

## Original article

## A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis

Katie Bechman <sup>1</sup>, Sujith Subesinghe<sup>1</sup>, Sam Norton <sup>2</sup>, Fabiola Atzeni<sup>3</sup>, Massimo Galli<sup>4,5</sup>, Andrew P. Cope <sup>1</sup>, Kevin L. Winthrop<sup>6</sup> and James B. Galloway <sup>1</sup>

## Abstract

**Objectives.** To evaluate the risk of serious infection (SI) and herpes zoster (HZ) in rheumatoid arthritis patients receiving JAK inhibitors.

**Methods.** We conducted a systematic literature review and meta-analysis of phase II and III randomized controlled trials of tofacitinib (5 mg bid), baricitinib (4 mg od) and upadacitinib (15 mg od). Patient-exposure years were calculated. A per-protocol analysis was applied, incorporating follow-up time from patients randomized to placebo who cross into the treatment arm. Pooled incidence rates per 100 person-years of SI and HZ were calculated. Incidence rate ratios (IRRs) of drug vs placebo were compared using a meta-synthesis approach.

**Results.** Twenty-one studies were included in the meta-analysis; 11 tofacitinib (5888 patients), six baricitinib (3520 patients) and four upadacitinib studies (1736 patients). For SI, the incidence rates were 1.97 (95% CI: 1.41, 2.68), 3.16 (95% CI: 2.07, 4.63) and 3.02 (95% CI: 0.98, 7.04), respectively. The IRRs comparing treatment arm to placebo were statistically non-significant: 1.22 (95% CI: 0.60, 2.45), 0.80 (95% CI: 0.46, 1.38) and 1.14 (95% CI: 0.24, 5.43), respectively. For HZ, the incidence rates were 2.51 (95% CI: 1.87, 3.30), 3.16 (95% CI: 2.07, 4.63) and 2.41 (95% CI: 0.66, 6.18), respectively. The IRR of HZ comparing baricitinib with placebo was 2.86 (95% CI: 1.26, 6.50). Non-significant IRRs were seen with tofacitinib and upadacitinib: 1.38 (95% CI: 0.66, 2.88) and 0.78 (95% CI: 0.19, 3.22), respectively. Indicator opportunistic infections excluding HZ were too rare to provide meaningful incidence rates.

**Conclusion.** The absolute SI rates were low. However across the JAK inhibitors, the incidence of HZ is higher than expected for the population (3.23 per 100 patient-years). While the risk was numerically greatest with baricitinib, indirect comparisons between the drugs did not demonstrate any significant difference in risk.

**Systematic review registration number.** Prospero 2017 CRD4201707879.

**Key words:** rheumatoid arthritis, systematic review, meta-analysis, immunosuppressants, viruses

## Rheumatology key messages

- The serious infection rate with licensed dose Janus kinase inhibitors in RA is low.
- The herpes zoster incidence with Janus kinase inhibitors is higher than expected in the RA population.
- Zoster risk is greatest with baricitinib, although differences were not statistically significant.

## Introduction

Biologic therapies have revolutionized the treatment of RA with targeted suppression of key inflammatory factors that underpin the disease pathogenesis. Their high selectivity and therapeutic efficacy have resulted in an achievable

goal of clinical remission. However not all patients respond to treatment. The cytokine network in RA is complex and targeting a single cytokine does not exclusively terminate the disease. Furthermore biologics are antibodies or fusion proteins that are susceptible to immunogenicity, which may result in a loss of efficacy over time [1].

<sup>1</sup>Centre for Rheumatic Disease, Kings College London, <sup>2</sup>Psychology Department, Institute of Psychiatry, Kings College London, London, UK, <sup>3</sup>Rheumatology Unit, Clinical and Experimental Medicine, University of Messina, Messina, <sup>4</sup>Luigi Sacco Department of Biomedical and Clinical Sciences, University of Milan, Milan, <sup>5</sup>III Division of Infectious Diseases, Luigi Sacco Hospital, ASST Fatebenefratelli Sacco, Milan, Italy and <sup>6</sup>Division of Infectious Diseases, Oregon Health & Science University, Portland, OR, USA

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Correspondence to: Katie Bechman, Department of Inflammation Biology, Academic Rheumatology Room 3.46, Third Floor, Weston Education Centre, King's College London, London SE5 9RJ, UK. E-mail: katie.bechman@kcl.ac.uk

Advances in our understanding of signal transduction pathways has resulted in the development of small-molecule inhibitors. These drugs target intracellular cytokine pathways and represent an attractive pharmacological alternative to biologics. The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway operates downstream of >50 cytokines and growth factors and is regarded as a central communication node for the immune system [2,3]. Four JAKs exist: JAK1, JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2. It is the specific combination of JAKs and STATs that determine functional outcomes of cytokine receptor stimulation.

For the treatment of RA there are currently two licensed small molecule inhibitors that target the JAK–STAT pathway. Tofacitinib inhibits JAK1, JAK3 and to a lesser extent JAK2. Tofacitinib was approved for use in RA by the Food and Drug Administration (FDA) in 2012. The European Medicines Agency did not approve tofacitinib until 2017 due to safety concerns including serious infection [4]. Baricitinib inhibits JAK1 and JAK2 and was approved by the European Medicines Agency in 2017. The FDA approved the 2 mg dose, declining approval of the 4 mg dose after citing safety concerns [5]. Tofacitinib and baricitinib have been incorporated into national and international RA guidelines [6,7]. Next-generation JAK inhibitors have been designed with a view to improved selective affinity for one or more of the four JAK enzymes. Upadacitinib is a selective JAK1 inhibitor and is being evaluated in six phase III trials, two of which have been published. At the time of writing, upadacitinib was not licensed for the treatment of RA. Filgotinib, a selective JAK1 inhibitor, decernotinib, a selective JAK3 inhibitor, and peficitinib, a pan-JAK inhibitor, are under evaluation in phase III trials that have not yet been published.

The development programmes for these JAK inhibitors (JAKi) have identified an infection signal when compared with placebo. A safety profile is emerging with viral opportunistic infections; the most characteristic infectious complication, specifically the reactivation of varicella zoster virus (VZV) leading to herpes zoster (HZ), also known as shingles [8]. This signal may be a ‘class effect’ as VZV reactivation has been reported with all JAKi. How JAKi increase the risk of HZ reactivation is unclear [9,10]. The role of the different JAKs in the immune response may suggest differences in safety profiles between drugs, underpinned by their differential JAK selectivity profiles. This has important clinical implications.

We undertook a systematic review and meta-analysis to evaluate serious infections (SI) and opportunistic indicator infections including HZ in RA phase II and III clinic trials with JAKi.

## Methods

The study was conducted in accordance with the preferred reporting items for systematic reviews guidelines [11] and registered with the international prospective register of systematic reviews (Prospero 2017 CRD42017078791). The literature was searched

systematically by two investigators (K.B. and S.S.) using MEDLINE, EMBASE and Cochrane Controlled Trials Register databases. The JAKi of interest were tofacitinib, baricitinib, upadacitinib, filgotinib, decernotinib and peficitinib. The search terms were ‘RA’ and ‘tofacitinib’, ‘CP-690, 550’, ‘baricitinib’, ‘LY3009104’, ‘upadacitinib’, ‘ABT-494’, ‘filgotinib’, ‘GLPG0634’, ‘decernotinib’, ‘VX-509’ and ‘peficitinib’, ‘ASP015K’. The search was undertaken in September 2017 and re-run prior to the final analysis to identify further studies that could be retrieved for incorporation in the systematic review.

## Study selection and data collection

We identified English language publications of phase II and III randomized controlled trials (RCTs). Conference abstracts were excluded. Phase II studies on JAKi were excluded if there were no phase III RCTs published. RCTs were included if they met the following criteria: (1) the study included patients diagnosed with RA based on the American College of Rheumatology criteria for RA, (2) the study evaluated tofacitinib 5 mg bid, baricitinib 4 mg od or upadacitinib 15 mg od or equivalent (6 mg bid); and (3) the study included a placebo comparator. Studies presenting duplicate data or no safety data were excluded. No restrictions were applied to the length of follow-up. Titles and abstracts of studies retrieved using the search strategy detailed above were screened independently by two investigators, K.B. and S.S. The full text of the potential studies for inclusion were retrieved and assessed for eligibility. Study quality and risk of bias were assessed using the Cochrane Collaboration’s tool [12].

The primary outcome of interest was SI, as defined in each study as any event associated with death, admission to hospital, or use of intravenous antibiotics. Secondary outcomes of interest included the number of opportunistic infections (OI) including rates of HZ. OI were identified from summary data, and categorized as ‘indicator’ infections from the proposed consensus definition of specific pathogens, or presentations of pathogens that ‘indicate’ the likelihood of an alteration in host immunity in the setting of biologic therapy [13]. This approach has been adopted previously for comparisons of infection risk between biologic therapies [14,15].

Data were extracted independently. Disagreements over study eligibility or risk of bias were resolved through discussion with a third reviewer (J.G.). Data collated included the source (author, journal and publication date), study design (e.g. early escape arms), patient demographics (age, disease duration and disease activity), anti-rheumatic drug and steroid exposure, and infection event rates.

## Data synthesis and statistical analysis

Analyses were undertaken using Stata 15 (StataCorp LLC, College Station, TX, USA). Infections were attributed to either drug or placebo based on the treatment exposure at the time of the event. Patient exposure years were calculated for placebo and treatment arms. Two separate analyses were undertaken. Firstly, a per protocol analysis

where patients could contribute time to both the unexposed and exposed groups (initially to the unexposed group when receiving placebo, and thereafter to the exposed group when crossed into the treatment arm to receive the study drug). Secondly, a limited analysis in which exposure time concluded at the point unexposed patients were crossed over into the treatment arm. The per protocol analysis allows the accrual of greater exposure time to the study drug but results in comparatively shorter unexposed time and may contribute to right censoring.

Crude incidence (IR) of SI and HZ were calculated for each RCT. Relative risk between JAKi and placebo was estimated and expressed as incidence rate ratios (IRR) with 95% confidence intervals. Analysis was performed using the random-effects Mantel-Haenszel method and compared graphically with forest plots. Summary data rather than individual level data were aggregated for quantitative analyses. Network meta-analysis was employed to allow indirect comparisons between the three JAKi. Since no head-to-head studies have been undertaken, each agent was compared directly with placebo, so the relative effectiveness of one JAK vs another was estimated indirectly, along with the level of uncertainty in this estimate. Each drug was ranked based on estimated probabilities using the parameters derived from the network meta-analysis. These were summarized by calculating the surface under the cumulative ranking curve (SUCRA). Publication bias was assessed using funnel plots.

## Results

### Search results and trial characteristics

The search identified 1920 articles of which 25 were eligible phase II or III RCTs (Fig. 1). Phase II studies for filgotinib, decernotinib and peficitinib were excluded as there were no published phase III trials in RA for each of these drugs. A further four studies were excluded based on the treatment arm not evaluating the current licensed dose of the drug or a lack of a placebo comparator. Upadacitinib is not licensed at present; a 15 mg dose was chosen in anticipation of the future licensing dosage. In total, 21 studies were eligible for inclusion in our analysis; 11 tofacitinib (5888 patients), six baricitinib (3520 patients) and four upadacitinib (1736 patients) (Table 1).

Assessment of study validity revealed few sources of bias. All studies reported randomization and blinding of participants and clinical assessors. Half did not describe methods of allocation concealment. Three studies did not account for incomplete outcome data (Supplementary Table S1, available at *Rheumatology* online). Half of the studies employed an escape design that involved advancing non-responder placebo-treated patients into the active treatment arm after a predefined period treatment.

Trials included in this meta-analysis were relatively homogeneous in the patient population. The majority included patients with an inadequate response to DMARDs. Four tofacitinib, one baricitinib and two

upadacitinib studies included patients with high disease activity despite biologics. Only one study for both tofacitinib and baricitinib included patients with early RA who were methotrexate naïve. Patients were distributed globally. Sixteen studies recruited patient from Asia, including three Japanese bridging studies. Six of the eleven tofacitinib trials and all of the baricitinib and upadacitinib trials recruited patients on background stable doses of methotrexate. The majority of the studies reported on steroid therapy, and across these the exposure was comparable.

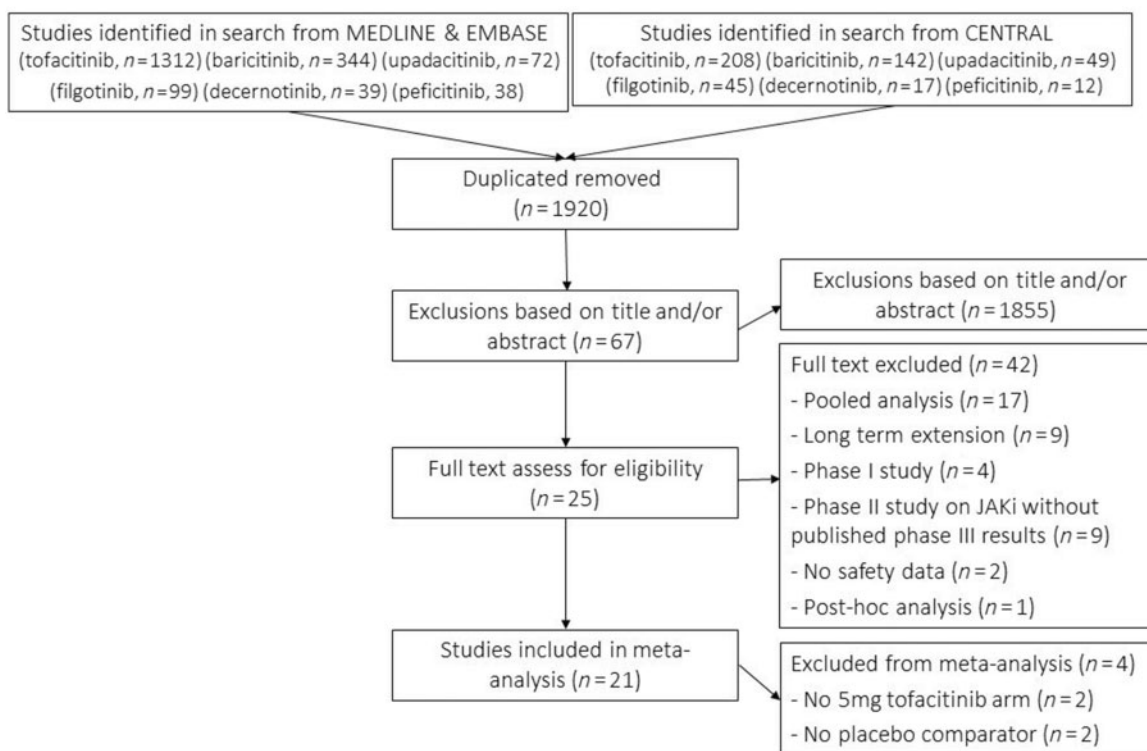
### Incidence rates and incidence risk ratio for serious infection

In the per protocol analysis, SIs were reported in 40 patients receiving 5 mg bid tofacitinib with 2032 patient exposure years (PEY), 26 patients receiving 4 mg baricitinib with 822 PEY and five patients receiving 15 mg or near equivalent upadacitinib with 166 PEY. Estimates of crude IR per 100 patient-years were 1.97 (95% CI: 1.41, 2.68) for tofacitinib, 3.16 (95% CI: 2.07, 4.63) for baricitinib and 3.02 (95% CI: 0.98, 7.04) for upadacitinib. In the pooled placebo group, estimates of IR were 2.50 (95% CI: 1.74, 3.48) per 100 person-years, derived from 1.19 (95% CI: 0.51, 2.34) from the tofacitinib placebo group, 4.09 (95% CI: 2.65, 6.04) from baricitinib and 1.75 (95% CI: 0.21, 6.32) from upadacitinib. The estimated IRs were similar in the limited analysis, in which duration of follow-up concluded at the point patients randomized to the placebo were crossed over into the treatment arm.

The estimated IRRs of SI compared with placebo in per protocol analyses were not statistically significant: 1.22 (95% CI: 0.60, 2.45) for tofacitinib, 0.80 (95% CI: 0.46, 1.38) for baricitinib and 1.14 (95% CI: 0.24, 5.43) for upadacitinib (Fig. 2). The pooled IRR for all three JAKi was 0.95 (95% CI: 0.63, 1.44), with statistical heterogeneity 0% (95% CI: 0%, 84%). Similar findings were seen in the limited analysis (Supplementary Fig. S2, available at *Rheumatology* online). An analysis separating tofacitinib monotherapy from tofacitinib-methotrexate combination studies did not demonstrate a significant IRR of SI compared with placebo (Supplementary Fig. S4, available at *Rheumatology* online). Indirect comparisons between the three JAKi using network meta-analysis did not demonstrate any significant difference in risk of SI. Using the SUCRA approach to rank SI risk, baricitinib was indicated as being associated with the lowest risk of SI and tofacitinib the highest. However due to the high levels of uncertainty in the risk estimates, no clear inference can be made regarding the SI risk, compared with either each other or placebo (Supplementary S5, available at *Rheumatology* online).

### Herpes zoster infection

In the per protocol analysis, there were 51 reported cases of HZ among patients receiving 5 mg bid tofacitinib with 2032 PEY; IR 2.51 (95% CI: 1.87, 3.30) per 100 patient-years. There were 26 cases in 822 PEY with baricitinib 4 mg [IR 3.16 (95% CI: 2.07, 4.63)] and four cases in 166

**Fig. 1** Flow chart of studies included in the systematic review and meta-analysis

JAKi: Janus kinase inhibitors.

PEY with upadacitinib 15 mg [IR 2.41 (95% CI: 0.66, 6.18)]. In the pooled placebo group there were 17 cases of HZ with 1398 PEY; IR 1.22 (95% CI: 0.71, 1.95). There were eight serious or disseminated cases (four with tofacitinib and four with baricitinib) vs three in the pooled placebo group.

The estimated IRR of HZ compared with placebo was 1.38 (95% CI: 0.66, 2.88) for tofacitinib, 2.86 (95% CI: 1.26, 6.50) for baricitinib and 0.78 (95% CI: 0.19, 3.22) for upadacitinib, with statistical heterogeneity 0% (95% CI: 0%, 7.5%) (Fig. 3). Similar findings were observed in the tofacitinib-methotrexate combination analysis. However, compared with the per protocol analysis, the limited analysis demonstrates marginally larger risk ratios for both baricitinib and tofacitinib (Supplementary Figs S3 and S4, available at *Rheumatology* online). Overall these data indicate a statistically significant difference in the risk of HZ with baricitinib compared with placebo that is not seen with tofacitinib 5 mg bid or upadacitinib 15 mg bid. Network meta-analysis confirms a greater risk of HZ with baricitinib than placebo. Indirect comparisons between the three JAKi did not demonstrate notable differences in HZ risk between the drugs. Using the SUCRA approach to rank HZ risk, baricitinib was indicated as being associated with the highest risk of HZ and upadacitinib the lowest. High levels of uncertainty in the risk estimates means no clear inference can be made

regarding the HR risk compared with each other or placebo (Supplementary Fig. S5, available at *Rheumatology* online).

There was no evidence of asymmetry on visual examination of funnel plots for both the SI and HZ analyses (Supplementary Fig. S6, available at *Rheumatology* online). However, due to the low incidence rates and large standard errors, it is impossible to rule out a small sample effect such as publication bias.

#### Indicator opportunistic infections

The incidence rates of opportunistic infections are reported in Table 2. Patients with active or latent *Mycobacterium tuberculosis* (LTBI) were excluded from phase II trials. In phase III studies, patients with LTBI were allowed entry after receiving at least 1 month of a planned 9-month isoniazid preventive regimen. In this analysis there was only one episode of tuberculosis in a baricitinib-treated patient for whom protocol-defined screening procedures for LTBI had not been fully completed. A combined crude rate of indicator infections excluding HZ was 0.23 per 100 patient-years. The rate of indicator infection was numerically lowest with tofacitinib. With the inclusion of serious or disseminated HZ events, the incidence rate doubled.

**TABLE 1** Characteristics of the studies included in the meta-analysis

Author (year), study	Phase of study	Population	Dosage and schedule (mg) + placebo	Duration of treatment	Number of subjects: JAKi: placebo	Age, mean (s.d.), years	RA duration years	DAS-28, mean (s.d.)	Prednisolone (%)
<b>Tofacitinib (5 mg bid dose)</b>									
Kremer (2009) [16]	IIb; NA, LA, EU	DMARD/biologic – IR	5, 15, 30	6 weeks	61	47.9 (11)	10.2 (1–35)	6.2**	63.9
					65	51.3 (12)	8.7 (1–27)	6.0**	61.5
<b>Tanaka (2011) [17]</b>									
	IIb; Japan	MTX – IR	1, 3, 5, 10; + MTX	12 weeks	27	50 (9.8)	8.3 (1–26)	6.0	55.6
					28	51 (12.4)	8.4 (1–24)	5.9	71.4
<b>Kremer (2012) [18]</b>									
	IIb; NA, LA, EU	MTX – IR	1, 3, 5, 10, 15, 20; + MTX	24 weeks (NR PBO advanced at 12w)	71	52 (12.8)	9.0 (1–46)	6.1	57.7
					69	53 (13.4)	9.2 (1–39)	6.1	44.9
<b>Fleischmann (2012) [19]</b>									
	IIb; NA, LA, EU, Korea	DMARD – IR	1, 3, 5, 10, 15; or ADA	24 weeks (NR PBO advanced at 12w)	49	54 (13.5)	8.1 (0.5–38)	6.6	55.1
					59	53 (13.7)	10.8 (1–44)	6.6	57.6
<b>Fleischmann (2012) [20], ORAL-Solo</b>									
	III; worldwide	DMARD/ biologic – IR	5, 10	24 weeks (all PBO advanced at 12w)	243	52.2 (12)	8 (0–42)	6.71	57.4
					122	49.7 (12)	7.7 (0–28)	6.65	63.1
<b>van Vollenhoven (2012) [21], ORAL-Standard</b>									
	III; worldwide	MTX – IR	5, 10 or ADA; + MTX	52 weeks (NR PBO advanced at 12w, all PBO advanced at 24w)	204	53.0 (12)	7.6	6.6	61.8
					108	55.5 (14) <sup>a</sup>	6.9 <sup>a</sup>	6.6 <sup>a</sup>	73.2 <sup>a</sup>
						51.9 (14) <sup>b</sup>	9.0 <sup>b</sup>	6.3 <sup>b</sup>	59.6 <sup>b</sup>
<b>Burnester (2013) [22], ORAL-Step</b>									
	III; NA, LA, EU	TNF/MTX – IR	5, 10; + MTX	24 weeks (all PBO advanced at 12w)	133	55.4 (12)	13 (1–55)	6.5 (1.1)	63.9
					132	54.4 (11)	11.3 (0–47)	6.4 (1.1)	62.9
<b>Kremer (2013) [23], ORAL-Sync</b>									
	III; worldwide	DMARD/biologic – IR	5, 10; + MTX	52 weeks (NR PBO advanced at 12w, all PBO advanced at 24w)	315	52.7 (12)	8.1 (0.2–40)	6.27 (1)	61.9
					159	50.8 (11) <sup>a</sup>	9.5 (0–39) <sup>a</sup>	6.44 (1) <sup>a</sup>	59.5 <sup>a</sup>
						53.3 (11) <sup>b</sup>	10.2 (0–49) <sup>b</sup>	6.14 (1) <sup>b</sup>	58.8 <sup>b</sup>
<b>van der Heijde (2013) [24], ORAL-Scan</b>									
	III; worldwide	MTX – IR	5, 10; + MTX	52 weeks (NR PBO advanced at 12w, all PBO advanced at 24w)	321	53.7 (12)	8.9 (0–43)	6.34	–
					160	53.2 (12) <sup>a</sup>	8.8 (1–31) <sup>a</sup>	6.25 <sup>a</sup>	–
						52.1 (12) <sup>b</sup>	9.5 (0–44) <sup>b</sup>	6.29 <sup>b</sup>	–
<b>Lee (2014) [25], ORAL-Start</b>									
	III; worldwide	MTX naïve	5, 10; or MTX	24 months	373	50.3	2.9	6.6	Nil
					186	48.8	2.7	6.6	–
<b>Tanaka (2015) [26]</b>									
	II; Japan	DMARD – IR	1, 3, 5, 10, 15	12 weeks	52	52.6 (11)	11.0 (0–34)	6.41 (1)	–
					52	53.3 (11)	6.4 (1–38)	5.83 (1)	–
<b>Baricitinib (4 mg od dose)</b>									
Keystone (2015) [27]	IIb; NA, CA, EU, India	MTX – IR	1, 2, 4, 8; + MTX	24 weeks (all PBO advanced at 12w)	52	53 (10)	5.3 (4.5)*	6.0 (0.9)	38
					98	49 (12)	5.4 (4.3)*	6.3 (0.8)	52

(continued)

TABLE 1 Continued

Author (year), study	Phase of study	Population	Dosage and schedule (mg) + placebo	Duration of treatment	Number of subjects: JAKi; placebo	Age, mean (s.d.), years	RA duration years	DAS-28, mean (s.d.)	Prednisolone (%)
Tanaka (2016) [28]	II; Japan	MTX – IR	1, 2, 4, 8; + MTX/DMARD	12 weeks (all PBO advanced at 12w)	24 49	58 (10) 51 (12.0)	5.9 (4.0)* 5.1 (4.0)*	5.77 (0.7) 5.53 (1.0)	75 59
Genovese (2016) [29], RA-Beacon	III; worldwide	Biologic – IR	2, 4; + MTX/DMARD	24 weeks (NR PBO advanced at 16w)	177 176	56 (11) 56 (11)	14 (9)* 14 (10)*	6.6 (1.1) 6.6 (0.9)	–
Taylor (2017) [30], RA-Beam	III; worldwide	MTX – IR	4 or ADA; + MTX	52 weeks (NR PBO advanced at 16w, all PBO advanced at 12w)	487 488	54 (2) 53 (2)	10 (9)* 10 (9)*	6.5 (0.9) 6.4 (1.0)	56 59
Fleischmann (2017) [31], RA-Begin	III; worldwide	MTX naïve	4 <sup>a</sup> or 4 +MTX <sup>b</sup>	52 weeks (NR PBO advanced at 24w)	159 <sup>a</sup> 215 <sup>b</sup> 210	51 (13) <sup>a</sup> 49 (14) <sup>b</sup> 51 (13)	1.9 (4.7) <sup>a*</sup> 1.3 (2.7) <sup>b*</sup> 1.3 (4.0)*	6.6 (1) <sup>a</sup> 6.6 (1) <sup>b</sup> 6.6 (1)	30 <sup>a</sup> 39 <sup>b</sup> 36
Dougados (2017) [32], RA-Build	III; worldwide	DMARD – IR	2, 4; + MTX/DMARD	24 weeks (NR PBO advanced at 16w)	227 228	52 (12) 51 (13)	8 (8)* 7 (8)*	6.2 (0.9) 6.2 (1.0)	–
Upadacitinib (6 mg bid or 15 mg od dose)									
Genovese (2016) [33]	IIb; worldwide	MTX – IR	3, 6, 12, 18 bid, 24 od; + MTX	12 weeks	50 50	55 (12) 55 (12)	7.0 (5.5)* 5.9 (5.3)*	5.8 (1)** 5.6 (1)**	32 16
Kremer (2016) [34]	IIb; worldwide	TNF – IR	3, 6, 12, 18 bid; + MTX/DMARD	12 weeks	55 56	56 (12) 58 (13)	12.3 (10.6)* 12.1 (9.0)*	5.9 (1)** 5.8 (1)**	–
Genovese (2018) [35], SELECT-Beyond	III; worldwide	Biologic – IR	15, 30 od; + MTX/DMARD	24 weeks (all PBO advanced at 24w)	164 169	56 (11) 58 (11)	12.4 (9.4)* 14.5 (9.2)*	5.9 (1)** 5.8 (1)**	51 44
Burmester (2018) [36], SELECT-Next	III; worldwide	DMARD – IR	15, 30 od; + MTX/DMARD	12 weeks	221 221	53 (12) 56 (12)	7.3 (7.9)* 7.2 (7.5)*	5.7 (1)** 5.6 (1)**	43 48

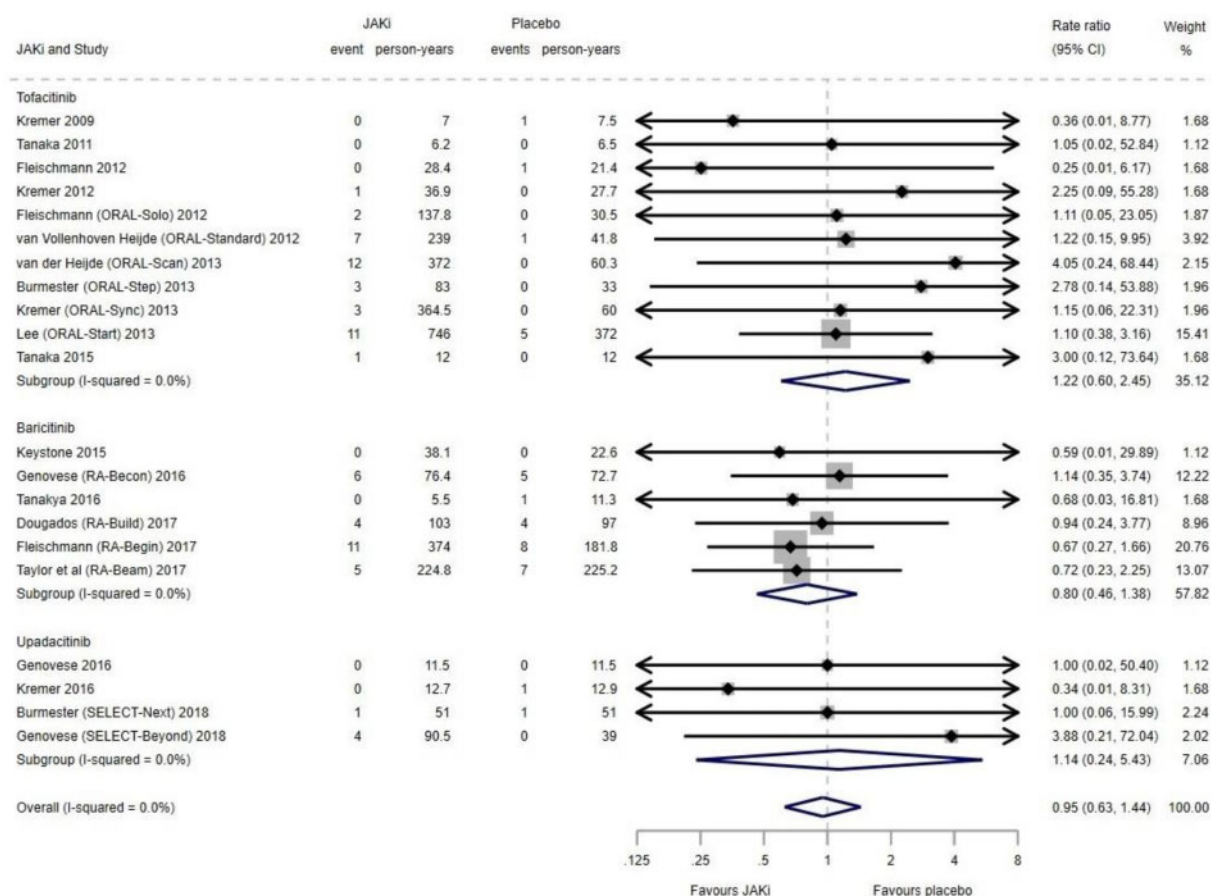
<sup>a,b</sup>denote data from two placebo groups in van Vollenhoven (2012) [21], Kremer (2013) [23] and van der Heijde (2013) [24] studies.

<sup>a,b</sup>denote data from two treatment arms (baricitinib monotherapy and baricitinib methotrexate combination) in the Fleischmann (2017) [31] study.

EU: European Union; LA: Latin America; NA: North America; IR: inadequate response; PBO: placebo; NR: non-responder.

Disease duration reported in median (range); \* : Disease duration in mean (s.d.), DAS28 calculated with ESR; \*\* : DAS28 calculated with CRP.

**FIG. 2** Forest plots for incident risk ratios of serious infections between patients receiving Janus kinase inhibitor or placebo



## Discussion

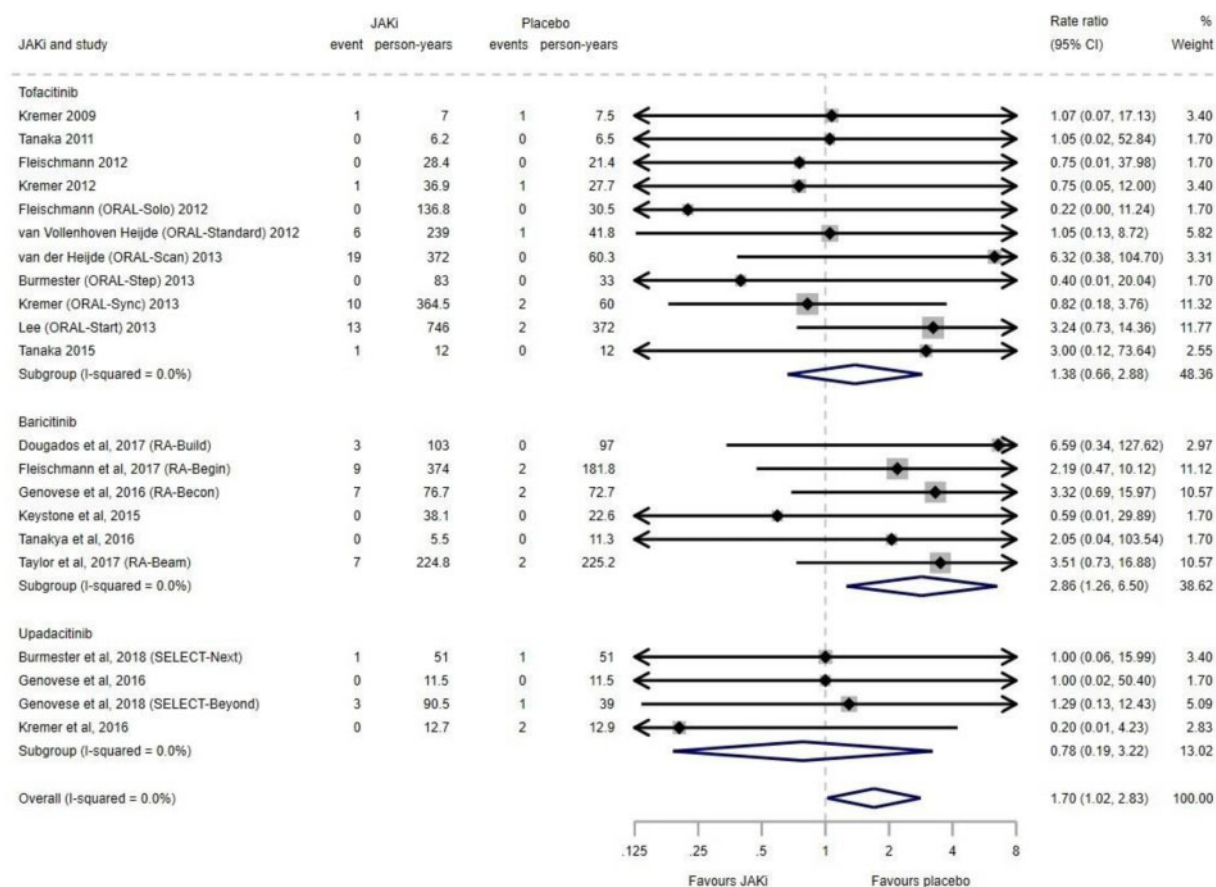
To our knowledge, this is the first systematic review and meta-analysis reporting on safety of licensed dose JAKi in RA. This study has demonstrated a greater risk of HZ with baricitinib than placebo, although indirect comparisons between the three drugs did not demonstrate any significant difference in risk.

The absolute event rates for SI were low. The incidence rate ratios comparing to placebo were numerically different between tofacitinib, baricitinib and upadacitinib. However uncertainty in the estimated rates is high due to the rare nature of SI, and thus it would be inappropriate to use this numerical difference as evidence of a differential risk between the agents. The placebo cohorts differed in their base incidence rate (tofacitinib 1.19, baricitinib 4.09 and upadacitinib 1.75), which impacts the overall incidence rate ratios. This difference in placebo base rate may reflect differences in inclusion criteria, indicating the possibility of selection bias. For example, only 1 of 6 baricitinib studies compared with 4 of 11 tofacitinib studies recruited patients who had received biologics. The SI incidence rate for tofacitinib is lower than that published by

Strand *et al.* and Cohen *et al.*, with rates of 3.0 and 2.7 per 100 patient-years, respectively [37,38]. This discrepancy may be explained by both authors having access to patient-level data and by the inclusion of the 10 mg treatment arm and long-term extension studies by Cohen *et al.*

The most characteristic infectious complication with JAKi has been the reactivation of VZV. Our meta-analysis confirms this signal. The incidence rate of HZ with tofacitinib was lower than that seen with the inclusion of LTE trials and the addition of higher doses (2.1 vs 4.4) [8]. With baricitinib, the rate was similar to that reported in LTE and with higher doses (3.4 vs 3.2) [39]. Across the JAKi, the rate was ~3.23 per 100 patient-years. This is higher than that seen with anti-TNF-therapy (1.6) [40]. The rate in the pooled placebo group was 1.05. This is in keeping with rates reported from the UK primary care database, ranging from 0.35 in those under 50 to 1.25 in those over 70 [41].

We demonstrated a significantly increased risk of HZ with baricitinib compared with placebo. A statistically significant increase was not apparent with tofacitinib or upadacitinib, although due to levels of uncertainty in the estimates a true effect cannot be ruled out. Identifying a

**Fig. 3** Forest plots for incidence risk ratios of herpes zoster infections between Janus kinase inhibitor or placebo**TABLE 2** Indicator infections with tofacitinib, baricitinib, upadacitinib and pooled placebo

	Pooled placebo	Tofacitinib	Baricitinib	Upadacitinib
Indicator infection (n)				
<i>Mycobacterium tuberculosis</i>	0	0	1	0
<i>Pneumocystis jirovecii</i> pneumonia	0	1	1	0
Oral or oesophageal candidiasis	2	2	1	1
Hepatitis C	1	0	0	0
Varicella-zoster	1	0	0	0
HZ (disseminated or serious)	3	4	4	0
HZ (non-serious infection)	14	47	22	4
Patient exposure years	1398	2032	822	166
Incidence rate (95% CI) <sup>a</sup>				
Excluding HZ	0.29 (0.08, 0.72)	0.15 (0.03, 0.43)	0.36 (0.08, 1.07)	0.60 (0.02, 3.36)
Including serious/disseminated HZ	0.50 (0.20, 1.03)	0.34 (0.14, 0.71)	0.85 (0.34, 1.75)	0.60 (0.02, 3.36)
Including all HZ events	1.50 (0.93, 2.30)	2.66 (2.00, 3.47)	3.53 (2.36, 5.07)	2.41 (0.66, 6.18)

<sup>a</sup>Incidence rate (per 100 years). HZ: herpes zoster.

biologically plausible mechanisms whereby HZ events are higher with baricitinib is challenging, especially since the pathogenesis underlying the risk of HZ with JAKi is poorly understood.

HZ occurs due to reactivation of VZV, which establishes latency in the dorsal root after primary infection [42]. Cell-mediated immunity plays a greater role than humoral responses in the prevention of VZV reactivation. Declining

cell-mediated immunity with age is associated with a reduction in VZV-specific T cells, disrupting immune surveillance and increasing the risk of reactivation. The immune response to VZV is mediated in part via the JAK-STAT pathway. Interferon signalling is essential for both innate and adaptive responses [43]. Type I interferon response is regulated by JAK1-TYK2 complexes and type II interferon mediated via JAK1-JAK2 complexes [44,45]. Baricitinib demonstrates greater inhibition of JAK2 and TYK2 than tofacitinib or upadacitinib [44]. Patients with deficiencies in NK cell function experience an extreme susceptibility to infection with VZV. NK development and activation are also dependent on cytokines mediated via the JAK-STAT pathway and a dose-dependent decline in peripheral blood NK cell counts has been reported with all JAKi [46–48].

The variable pharmacokinetics alongside the possibility of ‘pan-JAK’ inhibition may explain differences in HZ event profiles with JAKi. The selective targeting of specific JAKs is dose dependent. At higher doses JAKi can block other members of the JAK family, leading to ‘pan-JAK’ inhibition [44,48,49]. In the phase III RCTs, 4 mg of baricitinib was considered the higher of the therapeutic doses, while 5 mg of tofacitinib and 15 mg of upadacitinib were the lower treatment doses. This may explain the differences in risk profile of HZ. This potential for ‘pan-JAK’ inhibition is theoretically higher in routine care patients who have a greater number of co-morbidities and poly-pharmacy. The metabolism of tofacitinib is primarily mediated by CYP3A4, while baricitinib is dependent on renal elimination [50,51]. These pharmacokinetics properties may increase the possibility of dose toxicity and ‘pan-JAK’ inhibition.

There are several considerations when interpreting these results. The increasing incidence of HZ with age is well recognized. It is a critical confounder and subtle differences in age distribution from these clinical trials could cause significant differences in HZ events. A geographic variation in rates of HZ with JAKi exists, with highest rates seen in Japan and Korea [48]. This is relevant when examining data extrapolated from studies across different geographical regions. A quarter of the studies in this meta-analysis did not recruit from countries in Asia, which may contribute to a lower overall incidence of HZ. Without patient level data, it is difficult to examine this further. Prednisolone has been consistently shown to increase the risk of HZ by 1.5- to 2-fold [52]. Our ability to evaluate the influence of glucocorticoids is limited; the doses and the total duration of glucocorticoid exposure are not reported in detail and may be a potential confounder.

Indicator opportunistic infection events were too rare to provide meaningful incidence rates. A combined crude rate for all three drugs was 0.23 per 100 patient-years. This is higher than seen with biologic therapy in the UK registry data (0.13) [14]. The consensus definition of an indicator OI is broader than previous definitions, which may explain differences compared with previous analyses. The main driver of this rate differential is whether the authors considered HZ as an OI or not. There were no

cases of tuberculosis in the tofacitinib or upadacitinib trials. This is in keeping with the current literature; cases have been solely in the tofacitinib 10 mg treatment arms [37,53]. We did not include unlicensed doses in this analysis. Long term extension studies were also excluded from this analysis, which may explain the low event rate, as the median time from commencing tofacitinib therapy until TB diagnosis is 64 weeks (range 15–161) [53].

There are several strengths of this study. Restricting to licensed doses is of importance. Previous publications have included doses above the licensed level. Unlike biologics, where there is perfect target specificity (i.e. no matter how large the dose, you will only inhibit the TNF activity), with small molecules, the target specificity is dose dependant. Analysing licensed doses reduces the likelihood of detecting signal seen outside the therapeutic window [54].

We acknowledged the escape design employed by most studies. This design influences the incidence of adverse events, since one arm has a continuous exposure to the drug, whereas in the other arm, the exposure is first to placebo and then to drug [55]. To control for this, we calculated incidence rates using summations of the population exposure risk; a per protocol and a limited analysis were employed. The per protocol strategy may have led to an underestimation of infection risk. Compared with the limited analysis, the per protocol demonstrated a smaller risk of HZ with both tofacitinib and baricitinib compared with placebo. As seen with biological immunosuppression in RA, infection risk is time dependant with the greatest risk early on. The per protocol design includes a longer exposure time to JAKi than to placebo. Lengthening the follow-up exposure time would predictably lower the infection risk estimate. The opposite may hold true when considering other opportunistic infections that take time to establish and correctly diagnose, for example tuberculosis. In this scenario the per protocol strategy may overestimate the infection risk with the JAKi.

There are limitations to this study. Second generation JAKi filgotinib, decernotinib and peficitinib were excluded from the analysis. At the time of writing there were no published phase III trials for these drugs. We felt it was wrong to compare safety data between JAKi that had not been evaluated in phase III trials, as the dose for clinical use has not been delineated. For that reason, it would not be appropriate to comment on the risk of serious infections or HZ with these agents. Of the trials included in the analysis, the sample sizes were relatively small, powered for efficacy and not for the detection of adverse events. Alongside this, the stringent inclusion criteria that are essential for the internal validity of a trial can limit generalizability to the routine care population. It is possible that differences in infections become more obvious in patients who are at a higher risk and who do not meet the RCT inclusion criteria. The increased risk of HZ with TNF inhibitors was recognized during post-marketing surveillance in drug registry data, without a strong signal in phase II and III trials [40,56]. We acknowledge the background differences in the study placebo rates of infection. As such, the

differences seen with infection rates could possibly relate to the study population and not the JAKi. Despite acting as an important framework for identifying serious adverse events, summary data rather than individual level data were aggregated for analyses. This may have resulted in a lack of granularity regarding each infectious event. Lastly, the definition of an indicator infection has only been established in recent years and may have influenced the reporting of OI, resulting in ascertainment bias.

In conclusion, this study has not demonstrated a significant increased risk of SI with licensed-dose JAKi compared with placebo. A notable increased risk of HZ with baricitinib was observed. However, the network meta-analysis casts doubt over whether any difference between JAKi are of a magnitude that is clinically meaningful. The imminent publications of active phase III trials with the other JAKi and data from post-marketing surveillance by drug registries may provide new insights into the differential risk of infections with JAK inhibition, and the mechanisms behind the association with HZ.

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## Supplementary data

Supplementary data are available at *Rheumatology* online.

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