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CLINICAL SCIENCE

Incidence and risk factors for herpes zoster in patients with rheumatoid arthritis receiving upadacitinib: a pooled analysis of six phase III clinical trials

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ABSTRACT

Background Upadacitinib (UPA) is an oral Janus kinase (JAK) inhibitor approved for the treatment of rheumatoid arthritis (RA). JAK inhibitors have been associated with an increased risk of herpes zoster (HZ) in patients with RA.

Objectives To evaluate the incidence and risk factors for HZ in UPA-treated patients with RA from the UPA phase III clinical trial programme.

Methods Exposure-adjusted incidence/event rates for HZ were determined in patients receiving UPA (monotherapy or combination therapy) in six randomised phase III trials (data cut-off on 30 June 2020). HZ incidence and event rates were also determined in patients receiving methotrexate (MTX) monotherapy or adalimumab (ADA) + MTX. Multivariable Cox regression analysis was used to identify HZ risk factors in UPA-treated patients.

Results A total of 5306 patients were included in this analysis. The incidence rate of HZ/100 patient-years (95% CI) was 0.8 (0.3 to 1.9), 1.1 (0.5 to 1.9), 3.0 (2.6 to 3.5) and 5.3 (4.5 to 6.2), in the MTX monotherapy, ADA + MTX, UPA 15 mg and UPA 30 mg groups, respectively. The majority of HZ cases with UPA (71%) involved a single dermatome. Prior history of HZ and Asian region were HZ risk factors in UPA-treated patients.

Conclusion In the UPA phase III RA clinical programme, HZ incidence and event rates were higher with UPA versus ADA + MTX or MTX monotherapy, and higher with the 30 mg versus 15 mg dose. Patients from Asia and those with a history of HZ may be at increased risk of HZ while receiving UPA.

Key messages

What is already known about this subject?
► Upadacitinib (UPA) is an oral Janus kinase (JAK) inhibitor that is approved for the treatment of rheumatoid arthritis (RA) at a dose of 15 mg once daily.
► JAK inhibitors have been linked with an increased risk of herpes zoster (HZ) in patients with RA.

What does this study add?
► In this pooled safety analysis, which included 5306 patients with RA across the UPA phase III clinical trials, including patients who were methotrexate (MTX)-naïve and patients who had an inadequate response to conventional synthetic or biologic disease-modifying antirheumatic drugs, the rate of HZ was higher with UPA compared with MTX monotherapy or adalimumab + MTX, and higher with the 30 mg versus 15 mg dose.
► Risk factors for HZ among UPA-treated patients included Asian region and prior history of HZ (with both UPA doses).

How might this impact on clinical practice or future developments?
► Physicians should be aware of the risk of HZ in patients with RA receiving UPA, particularly those with risk factors.

INTRODUCTION

Herpes zoster (HZ) is a common and debilitating condition caused by reactivation of varicella zoster virus (VZV) and is frequently characterised by a painful vesicular dermatomal rash.[1 2]

The lifetime risk of HZ in the general population is around 30%, with increased risk in the elderly and those who are immunocompromised; in the last decade, incidence has increased globally among adults.[3] A common complication of HZ is postherpetic neuralgia, in which pain persists for months or years following resolution of the rash.[1 2] HZ can also cause complications beyond the skin, including neurological disorders such as meningoencephalitis and HZ oticus (Ramsay Hunt syndrome) and ophthalmic disorders such as uveitis and keratitis. In addition, immunocompromised patients may develop disseminated skin disease, which may also involve non-cutaneous organs such as the lungs or gastrointestinal tract.[1–3]

Patients with rheumatoid arthritis (RA) have approximately a twofold increased risk of HZ compared with the general population.[4 5] This risk can be further increased by immunomodulatory therapies prescribed for the treatment of RA, such as glucocorticoids, and some biologic disease-modifying antirheumatic drugs (bDMARDs).[4] More recently, Janus kinase (JAK) inhibitors, a class of targeted synthetic DMARDs that modulate

signalling downstream of cytokine receptors, have been linked with an increased risk of HZ in patients with RA.[6 7]

Upadacitinib (UPA) is an oral JAK inhibitor engineered to have greater selectivity for JAK1 versus JAK2, JAK3 and TYK2, and is approved for the treatment of RA at a dose of 15 mg once daily.[8 9] The aim of this analysis was to determine the incidence of HZ in the UPA phase III clinical trial programme, and to identify potential risk factors for the development of HZ in UPA-treated patients.

METHODS
Studies design and patients
Data from six randomised phase III trials were included in this analysis: SELECT-EARLY,[10] SELECT-NEXT,[11] SELECT-MONOTHERAPY,[12] SELECT-COMPARE,[13] SELECT-BEYOND[14] and SELECT-CHOICE[15] (online supplemental table S1). Patients were ≥18 years old with active RA and met the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria.[16] Active RA was defined as ≥6 swollen joints (of 66) and ≥6 tender joints (of 68), and a high-sensitivity C reactive protein level of ≥3 mg/L (≥5 mg/L for SELECT-EARLY and SELECT-COMPARE, which also required evidence of erosive joint damage and/or autoantibody positivity). The studies enrolled patients with RA who were methotrexate (MTX)-naïve (SELECT-EARLY), or had experienced an inadequate response or intolerance to conventional synthetic DMARDs (csDMARDs) (SELECT-NEXT), MTX (SELECT-MONOTHERAPY and SELECT-COMPARE) or bDMARDs (SELECT-BEYOND and SELECT-CHOICE).

Treatments
In SELECT-MONOTHERAPY, SELECT-EARLY, SELECT-NEXT and SELECT-BEYOND, patients received UPA 15 mg or 30 mg once daily. Patients in SELECT-MONOTHERAPY and SELECT-EARLY received UPA as monotherapy, while those in SELECT-NEXT and SELECT-BEYOND received UPA in combination with csDMARDs. The double-blind, controlled periods of these studies ranged from 12 to 48 weeks. Patients who switched from placebo (PBO) or MTX onto UPA were included in the UPA analysis set from the start of UPA treatment. No switching between different doses of UPA was permitted.

In SELECT-COMPARE, only the 15 mg once daily dose of UPA plus background treatment with MTX was assessed. The double-blind, controlled period was 48 weeks and blinded rescue treatment was permitted at weeks 14, 18, 22 and 26 in patients with an inadequate response ('non-responders'; those who achieved <20% improvement from baseline in swollen joint count and tender joint count); and at week 26 if they also did not achieve Clinical Disease Activity Index ≤10 ('incomplete responders'). Patients who switched from PBO or adalimumab (ADA) onto UPA were included in the UPA analysis set from the start of UPA treatment, and those who switched from UPA to ADA were included in the ADA dataset from the start of ADA treatment. In the UPA 15 mg group, 252/651 (38.7%) patients were incomplete responders or non-responders and switched from UPA to ADA, with 159/327 (48.6%) patients in the ADA group switching from ADA to UPA.[17]

In SELECT-CHOICE, the 15 mg once daily dose of UPA was assessed in patients receiving background csDMARDs. During the 24-week double-blind period, background medication could be added or adjusted in patients with an inadequate response. All patients completing the 24-week double-blind period were eligible to enter an open-label extension in which all patients received UPA 15 mg once daily; patients who switched from abatacept to UPA were included in the UPA dataset from the start of UPA treatment.

Statistical analysis
Treatment-emergent infection was defined as an onset date on or after the first dose of study drug and no more than 30 days (70 days for ADA) after last dose of study drug in cases of premature discontinuation. The duration of the follow-up period differs due to the respective half-lives of UPA (30 days >5 half-lives) and ADA (70 days = 5 half-lives). Non-serious HZ events did not result in mandatory study termination. However, any serious infections (including HZ), if not able to be controlled within 2 weeks, were a reason for discontinuation. HZ recurrence was defined as an event ≥91 days after the first episode.

Rates of treatment-emergent infections for UPA 15 mg once daily (monotherapy or in combination with csDMARDs), UPA 30 mg once daily (monotherapy or in combination with csDMARDs), MTX monotherapy (SELECT-EARLY only) and ADA + MTX (SELECT-COMPARE only) were summarised in terms of exposure-adjusted incidence rate (EAIR), which was calculated as the total number of patients in a particular treatment group who experienced an event adjusted for exposure (with exposure time censored at the first event), and is expressed as n/100 patient-years (PY). Exposure-adjusted event rates (EAERs) were also calculated, defined as the total number of events (including multiple events in the same patient) adjusted for total exposure (number of days on drug), and are expressed as E/100 PY. Events were attributed to the treatment the patient was taking when the event occurred. HZ incidence by baseline concomitant glucocorticoid and/or MTX use and HZ recurrence were also analysed among UPA-treated patients only.

Time to first HZ event with UPA was estimated using Kaplan–Meier analysis. Risk factors for HZ in UPA-treated patients were assessed using multivariable Cox regression models, with baseline MTX use, baseline glucocorticoid dose, prior history of HZ, region, age, body mass index (BMI) and sex as covariates. The covariates were prespecified and no model selection method was applied. HZ onset and change in Disease Activity Score in 28 joints with C reactive protein (DAS28(CRP)) over time was assessed using a multivariable Cox regression model with time to first HZ as response and DAS28(CRP) change from baseline as a time-varying covariate. Prior HZ and HZ vaccination status were captured at baseline as part of the patient's medical history.

Patient and public involvement
This research was done without patient and public involvement.

RESULTS
Patients
A total of 5306 patients were included in this analysis, of whom 314 patients received MTX monotherapy (637.4 PY), 579 patients received ADA + MTX (1051.8 PY), 3209 received UPA 15 mg once daily (7023.8 PY exposure) and 1204 received UPA 30 mg once daily (3091.6 PY) at the time of data cut-off (30 June 2020). The majority of patients were female, and mean age was 53.3–61.1 years across the treatment groups (table 1). Around half of the patients were receiving concomitant glucocorticoids at baseline, with a mean dose of ≥5 mg/day across all groups (table 1). Fewer than 5% of patients reported prior HZ vaccination.

Table 1 Baseline demographics and disease characteristics of patients with and without treatment-emergent HZ event

Characteristic	MTX monotherapy		ADA 40 mg EOW + MTX		Any UPA 15 mg QD		Any UPA 30 mg QD	
	Patients with HZ (n=5)	Patients without HZ (n=309)	Patients with HZ (n=11)	Patients without HZ (n=568)	Patients with HZ (n=204)	Patients without HZ (n=3005)	Patients with HZ (n=150)	Patients without HZ (n=1054)
Female, n (%)	3 (60.0)	237 (76.7)	9 (81.8)	461 (81.2)	174 (85.3)	2407 (80.1)	113 (75.3)	835 (79.2)
Age, years, mean/median	54.8 (8.8)/56.0	53.3 (13.0)/55.0	61.1 (14.3)/62.0	54.0 (11.6)/55.0	57.7 (11.4)/59.0	54.1 (12.0)/55.0	55.9 (10.8)/57.0	55.2 (12.0)/56.0
Time since RA diagnosis, years	3.0 (5.7)	2.6 (5.1)	11.3 (11.9)	8.1 (7.9)	8.0 (8.1)	8.5 (8.4)	7.6 (8.7)	7.0 (8.3)
BMI, kg/m^2, mean/median	27.1 (4.3)/27.7	28.0 (6.4)/27.0	28.1 (4.8)/27.4	29.5 (7.2)/28.0	27.5 (5.6)/26.8	29.2 (6.7)/28.1*	28.3 (7.1)/26.8	29.4 (7.0)/28.4†
Region, n (%)								
North America	1 (20.0)	45 (14.6)	1 (9.1)	121 (21.3)	55 (27.0)	760 (25.3)	46 (30.7)	383 (36.3)
South/Central America	1 (20.0)	89 (28.8)	4 (36.4)	122 (21.5)	39 (19.1)	686 (22.8)	12 (8.0)	141 (13.4)
Europe	2 (40.0)	120 (38.8)	3 (27.3)	275 (48.4)	64 (31.4)	1301 (43.3)	52 (34.7)	428 (40.6)
Asia	0	32 (10.4)	2 (18.2)	16 (2.8)	34 (16.7)	109 (3.6)	30 (20.0)	55 (5.2)
Japan	0	28 (9.1)	0	0	16 (7.8)	46 (1.5)	17 (11.3)	41 (3.9)
Korea	0	0	1 (9.1)	5 (0.9)	10 (4.9)	19 (0.6)	5 (3.3)	7 (0.7)
China/Taiwan/Hong Kong	0	4 (1.3)	1 (9.1)	8 (1.4)	7 (3.4)	37 (1.2)	8 (5.3)	7 (0.7)
Malaysia	0	0	0	3 (0.5)	1 (0.5)	7 (0.2)	0	0
Other	1 (20.0)	23 (7.4)	1 (9.1)	34 (6.0)	12 (5.9)	149 (5.0)	10 (6.7)	47 (4.5)
Prior history of HZ, n (%)	0 (0)	4 (1.3)	1 (9.1)	11 (1.9)	16 (7.8)	50 (1.7)	18 (12.0)	23 (2.2)
History of HZ vaccination, n (%)	0	4 (1.4)‡	1 (10.0)§	14 (2.7)¶	12 (6.3)**	79 (2.8)††	10 (7.1)‡‡	61 (6.1)§§
DAS28(CRP)	6.3 (0.9)	5.9 (1.0)	5.7 (0.7)	5.9 (1.0)¶¶	5.7 (1.0)	5.8 (1.0)***	5.6 (1.0)	5.7 (1.0)†††
Concomitant csDMARDs at baseline, n (%)	N/A	N/A	11 (100.0)	567 (99.8)	143 (70.1)	2405 (80.0)	82 (54.7)	479 (45.4)
Concomitant glucocorticoids at baseline, n (%)	3 (60.0)	161 (52.1)	7 (63.6)	342 (60.2)	105 (51.5)	1656 (55.1)	77 (51.3)	494 (46.9)
Baseline glucocorticoid dose, mg/day‡‡‡	5.0 (0.0)	6.4 (2.4)	6.8 (3.1)	6.4 (2.4)	5.8 (2.3)	6.2 (2.5)	6.0 (2.5)	6.4 (3.4)

Values are mean (SD) unless otherwise stated. Percentages are calculated on non-missing values.
*n=3000.
†n=1048.
‡n=294.
§n=10.
¶n=522.
**n=189.
††n=2773.
‡‡n=141.
§§n=1000.
¶¶n=564.
***n=2990.
†††n=1047.
‡‡‡In patients receiving glucocorticoids at baseline.
ADA, adalimumab; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28(CRP), Disease Activity Score in 28 joints with C reactive protein; EOW, every other week; HZ, herpes zoster; MTX, methotrexate; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

Overview of infections

The rates of infections and serious infections observed with UPA 15 mg were similar to those observed with MTX monotherapy or ADA + MTX, whereas they were lower than with UPA 30 mg (figure 1). Opportunistic infection (excluding oral candidiasis, tuberculosis and HZ) rates and rates of active tuberculosis were similar across all treatment groups. HZ events occurred with greatest frequency in the UPA 30 mg once daily group (150/1204 (12.5%)), followed by the UPA 15 mg (204/3209 (6.4%)), ADA + MTX (11/579 (1.9%)) and MTX monotherapy (5/314 (1.6%)) groups, with similar comparative results seen using EAIRs (figure 1) and EAERs (online supplemental figure S1).

Overview of HZ in patients receiving UPA

In the UPA 15 and 30 mg once daily groups, 12 (0.3%) and 15 (1.2%) patients had a serious HZ event, respectively. Disseminated HZ (with cutaneous involvement only) occurred in 12 (5.9%) and 11 (7.3%) patients in the UPA 15 mg and 30 mg groups, respectively (table 2). Approximately 75% of HZ cases in patients receiving UPA, and 100% and 82% of cases, in patients receiving MTX monotherapy or ADA + MTX, respectively, involved a single dermatome. Of the total events, ophthalmic involvement occurred in 13 (6.4%) and 3 (2.0%) patients in the UPA 15 and 30 mg once daily groups, respectively, and unilateral involvement with multiple dermatomes was seen in 35 (17.2%) and 27 (18.0%) cases. One case of HZ meningitis was reported in a 64-year-old, male, Japanese patient who had received UPA 30 mg once daily for approximately 18 months and was also receiving loxoprofen 100 mg as required. The patient was withdrawn from the study, and the event resolved after hospital treatment. Of patients who experienced HZ, postherpetic neuralgia was observed in 17/235 events (7.2%) and 13/181 events (7.2%) in the UPA 15 and 30 mg once daily groups, respectively. Hospitalisation due to HZ occurred in 11/235 events (4.7%) in the UPA 15 mg group and in 15/181 events (8.3%) in the UPA 30 mg group.

No clear pattern in the timing of HZ onset with UPA was evident from Kaplan–Meier analysis (figure 2). As expected, the cumulative probability of HZ increased with time, with probabilities of 3.3% (95% CI: 2.7% to 4.0%), 6.7% (95% CI: 5.7% to 7.8%), 8.5% (95% CI: 7.4% to 9.7%) and 10.0% (95% CI: 8.4% to 11.7%) with UPA 15 mg at 1, 2, 3 and 4 years, respectively.
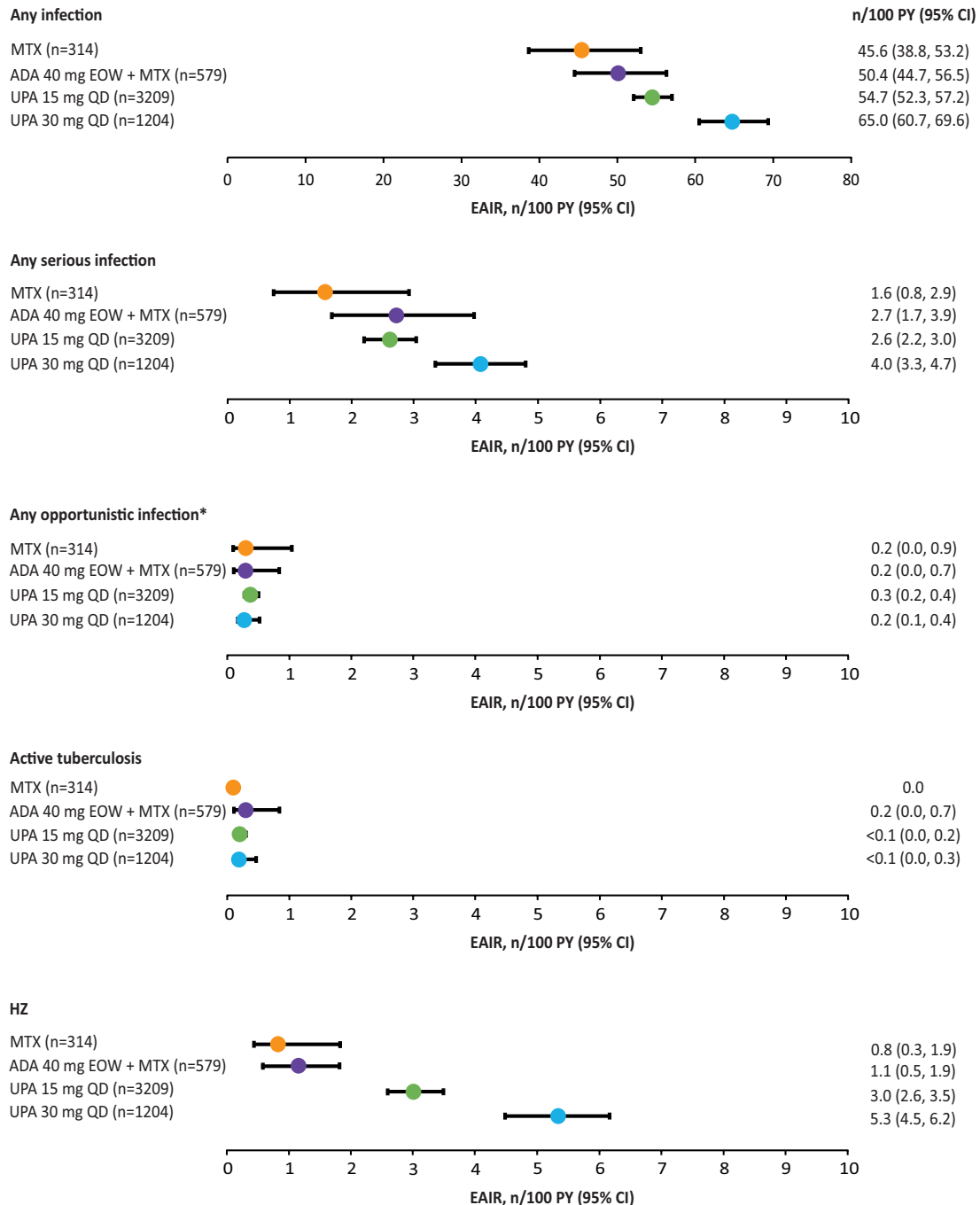
Figure 1 Exposure-adjusted incidence rates of infection. *Excluding oral candidiasis, tuberculosis and HZ. One case of cytomegalovirus infection was observed in the UPA 15 mg arm. ADA, adalimumab; EAIR, exposure-adjusted incidence rate; EOW, every other week; HZ, herpes zoster; MTX, methotrexate; PY, patient years; QD, once daily; UPA, upadacitinib.

In patients who experienced HZ during an UPA trial, 6.4% (13/204) and 9.3% (14/150) had a recurrence of HZ in the UPA 15 and 30 mg once daily groups, respectively, at a median follow-up time after first HZ episode of 476 and 593 days, respectively. Of the 13 recurrences in the UPA 15 mg once daily group, only one was more severe than the initial event; no recurrences in the 30 mg once daily group were more severe than the initial event. The mean age of patients with recurrent HZ was 58.7 years (median 59.0 years), mean BMI was 26.9 kg/m^2 and 23/27 (85.2%) were female. Fifteen (55.6%) were receiving concomitant glucocorticoids at baseline, at a mean dose of 6.3 mg/day.

Risk factors for HZ in patients receiving UPA

Multivariable Cox regression analysis showed that prior history of HZ and Asian region were associated with an increased risk of HZ in both the UPA groups (figure 3). In patients with a prior history of HZ, EAIRs of HZ were 13.9 (95% CI: 8.0 to 22.6) and 22.5 (95% CI: 13.4 to 35.6), respectively, with HRs of 3.3 (1.9–5.6) in the UPA 15 mg group and 3.4 (2.0–5.8) in the UPA 30 mg group compared with patients without a prior history of HZ. In patients from Asia, HZ EAIRs were 10.7 (7.4–14.9) and 17.0 (11.5–24.2), respectively, with Asian patients at a significantly greater HZ risk than patients in other regions (figure 3).

Table 2 Summary of extent of involvement in patients with HZ

Categories, n (%)*	MTX monotherapy (n=314)	ADA 40 mg EOW + MTX (n=579)	Any UPA 15 mg QD (n=3209)	Any UPA 30 mg QD (n=1204)
Total patients with ≥1 HZ event	5 (1.6)	11 (1.9)	204 (6.4)	150 (12.5)
Single dermatome	5 (100)	9 (81.8)	153 (75.0)	110 (73.3)
Ophthalmic involvement	0	2 (18.2)	13 (6.4)	3 (2.0)
Meningoencephalopathic involvement	0	0	0	1 (0.7)
Unilateral involving multiple dermatomes†	0	0	35 (17.2)	27 (18.0)
HZ oticus (Ramsay Hunt syndrome)	0	0	2 (1.0)	1 (0.7)
Disseminated, cutaneous only (no CNS involvement)‡	0	1 (9.1)	12 (5.9)	11 (7.3)
Disseminated with other non-cutaneous organ involvement (no CNS involvement)§	0	0	0	0
Postherpetic neuralgia¶	0	1 (8.3)	17 (7.2)	13 (7.2)
Hospitalisations because of HZ event¶	0	0	11 (4.7)	15 (8.3)
Missing	0	0	5 (2.5)	2 (1.3)

*Patients may fall into >1 category.
†≤2 adjacent dermatomes.
‡≥3 dermatomes, unilateral non-adjacent dermatomes or bilateral dermatomes.
§Involvement of visceral organs (eg, HZ pneumonia or HZ hepatitis).
¶Percentages based on total number of HZ events.
ADA, adalimumab; CNS, central nervous system; EOW, every other week; HZ, herpes zoster; MTX, methotrexate; QD, once daily; UPA, upadacitinib.

Of patients from Asia who developed HZ, the majority were from Japan (although Japanese patients made up the majority of patients from Asia in the study). The EAIRs of HZ in Japanese patients were 10.7 (6.1–17.3) in the UPA 15 mg once daily group and 13.6 (7.9–21.8) in the UPA 30 mg once daily group. Female sex, older age and North American region (vs European region) were also significant risk factors in the UPA 15 mg group only (figure 3).

There was no clear relationship observed between incidence of HZ and concomitant glucocorticoids and/or MTX among UPA-treated patients (figure 3 and online supplemental figure S2). The lack of association between glucocorticoid use and HZ was also observed in univariate analyses (online supplemental figure S3) and in a subanalysis of UPA-treated patients who did not have a prior history of HZ (online supplemental figure S4). In addition, there was no significant association between HZ onset and change in DAS28(CRP) over time (HR 1.0 (0.9–1.2)) in UPA-treated patients.

DISCUSSION

We evaluated the risk of HZ for UPA, a JAK inhibitor, within the phase III clinical trial programme for RA. We identified a dose-dependent risk of HZ with UPA relative to the active comparators MTX monotherapy and ADA in combination with MTX. Similar to HZ reported with other JAK inhibitors, the majority of HZ cases in UPA-treated patients were non-serious and involved a single dermatome. Asian region was a risk factor for HZ among UPA-treated patients (compared with Europe), and a history of HZ before study entry was also a strong risk factor for developing HZ after UPA initiation, a risk factor not previously evaluated in other JAK inhibitor HZ studies. Furthermore, in contrast to previous studies with JAK inhibitors, we did not find an association between HZ and concomitant use of glucocorticoids.

In general, Asian populations appear to have a higher rate of HZ compared with other populations: in a recent systematic review, the highest incidences of HZ were found in the Asia-Pacific region, although there was significant variation within this region and high rates were also observed in Caucasian populations.[18] This apparent increased risk of HZ in Asian populations, particularly Japanese patients, versus other geographical areas has also been previously observed in Japanese and Korean patients receiving baricitinib, peficitinib and tofacitinib,[19–22] as well as with Japanese patients receiving UPA.[23 24] The reasons for this are currently unknown, although it has been suggested that genetic predisposition, regional differences in reporting and
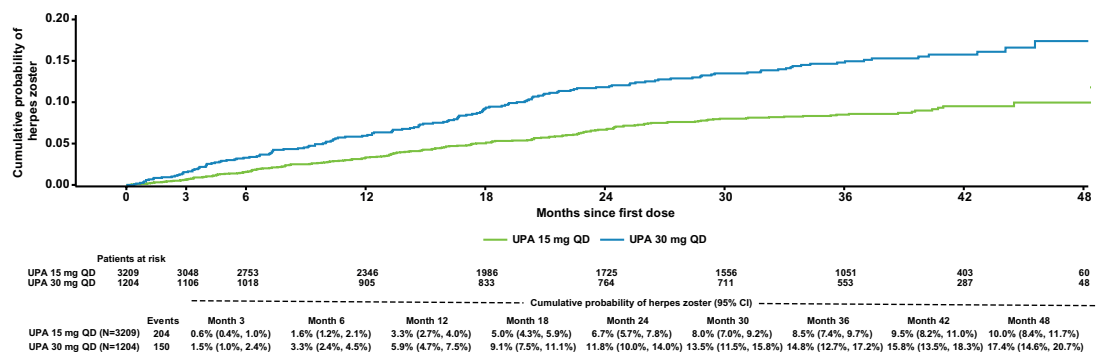

Figure 2 Kaplan–Meier estimate for time to HZ event in patients who received UPA. HZ, herpes zoster; QD, once daily; UPA, upadacitinib.
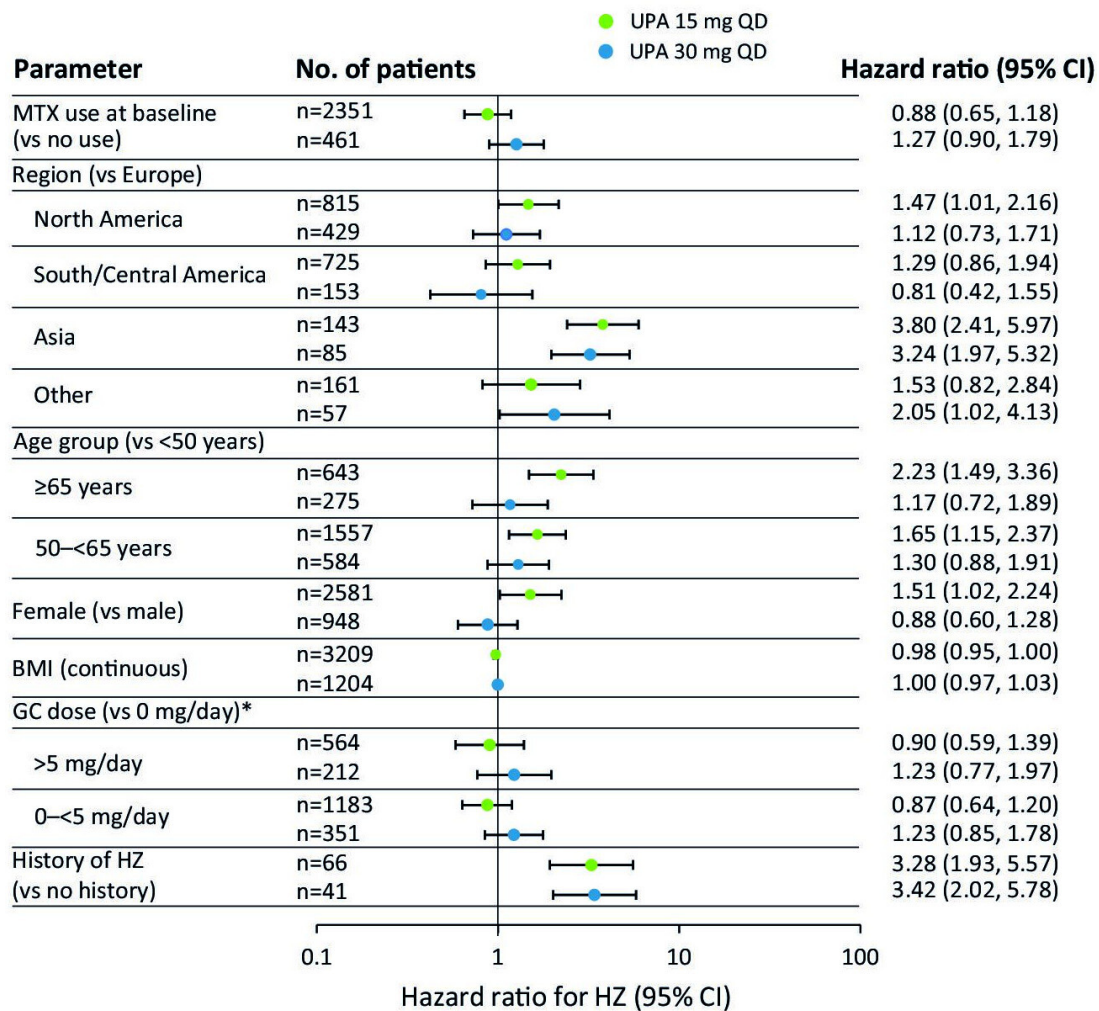
Figure 3 Risk factors for HZ in patients receiving UPA (multivariate analysis). *Prednisone or equivalent dose; doses of ≤10 mg/day were permitted. BMI, body mass index; GC, glucocorticoid; HZ, herpes zoster; MTX, methotrexate; QD, once daily; UPA, upadacitinib.

other cultural or medical factors could be involved.[6 7] Further research is warranted to determine why Asian patients with RA who are treated with JAK inhibitors, particularly those from East Asia, are at higher risk of HZ.

In our study, concomitant glucocorticoids did not significantly increase HZ risk in patients receiving UPA, both in terms of crude incidence rates and in univariate and multivariate analyses. This is in contrast with previous studies, which have shown an increased risk of HZ in patients with RA receiving JAK inhibitors in combination with glucocorticoids.[6 25] For example, Curtis et al[25] found a twofold increased risk of HZ in patients with RA receiving tofacitinib together with glucocorticoids versus those receiving tofacitinib alone, with similar results observed by Winthrop et al.[6] As glucocorticoids are a well-established risk factor for HZ, it is unclear why we did not observe this in our study, and this potential risk warrants further investigation in real-world data. It may be that the rate of HZ associated with UPA, particularly at the 30 mg dose, dominates other treatment-related risk factors. Our study also found that MTX had no significant effect on HZ incidence, which is consistent with previous results.[6 25]

Current EULAR and ACR guidelines state that live attenuated HZ vaccination may be considered in high-risk patients with autoimmune inflammatory rheumatic diseases, including RA, preferably 2–4 weeks prior to initiation of advanced therapy.[26 27]

In this study we were unable to assess the effectiveness of HZ vaccination in patients receiving UPA, as fewer than 5% of patients had received vaccination with the live virus vaccine at baseline, and the study was conducted prior to the introduction of the HZ subunit vaccine (Shingrix).

The strongest risk factor of HZ identified among UPA-treated patients in our study was a prior history of HZ. As individuals typically boost their cell-mediated immunity with an episode of HZ, recurrent HZ is relatively rare, with only 0.4% of individuals in the general population who experience HZ going on to develop another episode later in life.[28] One would speculate that a history of HZ would therefore be protective for most individuals. To our knowledge, a history of HZ was not evaluated as a potential risk factor in the context of other JAK inhibitor studies. However, like other JAK inhibitors, a small percentage of individuals developed recurrent HZ within the phase III programme. In the literature, this has ranged typically between 2.5% and 6% depending on the study.[29 30] This seems consistent with our observation of prior HZ being a strong risk factor (although the rates in our study (6.4% for UPA 15 mg and 9.3% for UPA 30 mg for recurrent HZ) were slightly higher than in these studies), and is suggestive of a pathophysiology of JAK inhibitor-induced HZ beyond that of diminished cell-mediated immunity. It should be noted too, however, that the definition of recurrence can be different across studies.

Other significant risks included female sex, older age and North American region (vs Europe), but these were limited to the UPA 15 mg group only. It is unclear why these factors were not significant in the UPA 30 mg group as well. The increased risk in female patients may reflect the fact that around 80% of patients in this analysis were female, and the risk in North American patients appeared minimal compared with the much larger increased risk in Asian patients with both UPA doses. Conclusions about the risks of HZ in female and North American patients should therefore be made with caution, and additional data may be needed to clarify the risks of HZ in these populations.

In this analysis, HZ with ophthalmic involvement was more frequently reported in the UPA 15 mg group compared with the UPA 30 mg group. It is unclear what the reason may be for this observation. Of the patients who experienced HZ with ophthalmic involvement, 5/13 patients treated with UPA 15 mg and all three patients treated with UPA 30 mg were receiving concomitant glucocorticoids.

Postherpetic neuralgia is a common complication of HZ and is typically defined as pain that persists for ≥90 days after resolution.[3 31] As patients receiving UPA in this study were followed for 30 days after their last dose of study drug, this may mean that some cases of postherpetic neuralgia may not have been recorded. In keeping with this, the rates of postherpetic neuralgia observed in this study (3.8% and 7.3% with UPA 15 mg and 30 mg, respectively) were lower than the rate of 9.1% reported in a large analysis of patients with RA by Forbes et al.[31]

We would note that the rate of HZ observed with UPA was relatively constant over time, suggesting that there is not a 'high-risk period' shortly after starting therapy, as has been observed for serious bacterial infections in RA.[32] As a corollary, this observation implies that vaccination against HZ remains important over a patient's entire course of UPA treatment, and that it is 'never too late' to vaccinate. However, it should be noted that a recent study suggested that live attenuated HZ vaccination had limited efficacy in preventing HZ in patients with RA receiving tofacitinib,[33] despite patients showing VZV-specific humoral and cell-mediated immune responses.[34] Further research is required to determine the value of HZ vaccination in patients with RA receiving JAK inhibitors, particularly with the recently approved subunit vaccine (Shingrix).

Given the lack of direct comparison in head-to-head studies between JAK inhibitors, we are limited in drawing conclusions regarding the relative risk of HZ with UPA as compared with other JAK inhibitors (tofacitinib, baricitinib and filgotinib).[35] Differences in study design, length of follow-up, inclusion and exclusion criteria, study sites and data analysis limit the ability to compare data across clinical trials. With those limitations in mind, the incidence rates described within the UPA programme are similar to those described in the RA programmes for tofacitinib and baricitinib, with the highest rates in all three programmes observed in the Asian region.[20 22 36] Rates of HZ in patients within the filgotinib clinical programme appear to be lower than those seen in the tofacitinib, baricitinib and UPA clinical programmes across all treatment arms, including both the PBO and active comparator arms, illustrating the challenges in cross-trial comparisons. Taken alone, the rates of HZ appear to be lower for filgotinib compared with other JAK inhibitors, but the relative differences between filgotinib and PBO and other JAK inhibitors and PBO are consistent.[20 22 36–38] Long-term integrated safety data showed EAIRs (95% CI) of 1.1 (0.8 to 1.7) and 1.8 (1.4 to 2.3) for filgotinib 100 mg and 200 mg, respectively, also showing a dose response.[37] In a pooled analysis of phase II, phase III and long-term extension studies, HZ was more common with filgotinib (100 mg and 200 mg) compared with ADA or MTX up to 52 weeks, but comparable versus PBO during the 12-week PBO-controlled period.[37–40] A recent systematic review and network meta-analysis found an increased risk of HZ infection with ADA, etanercept, peficitinib, tofacitinib and UPA compared with filgotinib, although the risk differences became statistically non-significant following a sensitivity analysis.[41]

In conclusion, this analysis provides further support for the need for continued vigilance and monitoring for signs of HZ in patients receiving UPA, particularly in Asian populations and those with a history of HZ. The study also emphasises the importance of future research clarifying whether treatment with UPA or other JAK inhibitor therapies may attenuate the expected benefit and durability of vaccination with the most recent HZ adjuvant vaccine.

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