific gene regulatory sequences, inducing transcription of target genes.
B: 5. IFNα/β binding leads to transactivation of JAK1/Tyk2, resulting in phosphorylation of STAT1 and STAT2; 6. STAT1/STAT2 dimer binds to IRF9, forming the ISGF3 complex; 7. ISGF3 complex binds to ISRE promoter site, leading to transcription of ISGs (38, 41).
C: 8. VZV fuses with PM leading to uncoating of viral capsid; 9. Viral capsid translocates to nucleus and hijacks cellular DNA replication and gene transcription machinery; 10. Viral proteins are expressed, including ORF63 and ORF66; 11. ORF63 can regulate both viral and cellular gene transcription, and induces IRF9 protein degradation, leading to a reduction in steady-state levels of IRF9; 11. ORF66 inhibits STAT1; 12. Inhibition of IRF9 and STAT1 prevent the formation of the ISGF3 complex, thus inhibiting IFN-induced gene transcription (42, 43).
*Type II cytokine receptors (*e.g.* gp-130 subunit-sharing receptors), including IL-6 and IL-27, mainly signal via JAK1, but are also associated with JAK2 and Tyk2.
¥IL-13 signals via receptors associated with JAK1 and JAK2 or Tyk2 (36-39).
JAK: Janus kinase; STAT: signal transducers and activators of transcription; IFN: interferon; VZV: varicella zoster virus; PM: plasma membrane; L: ligand; IL: interleukin; Tyk: tyrosine kinase; ISGF3: ISG factor 3; IRF: IFN regulatory factor; ISG: IFN-stimulated gene; ISRE: IFN-stimulated response element; Mx: myxovirus resistance; TRIM: tripartite motif; PKR: protein kinase R; OAS: 2',5' oligo-adenylate synthetase; ORF: open reading frame.

aly/birth defect or death; was not life-threatening; was not otherwise determined to be an important medical event in the opinion of the investigators opinion; or did not require treatment with parenteral therapy]), and most (90.2%) involved only a single dermatome.

In multivariate analyses, HZ risk was significantly increased in older *versus* younger patients, in ex-smokers *versus* those who never smoked, in patients receiving baseline corticosteroids (all doses *versus* no use), and in patients receiving higher *versus* lower tofacitinib doses. Compared with other geographical regions, HZ risk was significantly higher in the Asia region (defined as Japan, Republic of Korea, Thailand/Malaysia/Philippines, India and China/Taiwan), mainly due to elevated HZ IRs in the Republic of Korea and Japan (57).

Real-world data indicate that HZ risk is increased approximately two-fold in patients with RA receiving tofacitinib, compared with those receiving biologic disease-modifying anti-rheumatic drugs (bDMARDs) (9, 58). In the US CorEvitas RA registry, HZ IRs (events per 100 PY) were 1.6 (95% confidence interval [CI] 1.0–2.4) and 0.7 (95% CI 0.5–0.9) with tofacitinib and bDMARDs, respectively; all HZ cases with tofacitinib were non-serious (58).

HZ IRs have also been reported for JAK1 inhibitors, including baricitinib, upadacitinib and filgotinib (Table I) (59-61). In an integrated analysis of data from phase III/II/Ib studies and one LTE study of baricitinib in RA, HZ IRs were higher for baricitinib 2 mg (IR 3.1) and 4 mg (IR 4.3; $p \leq 0.01$) *versus* placebo (IR 1.0) to Week 24, with rates remaining stable through 6 years (59). Most of the 258 reported HZ infections were mild or moderate in severity; serious infections occurred in 12% of patients, and 8.5% of patients had infections that were classed as multidermatomal (59). In patients receiving any baricitinib dose, older age and geographic region (Asia [excluding Japan] and Japan) were independent factors associated with increased risk of HZ (59). Similar findings were reported in an integrated analysis of data from the upadacitinib phase III programme for RA, which reported higher rates of HZ IRs for upadacitinib 15 mg (IR 3.5) and 30 mg (IR 6.2) *versus* placebo (IR 1.2), as well as adalimumab (IR 1.1) and methotrexate (1.4) (60). In both upadacitinib treatment groups (15 mg and 30 mg), most HZ cases were non-serious (96% and 93%, respectively) and limited to a single dermatome (74% and 76%, respectively) (60). In patients who received upadacitinib 15 mg, higher risk of HZ was seen for patients who were Asian, aged ≥50 years or had a history of HZ (60). In an integrated analysis of data from the phase II and phase III studies of filgotinib in patients with RA, HZ IRs were low overall, but numerically higher for filgotinib 200 mg (IR 1.7) *versus* placebo (IR 1.0), adalimumab (IR 0.7) and methotrexate (IR 1.1) (61). HZ IR for filgotinib 100 mg (IR 1.1) was similar to placebo and methotrexate (61). In multivariate analyses, factors associated with an increased risk of HZ included older age (≥50 years), the Asian region and prior HZ (62).

Patients with PsA are generally younger than patients with RA, have lower rates of corticosteroid use, and lower incidences of HZ (8, 22). Data pooled from two phase III studies and one LTE study of patients with PsA described an HZ IR of 2.0–2.7 in those receiving tofacitinib (Table I), compared with an HZ IR of 0.8–2.0 in an observational cohort of patients with PsA receiving conventional synthetic DMARDs (cs-DMARDs), bDMARDs or apremilast (63). HZ cases in phase III and LTE tofacitinib studies in PsA were mostly non-serious (64-66). In an interim analysis of the EQUATOR-2 open-label extension study of filgotinib 200 mg QD, HZ IRs (events per 100 PY) were 0.6 at Week 52 and 0.8 at Week 100 (67). In the SELECT-PsA 2 study of upadacitinib, HZ IRs were 3.8 and 8.5 in 15 mg and 30 mg upadacitinib, respectively, through Week 56 (68).

Patients with UC are generally younger than patients with RA (22-24). Data pooled from phase II, phase III and LTE studies included in the tofacitinib UC clinical programme found similar HZ IRs in patients receiving tofacitinib 5 mg twice daily (BID) compared with 10 mg BID (IRs of 3.4 and 3.5 respectively; Table I). No increased risk was observed with increasing tofacitinib exposure, and >90% of HZ were non-serious (69). Age and prior inadequate response to TNFi were identified as independent risk factors for HZ in patients with UC receiving tofacitinib (70).

The European Medicines Agency (EMA) summary of product characteristics for tofacitinib notes that the risk of HZ reactivation appears to be higher in patients with RA, PsA and UC who are Japanese or Korean, in patients with an absolute lymphocyte count <1000 cells/mm^3, and in patients with long-standing RA who have previously received ≥2 bDMARDs (47). HZ reactivation risk may also be higher in patients receiving tofacitinib 10 *versus* 5 mg BID (47). Tofacitinib 10 mg BID is only approved by the EMA for patients with UC.

Although a numerical dose-dependent increase in HZ risk was observed at 52 weeks in the maintenance cohort, the overall LTE cohort HZ IRs between doses remained stable (≤6.8 years, May 2019 data cut) (69).

Current guidelines on VZV vaccination in patients with no documented/serological evidence of VZV exposure

Vaccines are available to protect against primary VZV infection (chickenpox) or VZV reactivation (shingles).

The UK currently has no chickenpox vaccination programme. In contrast, in countries such as the US and Australia, children, adolescents and adults are vaccinated against chickenpox (71, 72). VZV vaccination efficacy is ~98% in children and ~75% in adolescents/adults (73, 74). Varicella zoster immunoglobulin (VZIG) administered by intramuscular injection can be used in groups at high risk of severe chickenpox. However, due to significant VZIG shortages, antiviral agents (*e.g.* aciclovir) have been recommended for post-exposure prophylaxis for chickenpox in high-risk groups (75, 76).

Current and emerging HZ vaccination options

Two vaccines are licensed for HZ (shingles) in the UK and European Union (EU): a live zoster vaccine (LZV) and a non-live, adjuvant recombinant subunit zoster vaccine (RZV).

LZV

LZV is a live attenuated strain of VZV, approved for healthy individuals aged ≥50 years. Efficacy of LZV in healthy individuals has been reported as 49.1% (95% CI 47.5–50.6). However, efficacy has been shown to decrease over time, from 67.5% (95% CI 65.4–69.5) during the first year after vaccination to 31.8% (95% CI 15.1–45.2) after 8 years (77).

The most frequently reported (occurring in ≥1/10 subjects) adverse reactions with LZV vaccination occurred at the injection site (erythema, pain/tenderness, pruritis and swelling). In addition, the injection site was the area of other less frequent (≥1/100 to <1/10) adverse reactions such as rash, warm-

Table I. Current EMA-approved JAK inhibitors for chronic inflammatory diseases.*

	Tofacitinib	Baricitinib	Upadacitinib	Filgotinib
Target	JAK1/JAK3	JAK1/JAK2	JAK1	JAK1
Indications	RA, PsA, UC	RA, AD	RA, PsA, AS	RA
Approval date				
RA	2017	2017	2019	2020
PsA	2018	Not approved	2021	Not approved
UC	2018	Not approved	Not approved	Not approved
Approved dose/concomitant therapy				
RA	5 mg BID[¥] or 11 mg QD[·] in combination with background MTX; or as monotherapy in cases where MTX is inappropriate or not tolerated[‖]	2 mg QD or 4 mg QD in combination with background MTX; or as monotherapy[‖]	15 mg QD in combination with background MTX; or as monotherapy[‖]	200 mg QD[¶] in combination with background MTX; or as monotherapy[‖]
PsA	5 mg BID[¥] with background MTX[‖]	Not approved	15 mg QD in combination with background MTX; or as monotherapy[‖]	Not approved
UC	10 mg BID[¥] 8-week induction therapy[$,§] 5 mg BID[·] maintenance therapy**	Not approved	Not approved	Not approved
HR IR (95% CI)				
RA	5 mg BID:[¥] IR 3.5 (3.1–3.9)[¥¥,¨] 10 mg BID:[¥] IR 3.7 (3.4–4.1)[¥¥,¨,‖]	2 mg QD: IR 3.1 (1.1–6.8)[¥¥,¶¶] 4 mg QD: IR 4.3 (2.6–6.8)[¥¥,¶¶]	15 mg QD: IR 3.5 (2.8–4.2)[¥¥,§§] 30 mg QD: IR 6.2 (5.0–7.7)[‖,¥¥,§§]	100 mg QD: IR 1.1 (0.7–1.8)*** 200 mg QD: IR 1.7 (1.3–2.3)***
PsA	5 mg BID:[·] IR 2.0 (0.4–5.7)[¥¥,¥¥¥] 10 mg BID:[¥] IR 2.7 (0.7–6.8)[¥¥,‖,¥¥¥]	Not available	15 mg QD: IR 3.8 (2.3–6.2)[$$,¶¶¶] 30 mg QD: IR 8.5 (6.1–11.8)[$$,¶¶¶]	200 mg QD: IR 0.8[$$,¨¨]
UC	5 mg BID:[¥] IR 3.4 (2.1–5.2)[¥¥,‖‖‖‖] 10 mg BID:[¥] IR 3.5 (2.7–4.5)[¥¥,‖,‖‖‖]	Not available	Not available	Not available

*As of November 2020.
[¥]Immediate-release formulation.
[·]Prolonged-release formulation.
[‖]In patients with an inadequate response or intolerance to prior csDMARDs (46, 47, 107-109).
[¶]In patients aged ≥75 years, a starting dose of filgotinib 100 mg QD is recommended, as clinical experience is limited.
[$]Can be extended for an additional 8 weeks for patients who do not achieve an adequate response by Week 8.
[§]In patients with an inadequate response, lost response or intolerance to prior conventional or biological therapy.
**10 mg BID is allowed as maintenance therapy in patients with loss of response.
[¥¥]IR calculated as number of unique patients with events per 100 PY.
[¨]Data from an integrated summary of safety in patients with RA (data cut, March 2017).
[‖]Not an approved dose in the EMA area.
[¶¶]IR for placebo-controlled trials across phase II/III studies through 24 weeks (59).
[$$]IR calculated as events per 100 PY.
[§§]Data pooled from five phase III trials of upadacitinib in RA (data as of June 2019) (60).
***Exposure-adjusted IR per 100 PY; data pooled from three phase II and four phase III trials of filgotinib in RA (data as of June 2020) (61).
[¥¥¥]Data from an integrated summary of data from the tofacitinib PsA global development programme (data cut, May 2016) (63).
[¶¶¶]Data from a randomised controlled phase III trial of upadacitinib in PsA through 56 weeks (68).
[¨¨]Data at week 100 from an ongoing phase II LTE study of filgotinib in PsA (data cut, April 2020) (67).
[‖‖‖‖]Data from an integrated summary of safety data from the tofacitinib UC global clinical development programme (data cut, May 2019) (110).
EMA: European Medicines Agency; JAK: Janus kinase; RA: rheumatoid arthritis; PsA: psoriatic arthritis; UC: ulcerative colitis; AD: atopic dermatitis; AS: ankylosing spondylitis; BID: twice daily; QD: once daily; MTX: methotrexate; HZ: herpes zoster; IR: incidence rate; csDMARD: conventional synthetic disease-modifying antirheumatic drug; PY: patient-years; LTE: long-term extension; CI: confidence interval.

th, haematoma, induration and pyrexia. Less frequent adverse reactions included skin rashes outside the injection site area, arthralgia, myalgia, pain and headache (78).

There are few clinical studies which have evaluated the efficacy and safety of HZ vaccination in patients with RA or PsA receiving JAKi therapy, with available evidence primarily in LZV vaccination in patients with RA (79). LZV was previously assessed in patients with RA 2–3 weeks prior to treatment with tofacitinib or placebo with background csDMARDs. Both groups had similar VZV-specific immune responses, and overall immune responses were comparable with healthy volunteers, although

one patient with no previous VZV exposure experienced disseminated vaccine-strain primary varicella infection (*i.e.* chickenpox) (80). Also, 100 patients from this vaccine sub-study subsequently entered the tofacitinib open-label LTE study, and five HZ cases were noted during follow-up; three of these patients had undetectable VZV cell-mediated immunity at baseline and Week 6, suggesting that LZV may not provide adequate long-term protection (81). The safety and immunogenicity of LZV will be further clarified in an ongoing, randomised controlled trial (VERVE; NCT02538341) evaluating LZV in patients with chronic inflammatory diseases (including RA and PsA) aged ≥50 years actively using TNFi. Larger, controlled clinical trials are required to confirm HZ vaccination strategies for patients receiving JAKi therapy.

RZV

RZV is a non-live, adjuvant recombinant subunit vaccine approved in the US and EU for immunocompetent individuals aged ≥50 years (82, 83). Previously, it was demonstrated that RZV induced 97% protection against HZ in healthy individuals aged ≥50 years, which was maintained, with no apparent decline in protection, for >3 years (84). Clinical efficacy and safety of RZV has not been determined in patients with chronic inflammatory diseases receiving immunomodulatory therapies, but has been demonstrated in patients with solid tumours receiving immunomodulatory chemotherapy (85, 86).

The most frequently reported (occurring in ≥1/10 subjects) adverse reactions with RZV include injection site reactions (pain, redness and swelling), myalgia, fatigue and headache (87). RZV has been associated with a greater risk of injection site reactions compared with LZV (88). There is some evidence to suggest that the AS01B adjuvant system used in formulating RZV (82) may induce additional adverse events, limiting the clinical use of RZV. In data pooled from approximately 10 000 individuals enrolled in phase III clinical trials, a higher proportion of patients receiving RZV, compared with placebo, experienced Grade 3 injection-site reactions (9.4% *vs.* 0.3%, respectively) and systemic reactions (10.8% *vs.* 2.4%, respectively) (89).

Current guidelines on HZ vaccination

HZ vaccines are licensed for use in those aged ≥50 years in the UK. Current UK National Health Service (NHS) guidelines state that in adults aged 70–79 years, LZV can be considered for those without prior VZV exposure or vaccination, or those receiving low-dose immunomodulatory therapies (90, 91). RZV is recommended for individuals who are receiving, or have received, targeted therapy such as JAKi or biologic therapies in the previous 3 months (91). RZV is also recommended for those receiving other immunosuppressive therapies, including prednisolone (≥20 mg/day for >10 days in the previous month or ≥10 mg/day for >4 weeks in the previous 3 months), methotrexate >20 mg/week, azathioprine >3.0 mg/kg/day or 6-mercaptopurine >1.5 mg/kg/day (91). Public Health England does not recommend LZV in patients who have received biological therapy within the previous 3 months (91).

Current British Society of Rheumatology (BSR) guidelines conditionally recommend that patients with RA and PsA aged ≥50 years receive live HZ vaccine >2 weeks prior to bDMARDs (92), while the European Alliance of Associations for Rheumatology (EULAR) recommends that LZV should be administered 4 weeks prior to tofacitinib or bDMARDs, due to increased risk of HZ (85). Likewise, for UC, British Society for Gastroenterology (BSG) guidelines recommend that live HZ vaccine should be administered before starting tofacitinib (93). Recent European Crohn's and Colitis Organisation (ECCO) guidelines recommend RZV for patients with IBD and in those with inflammatory bowel disease (IBD) receiving immunosuppressive therapy (94). If RZV is unavailable, LZV is recommended in immunocompetent patients with IBD aged ≥50 years and can be considered in patients receiving low-dose immunosuppression (94).

HZ vaccines are not licensed for individuals aged <50 years; this could be an area for further research. The BSR guidelines recommend (Grade 2C) chickenpox vaccine, rather than LZV, for VZV-naïve patients with no contraindications before starting biological therapies (92). Individuals aged >50 years with previous history of VZV infection can also be seronegative, as most VZV infections occur during childhood (3), and anti-VZV immunity declines over time (14). RZV may be an alternative in this cohort. In the US, the Advisory Committee on Immunization Practices recommends RZV in adults aged ≥50 years, irrespective of prior immunisation with chickenpox vaccine or LZV (82).

BSG guidelines state that LZV should not be administered to patients with UC until ≥3 months after the last dose of biological therapy (93). Temporary discontinuation of immunomodulatory therapy to allow administration of LZV may be possible, although this approach is often impractical in patients with active disease. However, in a previous study, patients with IBD receiving low-dose immunomodulatory therapy (defined as methotrexate ≤0.4 mg/kg/week, azathioprine ≤3.0 mg/kg/day or 6-mercaptopurine ≤1.5 mg/kg/day) had a statistically significant increase in circulating anti-VZV antibodies 2 weeks post-vaccination, compared with pre-vaccination levels, suggesting that these patients were able to mount an anti-VZV response (95). Therefore, LZV may be a viable option for patients with chronic inflammatory diseases receiving immunomodulatory therapies that are not contraindicated. A benefits/risks assessment of treatment withdrawal prior to LZV should be carried out by healthcare providers to determine the most appropriate approach for individual patients.

Factors affecting decision making regarding HZ vaccination in patients with chronic inflammatory diseases receiving JAK inhibitors

A number of factors may influence the choice of vaccine for patients with chronic inflammatory diseases.

Vaccine availability

LZV is widely available globally, however, RVZ has only recently been made

available in the UK (91). Both vaccines are included in the National immunisation programme for those aged 70–79 years. RZV is restricted to those meeting certain additional criteria as the supply of RZV is currently limited (91). In the US, discussions on RZV use in patients receiving high-dose immunomodulatory therapy are ongoing (82). As more data become available, this will help to inform future vaccination guidelines in the immunocompromised population.

Vaccine scheduling

LZV is administered as one subcutaneous or intramuscular injection, whereas RZV is administered as two intramuscular doses, 2–6 months apart (83, 96).

Use of vaccines with immunomodulatory therapy

When evaluating HZ vaccination options, it is important to also consider the extent of concomitant immunomodulatory treatments. LZV may be appropriate for some patients receiving low-dose immunomodulatory treatments; however, in the UK, RZV is recommended for patients receiving high-dose or advanced immunomodulatory therapies (91).

Policy limitations

UK NHS reimbursement policy (based on cost-effectiveness) recommends routine HZ vaccination primarily in patients aged 70–79 years who are not contraindicated, usually administered in primary care settings (91, 97, 98). This age group is likely to derive the greatest benefit from LZV because of the increased burden of shingles in this age group; LZV effectiveness (which decreases with age), duration of protection and the limited available evidence on the effectiveness of a second dose of LZV (91). However, a cost-effectiveness model of individuals aged ≥60 years in the general population concluded that a booster dose of LZV administered 10 years after initial vaccination was feasible and cost-effective (99).

Consideration of patients outside current age guidelines may preclude reimbursement, which could deter clinicians in favour of increased HZ vaccination. Consequently, HZ vaccination of patients not covered by current reimbursement policy is generally uncommon in primary care. Decisions on HZ vaccination in secondary/tertiary care settings are made on a case-by-case basis, considering possible delays in subsequent use of some treatments (such as JAK inhibitors), or requirements for washout if switching therapies. UK Joint Committee on Vaccination and Immunisation (JCVI) policies are continuously reviewed as data in at-risk groups accumulate; this is an important topic for further consideration by the UK JCVI.

With respect to LZV *versus* RZV, a recent UK public health impact (PHI) study in healthy individuals found that RZV use was associated with fewer cases of HZ, compared with LZV, and RZV was superior to LZV in all age cohorts assessed (with the highest PHI in those aged 60 or 65 years); however, further analysis into RZV cost-effectiveness was recommended (100). Also, a recent systematic review of 41 studies recommended that RZV should be preferred over LZV for all patients with PsA aged >50 years and those aged <50 years receiving tofacitinib or systemic corticosteroid or combination therapy (101).

Vaccine efficacy over time

Another factor influencing choice of vaccine could be long-term efficacy. LZV efficacy declines over time (102), and HZ incidence is higher, and HZ-induced skin lesions more severe, in those with lower levels of VZV-specific cell-mediated immunity (103). Clinical assessment of anti-VZV immune responses can help inform on those patients most likely to benefit from booster doses of HZ vaccine (as lower anti-VZV immunity correlates with increased HZ incidence and more severe HZ).

In contrast, current data suggest that protection against infection with RZV remains stable for >3 years (84). However, further analysis of RZV efficacy over longer time periods, RZV use with concomitant immunomodulatory therapy (*e.g.* corticosteroids, methotrexate or biological therapies), and the feasibility of booster doses of RZV in immunosuppressed individuals, will be required to inform on the potential use of RZV in patients receiving advanced immunomodulatory therapy.

Use of antiviral prophylaxis for long-term protection, as an alternative to HZ vaccination

An alternative for immunosuppressed patients who cannot receive HZ vaccination may be the aciclovir prophylaxis, to prevent viral reactivation. Aciclovir prophylaxis is not currently used in patients with chronic inflammatory diseases, due to concerns around possible toxicity; however, this approach has been effective in immunosuppressed patients receiving haematopoietic stem cell transplantation (HSCT) (104). Aciclovir-induced toxicity is common in those receiving aciclovir 800 mg administered 2–5 times daily (105); however, it has been demonstrated that aciclovir 400 mg BID was effective in the prevention of VZV reactivation following HSCT (106). Therefore, this approach may also be practical in patients with chronic inflammatory diseases who are also immunosuppressed and at increased risk of HZ.

Conclusions

Strategies for reducing HZ risk are key considerations in patients with chronic inflammatory diseases. While HZ risk is increased in patients treated with JAK inhibitors, these risks may be influenced by factors such as age, ethnicity, effects of increasing tofacitinib dose, and concomitant treatments. In this review, we have summarised existing UK and selected international vaccination guidelines, and discussed the two licensed vaccines and limitations in the use of HZ vaccination in patients with chronic inflammatory diseases such as RA, PsA and UC. Current evidence suggests that HZ vaccination reduces HZ risk in healthy individuals; however, discrepancies exist between recommendations in the use of HZ vaccination for patients with chronic inflammatory diseases, as well as NHS guidelines on HZ vaccination and reimbursement. Particular consideration should be given to patients with long-standing RA, and those who have previously received ≥2 bDMARDs. NHS reimbursement policy for HZ vaccination currently applies in those aged 70–79 years, which may hinder access to vaccination for younger patients requiring treat-

ment escalation. RZV may be more beneficial than LZV in patients with chronic inflammatory diseases, but further study is required to fully elucidate the long-term efficacy and feasibility of RZV in immunocompetent and immunosuppressed individuals.

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