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CLINICAL SCIENCE

Infections in baricitinib clinical trials for patients with active rheumatoid arthritis

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ABSTRACT

Objectives To evaluate the incidence of infection in patients with active rheumatoid arthritis (RA) treated with baricitinib, an oral selective Janus kinase (JAK)1 and JAK2 inhibitor.

Methods Infections are summarised from an integrated database (8 phase 3/2/1b clinical trials and 1 long-term extension (LTE)) with data to 1 April 2017. The 'all-bari-RA' analysis set included patients who received any baricitinib dose. Placebo comparison was based on six studies with 4 mg and placebo to week 24, including four trials with 2 mg (placebo-controlled set). Dose–response assessment was based on four studies with 2 mg and 4 mg, including LTE data (2–4 mg extended set).

Results There were 3492 patients who received baricitinib for 7860 patient-years (PY) of exposure (median 2.6 years, maximum 6.1 years). Treatment-emergent infections were higher for baricitinib versus placebo (exposure-adjusted incidence rate (IR)/100 PY: placebo 75.9, 2 mg 84.0 (p not significant), 4 mg 88.4 (p≤0.001)). The IR of serious infection was similar for baricitinib versus placebo and stable over time (all-bari-RA IR 3.0/100 PY). There were 11 cases of tuberculosis (all-bari-RA IR 0.1/100 PY); all occurred with 4 mg in endemic regions. Herpes zoster (HZ) IR/100 PY was higher for baricitinib versus placebo (placebo 1.0, 2 mg 3.1 (p not significant), 4 mg 4.3 (p≤0.01)); rates remained elevated and stable over time (all-bari-RA 3.3). Opportunistic infections, including multidermatomal HZ, were infrequent in the baricitinib programme (all-bari-RA IR 0.5/100 PY).

Conclusions Increased rates of treatment-emergent infections including HZ were observed in patients with RA treated with baricitinib, consistent with baricitinib's immunomodulatory mode of action.

Key messages

What is already known about this subject?
► Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with an elevated risk of infection, which can be caused by the pathobiology of the disease, chronic comorbid conditions and use of immunosuppressive therapies, such as biologic (b), conventional synthetic and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs).

What does this study add?
► This study provides data to inform the understanding of risk of infection in patients with RA and the use of the emerging class of tsDMARDs, in particular Janus kinase (JAK) inhibitors.
► Increased rates of treatment-emergent infections including herpes zoster (HZ) were observed in patients with RA treated with baricitinib, similar to that observed for other JAK inhibitors.
► The incidence of serious infection did not increase with baricitinib versus placebo in the 24-week randomised, controlled period but was similar to that reported in other recent tsDMARD and bDMARD development programmes with both short-term and long-term data.
► There were 11 cases of tuberculosis reported within the baricitinib RA programme; all occurred with 4 mg and in endemic regions. Opportunistic infections, including multidermatomal HZ, were infrequent in the programme.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with an elevated risk of infection,[1 2] which can be caused by the pathobiology of the disease, chronic comorbid conditions and use of immunosuppressive therapies, including conventional synthetic (cs) and biological (b) disease-modifying antirheumatic drugs (DMARDs).[1–4] Within the emerging class of targeted synthetic DMARDs (tsDMARDs), Janus kinase (JAK) inhibitors target cytokine signalling pathways implicated in RA pathogenesis.[5] Like other RA therapies, JAK inhibition is associated with increased infection.[6 7] Further analyses of additional and long-term data are needed to understand this association and characterise the risk versus benefit.

Baricitinib, an oral selective JAK1 and JAK2 inhibitor,[8] demonstrated significant clinical efficacy in phase 3 RA trials.[9–12] Pooled data from these trials, including a long-term extension (LTE), inform the safety profile for baricitinib[13]; our objective was to further evaluate overall infection risk

Key messages

How might this impact on clinical practice or future developments?
► As with biological DMARD therapy, screening and treatment for latent tuberculosis infection should be employed prior to starting baricitinib.
► Although data on HZ vaccination in a small subgroup did not demonstrate a protective effect, current treatment guidelines recommend HZ vaccination prior to initiation of a Janus kinase inhibitor, particularly in RA patients ≥50 years at high risk for infection.
► Long-term population-based studies are necessary to better understand the comparative real-world risk of baricitinib and targeted synthetic DMARD therapies in RA.

with baricitinib, with a focus on serious infection, tuberculosis (TB), herpes zoster (HZ) and opportunistic infection (OI).

PATIENTS AND METHODS

Study designs and patients

We present data from eight double-blind randomised trials (four phase 3, three phase 2 and one phase 1b) and one ongoing phase 3 LTE trial, with data up to 6 years (as of 1 April 2017) (online supplementary table S1). Patients were ≥18 years with active RA, including those naive to DMARDs, csDMARD-inadequate responders (csDMARD-IRs), and bDMARD-IRs. Exclusion criteria included current or recent clinically serious infection requiring antimicrobial treatment (including active or untreated latent tuberculosis infection (LTBI)), immunocompromised patients (with an unacceptable risk for participation as determined by the investigator) and selected laboratory abnormalities. Baricitinib doses ranged from 1 to 15 mg daily, with 2 mg and 4 mg daily doses in phase 3 trials and LTE. All patients provided written informed consent.

Patients who completed the phase 3 trials and phase 2 trial NCT01185353 were eligible for the LTE. Patients randomised to 2 mg and not rescued in the originating study continued on 2 mg in the LTE; all others received 4 mg. Patients who received 4 mg for ≥15 months without rescue and achieved sustained low disease activity (Clinical Disease Activity Index (CDAI) score ≤10) or remission (CDAI score ≤2.8) were blindly rerandomised to 4 mg or 2 mg.

Methods for infection screening and monitoring processes, and case identification, description and review are included in the online supplementary methods and table S2.

Patient and public involvement

This research was done without patient and public involvement.

Analysis sets

Baricitinib RA clinical trials, including treatment groups, datasets and prior RA treatments, are described in online supplementary table S1.
1. 'Placebo controlled' includes data for patients in phase 2 and 3 trials randomised to placebo, 2 mg (four trials) or 4 mg (six trials) through 24 weeks of treatment or end of the placebo-controlled period with data censored at rescue.
2. '2–4 mg extended' includes data for patients randomised to 2 mg or 4 mg from four trials (phase 2 and 3), with data from the LTE up to 6 years. Data were censored at rescue or dose change.
3. 'All-bari-RA' includes all available data for all patients who received ≥1 dose of baricitinib without censoring for rescue or dose change, with data up to 6 years.

Statistical analysis

Each baricitinib dose was compared with placebo using the Cochran-Mantel-Haenszel test stratified by study. For adverse events including treatment-emergent (TE) events, exposure-adjusted incidence rates (EAIRs) were calculated as the number

Table 1 Overview of treatment-emergent infections, serious infection, TB, HZ, opportunistic infection and infection leading to death

	Placebo-controlled (to Week 24)*			2–4 mg-extended†		All-bari-RA
	Placebo N=1070 PYE=393.8‡	Bari 2 mg§ N=479 PYE=185.8‡	Bari 4 mg N=997 PYE=409.4‡	Bari 2 mg N=479 PYE=604.9‡	Bari 4 mg N=479 PYE=645.9‡	All-bari-RA N=3492¶ PYE=7860.3‡
TE infections, n (EAIR)	299 (75.9)	156 (84.0)	362 (88.4)***	230 (38.0)	266 (41.2)	2114 (26.9)
Led to temporary interruption of study drug	52 (13.4)	34 (18.3)	67 (16.6)	63 (10.4)	73 (11.3)	623 (8.0)
Led to permanent discontinuation from study drug	8 (2.0)	7 (3.8)	22 (5.2)**	11 (1.8)	22 (3.3)	139 (1.7)
Serious infection, n (IR)	17 (4.2)	8 (4.2)	16 (3.8)	20 (3.3)	31 (4.8)	231 (3.0)
Tuberculosis, n (IR)	0	0	1 (0.2)	0	6 (0.5)	11 (0.1)
HZ, n (IR)	4 (1.0)	6 (3.1)	18 (4.3)**	17 (2.8)	25 (3.9)	258 (3.3)
Opportunistic infection excluding TB, n (IR)						
Including MD HZ††	2 (0.5)	0	3 (0.8)	2 (0.3)	2 (0.3)	43 (0.5)‡‡
Excluding MD HZ††	1 (0.3)	0	2 (0.5)	2 (0.3)	1 (0.2)	21 (0.3)‡‡
Infection leading to death, n (EAIR)	2 (0.5)	0	1 (0.2)	0	1 (0.2)	7 (0.1)

*Data from treatment period up to week 24, with data up to rescue.
†All analysis based on as-treated method, with data censored at rescue or dose change.
‡Including postdrug follow-up period where applicable.
§Baricitinib 2 mg data in the placebo-controlled analysis set is derived from four studies in which both baricitinib 2 mg and 4 mg were options during randomisation.
¶All-bari-RA (patients who received any baricitinib dose) includes patients who switched from placebo, adalimumab or methotrexate to baricitinib, in addition to patients randomised to any baricitinib dose. Thus, it is a larger group than the 2 mg and 4 mg groups added together.
**p≤0.01, ***p≤0.001 for baricitinib 4 mg compared with placebo.
††Multidermatomal HZ, as defined by HZ infection distributed beyond primary and adjacent dermatomes.
‡‡Two patients reported two OIs; one patient with pneumonia (with infecting organisms of cytomegalovirus and *Pneumocystis*) and one patient with concurrent cytomegalovirus infection and oesophageal candidiasis. Overall, 43 patients reported 45 total OIs including MD HZ; 21 patients reported 23 OIs not including MD HZ.
Bari, baricitinib; EAIR, exposure-adjusted incidence rate; HZ, herpes zoster; IR, incidence rate; MD, multidermatomal; n, number of patients in the specified category; N, number of patients in the analysis set; OI, opportunistic infection; PYE, patient-years of exposure; RA, rheumatoid arthritis; TB, tuberculosis; TE, treatment-emergent.

of unique patients with an event per 100 patient-years of study drug exposure time. For events of special interest, including TE serious infections, TB, HZ and OIs, incidence rates (IRs) were calculated as the number of unique patients with an event per 100 patient-years of observation time, including any postdrug follow-up time, censored at event. A 95% CI was calculated for the IR by time and overall using the Poisson distribution.

Potential risk factors for serious infection and HZ were evaluated using the all-bari-RA dataset. Covariates with a significant association (p<0.05) from a univariable model were selected for a multivariable Cox regression model based on first infection event. Results from the multivariable models are presented.

RESULTS

Patients

Patient demographics and disease activity were generally similar between treatment groups across analysis sets (online supplementary table S3). In the all-bari-RA analysis set, 3492 patients with RA received baricitinib, with 7860 patient-years of exposure. Of these, 2723 (78.0%) and 1788 (51.2%) were treated for ≥52 weeks and ≥130 weeks, respectively.

Infections

TE infection

The TE infection EAIR was significantly higher for 4 mg compared with placebo (88.4 vs 75.9) in the placebo-controlled analysis set; the 2 mg EAIR was not (84.0; table 1). The higher TE infection EAIR for 4 mg is attributed to a higher incidence of upper respiratory tract, HZ and herpes simplex infections. Temporary interruptions and permanent discontinuations (required per protocol for HZ infections) of study drug were more common for 4 mg vs placebo (table 1). The 2–4 mg extended TE infection EAIRs were similar (38.0 vs 41.2, respectively), and the all-bari-RA EAIR was 26.9 (table 1).

Serious infection

The serious infection IR was similar for baricitinib versus placebo (figure 1A, table 1). The placebo-controlled IR was 4.2, 4.2, and 3.8, for placebo, 2 mg and 4 mg, respectively, and the 2–4 mg extended IR was 3.3 vs 4.8, respectively. The all-bari-RA IR was 3.0 (95% CI 2.6 to 3.4), with no increased incidence over time (figure 1B). In all-bari-RA, the most common serious infections were pneumonia (n=46, EAIR 0.6), HZ (n=31, EAIR 0.4), urinary tract infection (n=19, EAIR 0.2), cellulitis (n=12, EAIR 0.2) and sepsis (n=12, EAIR 0.2). Few events of serious pneumonia and serious HZ occurred in the placebo-controlled period. Advancing age (≥65 years), abnormal body mass index (BMI; <18 (underweight) or ≥30 (obese) vs 18–24 kg/mg^2 (normal)), region of enrolment (Asia (excluding Japan) and Rest of World vs USA/Canada) and concomitant glucocorticoids (regardless of dose (<5 or ≥5 mg/day)) were independent factors associated with increased risk of serious infection in all-bari-RA (figure 1C). In a stratified analysis of infection rates with these individual factors, while the number of patients in each subgroup was small, similar numbers were noted in the baricitinib and placebo groups within the placebo-controlled data set (online supplementary table S4). In all-bari-RA, infections led to death in seven patients (EAIR 0.2; table 1).

Tuberculosis

Eleven TB cases were reported in all-bari-RA (IR 0.1, 95% CI 0.1 to 0.2; table 1); all occurred with 4 mg and were confirmed through external medical review. One case occurred in the
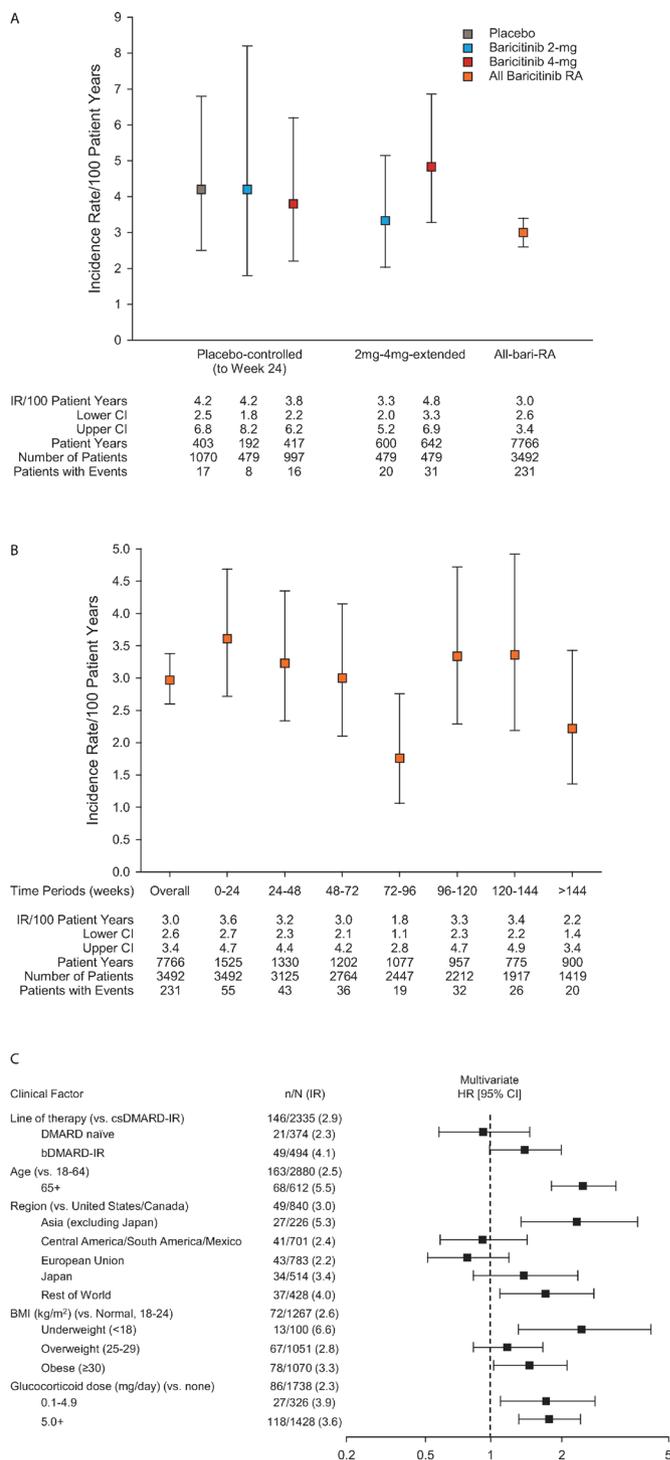

Figure 1 Serious infection IR and multivariable risk factor analysis. (A) Serious infection IR by analysis set (IR per 100 PY; 95% CI). Baricitinib 2 mg data in the placebo-controlled analysis set are derived from four studies in which both baricitinib 2 mg and 4 mg were options during randomisation. (B) Serious infection IR by time period in the all-bari-RA analysis set (IR per 100 PY; 95% CI). (C) Multivariable risk factor analysis for serious infection in the all-bari-RA analysis set (HR; 95% CI). Bari, baricitinib; bDMARD-IR, biologic DMARD inadequate responder; BMI, body mass index; CI, confidence interval; csDMARD-IR, conventional synthetic DMARD inadequate responder; DMARD, disease-modifying antirheumatic drug; HR, hazard ratio; IR, incidence rate; n, number of patients in the specified category; N, number of patients in the analysis set; PY, patient-years; RA, rheumatoid arthritis.

placebo-controlled period, one after rescue from placebo to 4 mg, and nine after LTE entry. Five cases were associated with pulmonary involvement, including one miliary TB. Seven cases involved extrapulmonary infection sites, including the abdomen (n=2, including one patient with pulmonary co-infection), lymph node (n=2), mediastinum (n=1) and vertebrae (n=2, including one patient with psoas abscess coinfection). In four cases, no organism was identified and the diagnosis was based on clinical presentation and course. All occurred in endemic regions, including Argentina, India, Russian Federation, South Africa, South Korea and Taiwan. Online supplementary table S5 presents IRs in all-bari-RA in the context of background rates for patients with RA in these regions. Characteristics of reported TB cases are presented in online supplementary table S6.

During screening for the four originating phase 3 trials, 45 (1.4%) and 101 (3.1%) patients were excluded from randomisation based on diagnosis of active TB or LTBI, respectively. Approximately 7%–12% of patients randomised to treatment in these trials had evidence of LTBI. Of 227 patients who received isoniazid at screening, two were later diagnosed with active TB after completing treatment per local guidelines. In one case, no organism was identified, and in the other, no susceptibility information was obtained (online supplementary table S6).

Of the 11 reported cases of clinically overt TB in all-bari-RA, seven patients had negative TB test results at screening. Two patients, as noted, received treatment for LTBI based on screening test results. Two patients had deviations in TB screening and did not receive treatment for LTBI. All 11 patients stopped baricitinib and received treatment for active TB; six patients were reported as recovered/recovering, of whom two resumed baricitinib. One patient with a negative purified protein derivative test at screening died from disseminated TB and sepsis despite TB treatment, antibiotics and supportive care. The remaining patients reported as not recovered were continuing TB treatment at the time of study discontinuation. An evaluation of hepatic safety in patients who received concomitant isoniazid is described in the online supplementary results and table S7.

Herpes zoster

In the placebo-controlled set, the HZ IR was statistically significantly higher for 4 mg compared with placebo (4.3 vs 1.0); the 2 mg IR was also increased (3.1), but did not reach statistical significance (figure 2A, table 1). The 2–4 mg extended IR was 2.8 vs 3.9, respectively, and the all-bari-RA IR was 3.3 (95% CI 2.9 to 3.8; figure 2A, table 1). In all-bari-RA, the HZ IR by 6-month intervals showed no increase over time (figure 2B). Most HZ infections reported in 258 patients were mild to moderate in severity; 31 (12.0%) patients had serious HZ infections and 22 (8.5%) had infections categorised as multidermatomal HZ (distribution beyond primary and adjacent dermatomes). All cases were cutaneous; four (1.6%) were associated with facial palsy (n=3) or other motor nerve palsy (n=1), seven (2.7%) had ocular involvement (cornea or deeper structure) and seven (2.7%) had recurrent HZ infections. There were no cases with visceral involvement.

HZ incidence was highest among patients from Japan (IR 6.9) and Asia (excluding Japan) (IR 6.3; online supplementary table S8). In all-bari-RA, advancing age and region (Asia (excluding Japan) and Japan) were independent factors associated with increased risk of HZ infection (figure 2C). Concomitant glucocorticoid use was not associated with increased risk of HZ in baricitinib-treated patients in the univariable analysis. More than half (51.6%) of patients with HZ-reported concomitant
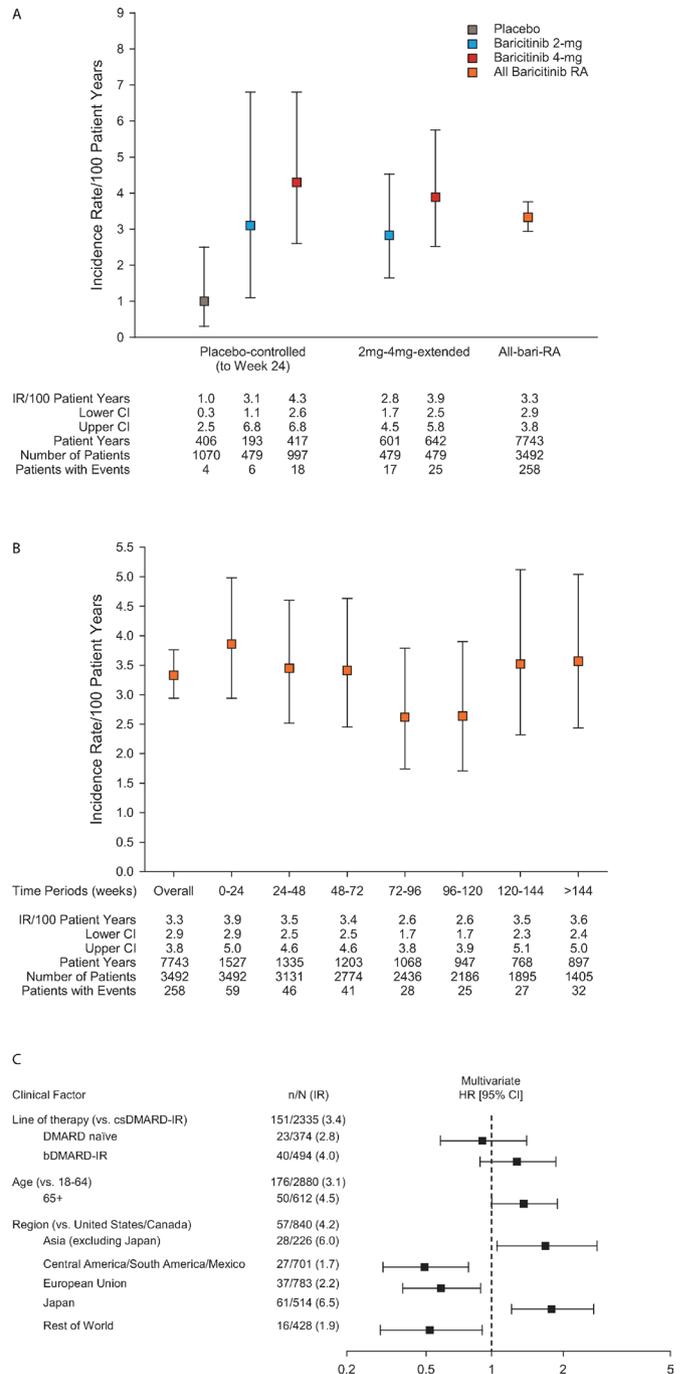

Figure 2 Herpes zoster IR and multivariable risk factor analysis. (A) Herpes zoster IR by analysis set (IR per 100 PY; 95% CI). Baricitinib 2 mg data in the placebo-controlled analysis set are derived from four studies in which both baricitinib 2 mg and 4 mg were options during randomisation. (B) Herpes zoster IR by time period in the all-bari-RA analysis set (IR per 100 PY; 95% CI). (C) Multivariable risk factor analysis for herpes zoster infection in the all-bari-RA analysis set (HR 95% CI). Other covariates, such as baseline disease activity, glucocorticoid use and concomitant methotrexate that did not show significance in the univariable model were not analysed in the multivariable model. Bari, baricitinib; bDMARD-IR; biological DMARD inadequate responder; CI, confidence interval; csDMARD-IR, conventional synthetic DMARD inadequate responder; DMARD, disease-modifying antirheumatic drug; HR, hazard ratio; IR, incidence rate; n, number of patients in the specified category; N, number of patients in the analysis set; PY, patient-years; RA, rheumatoid arthritis.

Table 2 Overview of opportunistic infections excluding tuberculosis

n (IR)	Placebo controlled (to week 24)*			2–4 mg-extended†		All-bari-RA
	Placebo N=1070	Bari 2 mg‡ N=479	Bari 4 mg N=997	Bari 2 mg N=479	Bari 4 mg N=479	All-bari-RA N=3492§
Multidermatomal HZ¶	1 (0.3)	0	1 (0.3)	0	1 (0.2)	22 (0.3)
Cytomegalovirus**	0	0	0	0	0	5 (0.1)
Aspergillus	0	0	0	0	0	1 (0.0)
Candida††	1 (0.3)	0	2 (0.5)	0	0	10 (0.1)
Cryptococcal	0	0	0	1 (0.2)	0	1 (0.0)
Histoplasmosis	0	0	0	1 (0.2)	0	1 (0.0)
Paracoccidioides	0	0	0	0	1 (0.2)	1 (0.0)
Pneumocystis‡‡	0	0	0	0	0	4 (0.1)

*Data from treatment period up to week 24, with data up to rescue.
†All analysis based on as-treated method, with data censored at rescue or dose change.
‡Baricitinib 2 mg data in the placebo-controlled analysis set is derived from four studies in which both baricitinib 2 mg and 4 mg were options during randomisation.
§All-bari-RA (patients who received any baricitinib dose) includes patients who switched from placebo, adalimumab or methotrexate to baricitinib, in addition to patients randomised to any baricitinib dose. Thus, it is a larger group than the 2 mg and 4 mg groups added together.
¶Multidermatomal HZ, as defined by HZ infection distributed beyond primary and adjacent dermatomes.
**Includes preferred terms cytomegalovirus infection (n=2), septic shock and cytomegalovirus infection (n=1), pneumonia cytomegaloviral (n=1) and pneumonia (with infecting organisms cytomegalovirus and *Pneumocystis carinii*; n=1).
††Includes oesophageal candidiasis (n=7 total; 2/7 events on baricitinib 4 mg in placebo-controlled period), lung infection (*Candida albicans*; n=1), sinusitis (*Candida glabrata*; n=1) and muscle abscess ((*C. albicans and C. tropicalis*; on placebo) and soft-tissue infection (*C. tropicalis*; on baricitinib); n=1).
‡‡Includes preferred terms *Pneumocystis jirovecii* pneumonia (n=3) and pneumonia (with infecting organisms reported as cytomegalovirus and *Pneumocystis carinii*; n=1). The infecting organism *Pneumocystis jirovecii* was previously classified as *Pneumocystis carinii*.
Bari, baricitinib; HZ, herpes zoster; IR, incidence rate; n, number of patients in the specified category; N, number of patients in the analysis set; RA, rheumatoid arthritis.

glucocorticoid use of any dose at the time of the first baricitinib dose, one-quarter of whom used <5 mg/day. Online supplementary table S9 shows the all-bari-RA HZ IR by glucocorticoid daily dose administered at the time of the first baricitinib dose.

Due to increased infection risk, the 2015 American College of Rheumatology guidelines[14] recommend HZ vaccination in RA patients ≥50 years. A total of 125 (4.3%) of 2890 patients enrolled in phase 3 trials received the HZ live-attenuated vaccine before randomisation, of whom 91 (72.8%) were vaccinated within 1 year prior to randomisation. Of the 125 patients who received HZ vaccination at any time before randomisation, 7 (5.6%, IR 2.9, 95% CI 1.2 to 6.0) developed ≥1 TE HZ event; of 91 patients who received the vaccine within 1 year of randomisation, 3 (3.3%, IR 1.8, 95% CI 0.4 to 5.2) developed ≥1 TE HZ event. Of patients who did not receive the vaccine before randomisation, 164 (5.9%, IR 3.2, 95% CI 2.7 to 3.7) developed ≥1 TE HZ event.

Opportunistic infection

OIs, including multidermatomal HZ, were infrequent (table 1). Few events occurred during the placebo-controlled period and incidence was similar across treatment groups (table 1). In all-bari-RA, 43 patients reported 45 OIs, including multidermatomal HZ (IR 0.5, 95% CI 0.4 to 0.7); 21 patients reported 23 OIs, excluding multidermatomal HZ (IR 0.3, 95% CI 0.2 to 0.4; table 1).

There were 22 cases of multidermatomal HZ in all-bari-RA (IR 0.3, 95% CI 0.2 to 0.4; table 2). Other OIs included cytomegalovirus infection (n=5; includes two cytomegalovirus infection, one septic shock and cytomegalovirus infection, and two pneumonia), pneumocystis (n=4), candidiasis (n=10; includes seven oesophageal, one lung, one sinusitis and one soft-tissue infection), and single cases of aspergillosis (skin), cryptococcal pneumonia (lung), histoplasmosis (thoracic cavity) and paracoccidioidomycosis (lung). Two patients each had two OIs; one patient had pneumonia with infecting organisms cytomegalovirus and pneumocystis, and one patient had cytomegalovirus infection and oesophageal candidiasis.

Characteristics of the reported OI cases are presented in online supplementary tables S10 and S11. No cases of progressive multifocal leukoencephalopathy (PML) were reported.

External medical review by a committee of clinicians with infectious disease expertise independently confirmed 34 of the 45 reported OI events, which included 22 multidermatomal HZ, 3 of 5 cytomegalovirus infections (1 cytomegalovirus, 1 septic shock and cytomegalovirus, and 1 pneumonia (with infecting organisms reported as cytomegalovirus and *Pneumocystis*)), 3 of 4 pneumocystis, 3 of 10 candidiasis (all oesophageal) and single cases of cryptococcal pneumonia, histoplasmosis and paracoccidioidomycosis.

Other infections of interest

Other TE infections of interest were few in number and included Epstein-Barr virus (EBV) (n=1), hepatitis E (n=2) and acute hepatitis B (n=2; online supplementary table S10). No cases of hepatitis C were reported.

Among 290 patients tested for hepatitis B virus (HBV) DNA based on screening HBV antibody status, 36 (12.4%) exhibited detectable HBV DNA at any time postbaseline (online supplementary table S12). These patients were predominantly positive for hepatitis surface and core antibodies and enrolled in endemic regions. The majority had detectable but not quantifiable DNA (<29 IU/mL). Of eight patients with baseline serology consistent with prior hepatitis B infection (antihepatitis B core antibody positive) and a quantifiable elevation in HBV DNA postbaseline, three received antiviral therapy, none had a diagnosis or clinical evidence suggestive of hepatitis, and hepatic transaminases were not elevated ≥3 times the ULN.

DISCUSSION

We evaluated the infectious disease profile of baricitinib in patients with RA from the global baricitinib clinical trial programme. We observed an overall increase in infectious events in those using baricitinib, including a dose-dependent elevated risk of HZ. Further, we identified a low incidence of

OI. The overall rates and types of infections observed with baricitinib were similar to those reported for other approved JAK inhibitors from clinical trials.[7]

A number of potential mechanisms, which are mediated through the JAK-STAT signalling pathway, may explain the increased risk of infection. Interleukin-6 (IL-6) plays an important role in fighting infection as a lymphocyte-stimulating factor.[15] Inhibition of IL-6 could lead to impaired innate and adaptive immunity, important in defence against viral, parasitic and bacterial infections.[15–17] Inhibition of CD4 +T cells and natural killer cells may also play a role in down-regulation of innate and cell-mediated immunity, however, in the baricitinib RA programme, changes in lymphocyte subsets were generally within normal reference ranges and not associated with increased risk of HZ or serious infections.[18] Disruption of interferon signalling, important for protection against viral and other pathogens, may further explain some of the increased risk.[19]

Patients with RA are at increased risk of infection from their disease and concomitant treatments.[1–4] Consistent with baricitinib's immunomodulatory mechanism of action,[7 8] a higher overall TE infection rate was observed for 4 mg versus placebo. In contrast, serious infections were not more common for baricitinib than placebo in the randomised, controlled data. This was a surprising observation, as increases in serious infection versus placebo have been reported from integrated, randomised data for other targeted RA therapies including the JAK inhibitor, tofacitinib.[6] The lack of observed imbalance in serious infection for baricitinib versus placebo was based on small numbers of patients with events (16/997 4 mg, 17/1070 placebo). The all-bari-RA serious infection IR was similar to those reported in analogous analysis sets from RA trials of tofacitinib and bDMARDs.[6 20 21] The types and risk factors for serious infection events with baricitinib were similar to those reported in prior trials.[6 20–24] Baricitinib-treated patients with advanced age, glucocorticoid use, Asian (excluding Japan) or Rest of World region, or abnormal BMI were at higher risk of serious infection. Most prior evaluations identified low BMI as an independent risk factor but had not evaluated high BMI as a separate category. Our evaluation found that patients with low or high BMI were at increased risk compared with patients with normal BMI.

Reactivation of latent viruses has become a common theme among patients using JAK inhibitors.[7] In the baricitinib placebo-controlled analysis set, the HZ IR was 4.3, 3.1 and 1.0 for the 4 mg, 2 mg and placebo groups, respectively, indicating an overall increased risk of HZ with baricitinib. Notably, the HZ IR did not increase over time. Multidermatomal HZ was the most common OI reported in the baricitinib RA programme; few cases of ocular or motor nerve involvement occurred and no cases were associated with visceral involvement or death. Data reporting HZ rates with baricitinib monotherapy versus combination with csDMARDs are limited.[11] Reactivation of varicella virus (HZ) is more common in RA patients, with advancing age and among those using glucocorticoids[25 26]; however, glucocorticoid use was not an identified risk factor for HZ infection in the baricitinib programme based on the univariable analysis. HZ risk is elevated with the JAK inhibitors tofacitinib and upadacitinib, with risks being dose-dependent and highest among Asian patients.[27–34] The results from our study of baricitinib are consistent with these observations; the potential rationale underlying this geographical pattern is unknown and would require further study. The occurrence of HZ in this context appears to be limited to cutaneous manifestations, although multidermatomal or cutaneously disseminated disease can occur.[27 30 33] This risk should be mitigated by vaccination prior to beginning a JAK inhibitor, particularly in RA patients ≥50 years, per treatment guidelines.[14 35] Recently, a non-live subunit vaccine has been approved in multiple countries; however, efficacy and safety data have not yet been reported for patients with RA or other inflammatory diseases. Only the live vaccine was available at the time of the phase 3 trials, and was offered prior to starting treatment; however, <5% of patients were vaccinated. While the occurrence of HZ was similar in vaccinated and unvaccinated patients, data are limited by the small number of vaccinated patients. The use of vaccines should be further studied in this setting. Lastly, decreasing or eliminating concomitant glucocorticoid use has been suggested to decrease HZ risk in patients using tofacitinib,[21 28 36] and observations of glucocorticoid use increasing HZ risk both within and outside the setting of RA are widely published.

Regarding the reactivation of other latent viruses, several cases of cytomegalovirus were reported among baricitinib-treated patients. While this was a rare complication, a similar number of cases have been reported among tofacitinib-treated patients.[37] One case of EBV was reported in the baricitinib RA programme and no cases of reactivation of JC viruses (ie, PML) were observed. No patients with prior hepatitis B infection and detectable HBV DNA postbaseline developed clinical/laboratory evidence of hepatitis in the baricitinib RA programme, although antiviral therapy was used concomitantly in a subset of these patients. Findings from a small subset of patients in the clinical trial setting suggest that patients with prior HBV exposure who lack evidence of active infection, can be treated with baricitinib with close observation for possible reactivation; however, further data are needed to ascertain the risk of HBV reactivation and inform treatment recommendations.

Events of TB occurred rarely with baricitinib, all with 4 mg, and in endemic areas. Incidence of TB among baricitinib-treated RA patients was generally 5–10-fold over the incidence within the background general populations of the countries of enrolment where cases occurred. This magnitude of risk elevation was similar to that reported in the tofacitinib clinical development programme,[37] and in real-world evaluations of TB risk with antitumour necrosis factor (TNF) therapy.[38] Screening and starting LTBI treatment prior to the start of anti-TNF therapy and tofacitinib appears safe and effective.[37 39 40] Our experience suggests the utility of TB screening and therapy with baricitinib use. Data from the limited subset of patients who initiated isoniazid for LTBI prior to enrolment do not suggest a significantly increased hepatic safety risk with concomitant isoniazid/baricitinib administration.

There are limitations of this analysis. The majority of patients assigned to placebo in the baricitinib RA programme were also taking ≥1 concomitant csDMARD and thus were at risk for infectious events. Concomitant csDMARD use was only assessed at baseline, so these variables could have changed after rescue. Like similar clinical trial programmes, the number of patient-years observed does not permit precise characterisation of risk for uncommon or rare event types, for example, individual OIs. The overall extent of exposure in this programme was smaller for the 2 mg dose vs 4 mg. While the 2–4 mg extended analysis set allowed for a randomised and balanced comparison between doses, all-bari-RA was mostly (~80%) composed of 4 mg exposure time.

In summary, baricitinib treatment was associated with an increased rate of TE infections in patients with RA versus

placebo. The incidence of serious infection was similar to that reported in other recent tsDMARD and bDMARD development programmes. HZ risk was elevated with baricitinib treatment and, similar to other JAK inhibitors, was more common among Asian patients. OIs, including multidermatomal HZ, were infrequent, and TB was reported in endemic areas. Long-term population-based studies are necessary to better understand the comparative real-world risk of baricitinib and tsDMARD therapies in RA.

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