RHEUMATOLOGY

Rheumatology 2019;58:i34–i42
doi:10.1093/rheumatology/key287

Growing evidence of the safety of JAK inhibitors in patients with rheumatoid arthritis

Masayoshi Harigai[1]

Abstract

To facitinib and baricitinib are two of the currently available Janus kinase (JAK) inhibitors for the treatment of patients with RA. Randomized controlled trials have shown that these JAK inhibitors are as efficacious as biological DMARDs. Safety profiles of these JAK inhibitors in randomized controlled trials and their long-term extension studies have been demonstrated; however, real world evidence remains to be established to bridge the gap between randomized controlled trials and rheumatology clinics. Fundamentally, no difference in the screening, prevention, and monitoring of infections between JAK inhibitors and biological DMARDs exists. However, increased risk of herpes zoster is probably common to all JAK inhibitors. No indication of increased risk for malignancy in patients with RA treated with JAK inhibitors has been reported. To evaluate risks of relatively rare serious adverse events such as thromboembolic events, gastrointestinal perforation, and interstitial lung disease in clinical settings, accumulation of cases with these events are needed. Continuous pharmacovigilance activity is absolutely warranted to establish the safety of JAK inhibitors in patients with RA and other rheumatic diseases.

Key words: Janus kinase, RA, safety, tofacitinib, baricitinib, adverse event, infection, herpes zoster, malignancy, thromboembolism

REVIEW

Rheumatology key messages

- Janus kinase inhibitor users have higher risk of herpes zoster, not serious infection, than biologics.
- Available evidence does not show increased risk of malignancy in Janus kinase inhibitor users.
- Long-term observational studies will reveal benefit-risk balance of Janus kinase inhibitors versus biologics.

Introduction

Small-molecule kinase inhibitors are emerging as a new option for the treatment of RA. As described in another article from this issue, Janus kinase (JAK) inhibitors with a different specificity to JAK family kinases have been launched into the market or under clinical development for RA. In the recent EULAR recommendations for the management of RA, JAK inhibitors are recommended in patients failing initial treatment with MTX or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) with poor prognostic factors [1]. Safety concerns, such as infections and malignancy, about JAK inhibitors have been reported because patients with mutations of JAKs and signal transducer of activation show primary immunodeficiency and JAK inhibitors block intracellular signalling pathways of inflammatory cytokines, which are relevant to the host defence mechanisms. Two JAK inhibitors with different specificity are currently available in clinical practice for the treatment of RA: tofacitinib (JAK 1 and 3 inhibitor) and baricitinib (JAK 1 and 2 inhibitor). Their safety data have been exhaustively collected in their clinical development programmes and post-marketing surveillance programmes. This review mainly discusses changes in laboratory parameters, and serious or potentially serious adverse events (AEs) of these two inhibitors, including infections, malignancy, thromboembolic events, gastrointestinal (GI) perforation, and interstitial lung disease (ILD), as well as their effects on pregnancy and breastfeeding.

[1]Division of Epidemiology and Pharmacoepidemiology, Department of Rheumatology, School of Medicine, Tokyo Women's Medical University, Tokyo, Japan

Submitted 31 January 2018; accepted 7 August 2018

Correspondence to: Masayoshi Harigai, Division of Epidemiology and Pharmacoepidemiology, Department of Rheumatology, School of Medicine, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan.
E-mail: harigai.masayoshi@twmu.ac.jp

Changes in laboratory parameters

Use of JAK inhibitors is associated with changes in laboratory parameters including blood cell counts and levels of haemoglobin, liver transaminase, creatine kinase, cholesterol and creatinine [2]. In patients treated with tofacitinib, initial decreases in the number of neutrophils, lymphocytes, NK cells and platelets are observed while haemoglobin levels increase [3]. No new safety risks of laboratory parameters were identified in the long-term extension (LTE) study [4]. In the case of baricitinib, initial decrease in neutrophil counts, no changes in lymphocyte counts, initial peak at 2 weeks and returning to baseline in platelet counts, initial decrease and returning to baseline in haemoglobin levels, and initial increase followed by decrease in NK cell counts are observed [5–7]. Increase in CD19+ B cells and other B cell subsets, decrease in Th1 T cells, and no changes in other T cell subsets were also reported in patients treated with baricitinib. Decrease in NK cell counts was not associated with serious infection or herpes zoster (HZ) [7]. The differential changes in haemoglobin levels between the two drugs are explained by their selectivity for each JAK, as erythropoietin stimulates erythrocyte production via the JAK2 signalling pathway. Elevation of liver transaminase, creatine kinase, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and creatinine levels are commonly observed in patients treated with tofacitinib and baricitinib [2, 8]. Similarities and differences of these changes in laboratory parameters are quite interesting from a point of differential biological roles of each JAK, and robust data from JAK inhibitors with other selectivity (i.e. JAK1-selective and JAK3-selective) are necessary to fully understand mechanisms of the changes in laboratory parameters. It is worthy of mention that only a small proportion of the patients treated with a JAK inhibitor develop serious AEs related to these changes. In clinical settings, however, rheumatologists should monitor these parameters regularly to find patients with significant elevation or decrease of these values and take appropriate measures according to local guidelines.

Infections

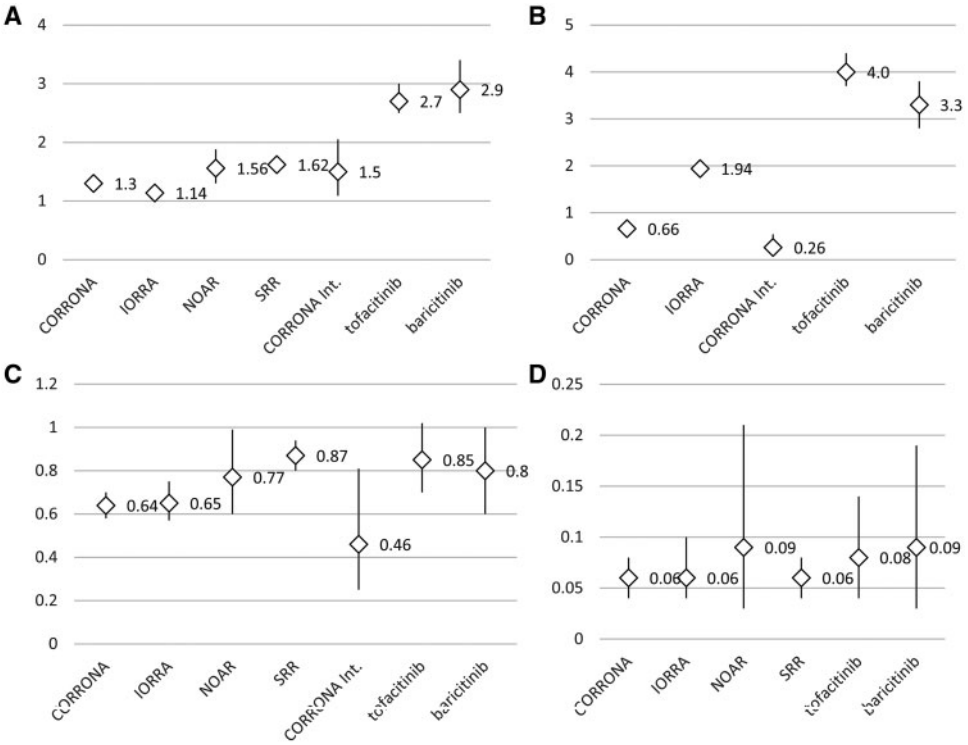
Serious infection

Patients with RA have a 1.5- to 2-fold higher risk of infection requiring hospitalization or serious infection than the general population [9, 10]. Infection rates in five large registries of RA (Consortium of Rheumatology Researchers of North America (CORRONA), Institute of Rheumatology Rheumatoid Arthritis, Norfolk Arthritis Register, Swedish Rheumatology Quality of Care Register, and CORRONA International) were compared with harmonization of the definition of infection [11]. Incidence (95% CIs) of infections requiring hospitalization standardized for age and sex distribution in the RA clinical trial programme were quite consistent across registries, ranging from 1.14 (1.05, 1.25)–1.62 (1.52, 1.72) per 100 patient years (PY) (Fig. 1A). The use of biological DMARDs (bDMARDs) increased the risk of serious infections compared with the use of csDMARDs, without differences across bDMARDs (adjusted hazard ratio 1.1–1.8) [18]. Of 4789 patients treated with tofacitinib (8460 PY of exposure) in phase II, phase III, and LTE studies, 259 patients had serious infections [3.09 events per 100 PY (95% CI 2.73, 3.49)], and the most common infection was pneumonia. A recent analysis of the integrated data throughout the RA development programme of tofacitinib including phase I, phase II, phase III and LTE study showed a similar risk for serious infections [2.7 events per 100 PY (95% CI 2.5, 3.0)] (Table 1) [12]. A pooled analysis of LTE studies showed that the incidence rates (IRs) of serious infections remained constant up to 96 months [19]. Risk factors included age, diabetes mellitus, corticosteroid use (>7.5 mg/day of prednisolone), and tofacitinib dosage (10 mg bid vs. 5 mg bid) [20]. An interim report of post-marketing surveillance programme of tofacitinib in Japan demonstrated that the most frequently reported AEs and serious AEs by MedDRA system organ class from the safety analysis population ($n = 2882$) were infections and infestations (AEs 12.7%, $n = 367$; serious AEs 3.5%, $n = 101$) in the 6-month observation period. Serious infectious events, including pneumonia ($n = 20$, 0.7%), HZ ($n = 16$, 0.6%), *Pneumocystis jirovecii* pneumonia ($n = 11$, 0.4%), cellulitis ($n = 8$, 0.3%) and bacterial pneumonia ($n = 9$, 0.3%), were reported in $\geqslant 0.3\%$ of the patients [21]. Analysis of pooled data of baricitinib clinical trials with 3492 patients enroled in phase I, phase II, phase III and LTE studies (6637 PY) identified 194 serious infections with IR (95% CI) of 2.9 events per 100 PY (2.5–3.4) (data cutoff: 1 September 2016) (Table 1). The IRs were quite stable over time up to week 72 and slightly declined thereafter; the 2-mg and 4-mg groups showed similar IRs of serious infections. Pneumonia was the most frequently reported serious infection, followed by HZ, urinary tract infection and cellulitis [15]. Independent risk factors for serious infections included age, non-normal body mass index (vs. normal, 18–24 kg/m^2), enrolment in Asian region excluding Japan and concomitant use of corticosteroid [13].

Herpes zoster

In patients with RA, the risk of HZ is elevated by 2- to 3-fold [22]. In an integrated analysis of the aforementioned five RA registries, the overall incidence (95% CI) of HZ ranged from 0.26 (0.11, 0.54)–1.94 (1.82, 2.07) and that of HZ requiring hospitalization ranged from 0.01 (0.01, 0.02)–0.15 (0.12, 0.19) [11] (Fig. 1B). A systematic literature review showed that treatment with tumour necrosis factor (TNF) inhibitors, particularly in studies with low risk of bias and/or those adjusted for dropouts, did not increase the risk of HZ versus conventional synthetic DMARDs (csDMARDs) [18]. Risk of HZ is apparently increased in patients receiving JAK inhibitors compared with that in the RA registries (Fig. 1B). Of 6192 patients who received tofacitinib in the two phase I, nine phase II, six phase III and two LTE studies, 636 patients developed HZ with a crude IR of 4.0 (95% CI 3.7, 4.4) per 100 PY.

Fig. 1 Incidence rates of serious adverse events in patients with RA



Incidence rates per 100 patient-years and 95% CIs of infection requiring hospitalization (for registries) or serious infection (for tofacitinib and baricitinib) (**A**) [11–13], all HZ, (**B**) [11, 12, 14], overall malignancy excluding non-melanoma skin cancer (**C**) [15–17], and lymphoma (**D**) [157–17] were plotted. Event rates in five large registries of RA (CORRONA, Institute of Rheumatology Rheumatoid Arthritis, Norfolk Arthritis Register, Swedish Rheumatology Quality of Care Register, and CORRONA International) were standardized for age and sex distribution in the RA clinical trial programme [11, 12]. For tofacitinib and baricitinib, crude incidence is presented. CORRONA: Consortium of Rheumatology Researchers of North America.

Serious HZ was reported in 46 patients (7.2%), but no fatal case was reported [23]. A recent pooled analysis of integrated database of clinical development programme reported a similar incidence of 3.9 (95% CI 3.6, 4.2) per 100 PY [12]. With unknown reasons, the IR was higher in Asian countries, particularly in Japan and Korea (8.0 per 100 PY, 95% CI 6.6, 9.6) and India (8.4 per 100 PY, 95% CI 6.4, 10.9), than in the rest of the world (2.7–4.3 per 100 PY). Age at baseline, corticosteroid dose at baseline, regions of recruitment, smoking status and tofacitinib dose during treatment were significant risk factors of HZ in the analysis [23]. Risks of HZ were compared among tofacitinib and bDMARDs using data from Medicare and MarketScan. The crude IR (95% CI) of HZ in RA patients who initiated tofacitinib ($n = 2526$) was 3.87 (2.82, 5.32); for other biologics, the crude IR (95% CI) in RA patients ranged from 1.95 (1.65, 2.31; adalimumab) to 2.71 (2.33, 3.08; infliximab). Adjusted hazard ratio (95% CI) of tofacitinib versus abatacept was 2.01 (1.40, 2.88), with a significant elevation. No bDMARD showed a significant change in hazard ratio versus abatacept, and the values were numerically close to 1.00. Older age, female sex, use of prednisone >7.5 mg/day, prior outpatient infection and greater number of hospitalizations were associated with increased risk of HZ [24].

In patients who received baricitinib in phase I, phase II, phase III and LTE studies ($n = 3492$, 5141 PY), 170 events including 11 multidermatomal cases were identified with an IR per 100 PY (95% CI) of 3.3 (2.8, 3.8); the IRs were stable over time [14]. Reanalysis with an extended observation period of 6637 PY provided similar IR (95% CI) of 3.2 (2.8, 3.7) [15]. No case of fatal or visceral dissemination of HZ was reported. The IRs were higher in Japan (6.5 per 100 PY) and other Asian countries (5.6 per 100 PY). In the placebo-controlled period of three phase II and three phase III studies of baricitinib, the IR (95% CI) of HZ was 4.3 per 100 PY for the baricitinib 4-mg group and 1.0 per 100 PY for the placebo group [14].

Tuberculosis

Patients with RA are more susceptible to tuberculosis (TB) than non-RA individuals [25–27]. The IRs (95% CI) of TB in the five large registries ranged from 0.02 (0.01, 0.03)–0.35 (0.17, 0.67) [11]. The use of TNF inhibitors increased the risk

Table 1 Incidence rates of adverse events of special interest in patients treated with tofacitinib or baricitinib in clinical development programmes for RA

Adverse events	Tofacitinib	Baricitinib
Serious infection	2.7 (2.5, 3.0)[a]	2.9 (2.5, 3.4)
Herpes zoster	3.9 (3.6, 4.2)[a]	3.2 (2.8, 3.7)
Tuberculosis	0.2 (0.1, 0.3)[a]	0.15 (0.07, 0.27)
Malignancy excluding NMSC	0.9 (0.8, 1.0)[a]	0.8 (0.6, 1.0)
NMSC	0.6 (0.5, 0.7)[a]	0.4 (0.2, 0.5)
Lymphoma	0.1 (0.1, 0.2)[a]	0.09 (0.03, 0.19)
MACE	0.58 (0.39, 0.88)[b]	0.5 (0.4, 0.7)
DVT/PE	DVT: 0 in PBO-controlled cohort and 0.1 (0, 0.3) in dose-comparison cohort[c] PE: 0 in PBO-controlled cohort and 0.1 (0, 0.4) for 5 mg bid and 0.2 (0, 0.4) for 10 mg bid in dose-comparison cohort[c]	DVT/PE: 0.5 (0.3, 0.7)
GI perforation	0.11 (0.07, 0.17)[a]	0.05 (0.01, 0.13)

Incidence rates (95% CIs) in RA patients treated with each JAK inhibitor were shown. Data for baricitinib were from reference [15] ($n = 3492$). [a]Data were from reference [12] ($n = 6194$). [b]Data were from reference [62] ($n = 3800$). [c]Data were from reference [47] ($n = 5368$). NMSC: non-melanoma skin cancer; MACE: major adverse cardiovascular event; DVT: deep vein thrombosis; PE: pulmonary embolism; PBO: placebo; GI: gastrointestinal; JAK: Janus kinase.

of TB, especially in an endemic area of the disease, and the adjusted hazard ratio (95% CI) versus csDMARDs was between 2.7 (2.1, 3.3) and 4.9 (2.1, 11.1) after 2013 [18, 28–30].

Of 5671 patients enroled in phase II, phase III and LTE studies of tofacitinib, 26 cases of TB were reported only in the tofacitinib-treated patients of phase III and LTE studies, and the crude IR (95% CI) was 0.21 per 100 PY (0.14–0.30). The median time between the start of tofacitinib treatment and TB diagnosis was 64 weeks (range 15–161). Fifteen (58%) cases involved extrapulmonary infection. Few were culture-confirmed, and most cases (20/26, 77%) occurred in those taking tofacitinib 10 mg twice a day. TB rate was strongly associated with a background country's IRs of TB. The crude IRs (95% CI) of TB in low, medium and high background TB incidence regions were 0.02 (0.003, 0.15), 0.08 (0.03, 0.21) and 0.75 (0.49, 1.15) per 100 PY, respectively. Screening and treatment of latent TB infection were successfully implemented in the phase III studies of tofacitinib. None developed TB among 286 patients who were reported to have untreated latent TB infection upon screening and were treated with tofacitinib and isoniazide concomitantly, and none developed clinically significant hepatitis by isoniazid [31]. A recent pooled analysis of integrated database of clinical development programme of tofacitinib reported a similar TB incidence of 0.2 (95% CI 0.1, 0.3) per 100 PY [12]. In the combined dataset of three phase II and three phase III trials of baricitinib (data cutoff: August 2015), two TB cases were reported during the placebo-controlled period (e.g. 0 to week 24): one in the baricitinib 4-mg group ($n = 997$) and one in the adalimumab group ($n = 330$). Six TB cases were reported during the uncontrolled period, and the bacteria were not identified in three of them. These TB cases were reported from endemic areas of the disease [32]. Reanalysis of the database with extended observation period provided TB IRs of 0.15 (0.07, 0.27) [15]. It is well recognized that the use of TNF inhibitors increased the risk of TB, with hazard ratios of 2.7–12.5, compared with that in the general population [18]. Extrapulmonary tuberculosis was more common in patients treated with TNF inhibitors [27], which was also observed in tofacitinib- and baricitinib-treated patients. A comparison of the IRs of TB between JAK inhibitor- and TNF inhibitor-treated patients in clinical settings remains to be established in each country or region using observational cohorts; for the time being, a screening and treatment strategy for latent TB infection similar to that for TNF inhibitors is strongly recommended [27].

Other opportunistic infections

Of 5671 patients enroled in phase II, phase III and LTE studies of tofacitinib, 34 non-TB opportunistic infections developed, including oesophageal candidiasis ($n = 9$), *Pneumocystis jirovecii* pneumonia ($n = 4$), CMV infection ($n = 6$), non-tuberculous mycobacterium pulmonary infection ($n = 2$), cryptococcal infection (pneumonia $n = 2$, meningitis $n = 1$), disseminated or multidermatomal HZ ($n = 8$), BK virus encephalopathy ($n = 1$), and toxoplasmosis ($n = 1$), with a crude IR (95% CI) of 0.25 (0.18, 0.36). No progressive multifocal leukoencephalopathy was reported. The presentations of CMV infection were diverse: no symptom, oesophageal ulcer, sialadenitis, hepatitis and gastritis. The interim analysis of a Japanese post-marketing surveillance programme of tofacitinib reported 12 cases (0.4%) of *Pneumocystis jirovecii* pneumonia [21]. Patients treated with TNF inhibitors were also susceptible to intracellular infections, including non-tuberculous mycobacterium, *Listeria monocytogenes*, *Legionella pneumophila*, *Salmonella sp*. and *Pneumocystis jirovecii* pneumonia [33–35]. However, the risks of opportunistic infection between tofacitinib and TNF inhibitors are quite difficult to compare because of different definitions of opportunistic infection. Hence, the use of a consensus definition for infection reporting in future studies is

recommended to facilitate comparison across small-molecule kinase inhibitors and bDMARDs [36]. Opportunistic infections except for TB and HZ reported during the clinical developing programme of baricitinib included CMV infection ($n = 1$), Epstein-Barr virus infection ($n = 1$), aspergillosis ($n = 1$), candidiasis ($n = 8$), cryptococcal pneumonia ($n = 1$), histoplasmosis ($n = 1$), paracoccidioidomycosis ($n = 1$) and *Pneumocystis jirovecii* pneumonia ($n = 3$) [37].

Malignancy

Previous studies demonstrated that the risk of overall malignancy in patients with RA is moderately increased compared with that in the general population. A recent meta-analysis reported a standardized incidence ratio (SIR) of 1.09 (95% CI 1.06, 1.13) for overall RA versus the general population. Patients with RA have an increased SIR (95% CI) for lymphoma [2.46 (2.05, 2.96)] and lung cancer [1.64 (1.51, 1.79)], whereas a decreased risk of colorectal [0.78 (0.71, 0.86)] and breast [0.86 (0.73, 1.01)] cancer was reported [38]. In the combined analysis of the five large registries (i.e. CORRONA, Institute of Rheumatology Rheumatoid Arthritis, Norfolk Arthritis Register, Swedish Rheumatology Quality of Care Register and CORRONA International), IR was standardized to the age and sex distribution of the RA trial programme patient population with CIs based on a gamma distribution [16]. The standardized IRs (95% CI) of malignancies were consistent across the databases and the ranges were as follows: overall malignancies excluding non-melanoma skin cancer, 0.46 (0.25, 0.81)–0.87 (0.80, 0.94) per 100 PY; solid malignancies, 0.41 (0.22, 0.73)–0.93 (0.86, 1.01); and malignant lymphomas, 0.06 (0.04, 0.10)–0.09 (0.03, 0.21) (Fig. 1C and D). Concerns about an elevated risk of malignancy in patients treated with TNF inhibitors exist; however, a spate of studies demonstrated that treatment with TNF inhibitors did not increase the risk of overall as well as specific malignancies in patients with RA [18, 39–42].

Tofacitinib inhibits signal transduction of several cytokines, including type I and type II interferons, and decreases the number of NK cells, both of which are relevant to the elimination of transformed cells in the process of cancer immunoediting [43]; thus, particular concerns about the risk of malignancy in patients treated with tofacitinib have been raised. In an experimental lung metastasis mouse model of colon cancer, continuous tofacitinib administration (15 mg/kg/day) significantly inhibited the proliferation and differentiation of NK cells and significantly increased the number of metastatic lung surface nodules [44]. Currently available evidence, however, does not indicate an increased risk of malignancy in RA patients treated with tofacitinib. Of 5677 adult patients who participated in phase II, phase III and LTE studies of tofacitinib, 107 patients developed malignancies (excluding non-melanoma skin cancer). The most common was lung cancer ($n = 24$), followed by breast cancer ($n = 19$), lymphomas ($n = 10$), and gastric cancer ($n = 6$). Patients receiving tofacitinib ($n = 21$), adalimumab ($n = 1$) and MTX ($n = 1$) had more than one malignancy. The overall IR (95% CI) was 0.85 (0.70, 1.02) per 100 PY (Fig. 1C). In phase III studies of tofacitinib, the IRs (95% CI) of overall malignancies were 0.55 (0.27, 1.09) for the 5-mg group, 0.87 (0.50, 1.40) for the 10-mg group, 0.00 (0.00, 1.82) for the placebo group and 0.56 (0.08, 3.97) for the adalimumab group. No clear increasing trend of IRs per 6-month intervals for the tofacitinib group was observed. The overall age- and sex-adjusted SIR (95% CI) of malignancy in the patients receiving tofacitinib compared with the US general population using the US National Cancer Institute Surveillance and Epidemiology and End Results database was 1.17 (0.96, 1.41). Similar observations were reported for the IRs of lung cancer, breast cancer and non-melanoma skin cancer. Five cases of lymphoma both in phase III and LTE studies were reported in patients treated with tofacitinib, and the overall IR (95% CI) was 0.08 (0.04, 0.14) (Fig. 1D). The age- and sex-adjusted SIR (95% CI) was 2.64 (1.27, 4.86) [17]. An updated analysis of lymphoma was conducted in 2017. Of 6194 patients treated with tofacitinib, 19 lymphomas occurred with a crude IR (95% CI) of 0.10 (0.06, 0.15), age- and sex-adjusted SIR (95% CI) versus the US general population using the Surveillance and Epidemiology and End Results database was 2.62 (1.58, 4.09), and the time to onset of events ranged from 149 to 1722 days following treatment initiation, which were consistent with a preceding report. Two cases of Hodgkin's lymphoma and 17 cases of non-Hodgkin's lymphoma, including 14 B cell lymphomas, two T cell lymphomas, and one unknown, were reported [45]. A recent pooled analysis of integrated database of clinical development programme with 6194 patients treated with tofacitinib showed a similar incidence (0.9, 95% CI 0.8, 1.0) and SIR (1.0, 95% CI 0.8, 1.1) of malignancies [12]. Further, a meta-analysis and network meta-analysis showed no statistically significant increase in the risk of malignancies or any specific type of malignancy in RA patients treated with either bDMARDs or tofacitinib in randomized controlled trials (RCTs) compared with those treated with a placebo or csDMARDs [46]. Of 3492 patients treated with baricitinib in one phase I, three phase II, four phase III studies and one LTE study, 52 malignancies were reported with crude IR (95% CI) of 0.8 (0.6, 1.0) per 100 PY. IRs per 24-week intervals were stable for 120 weeks. The age- and sex-adjusted SIR (95% CI) based on the Surveillance and Epidemiology and End Results database was 1.04 (0.79, 1.36) [15]. Details of the malignancy events have not been reported yet.

Thromboembolic events

In patients treated with baricitinib, the mean platelet counts peaked at week 2, returned towards baseline, stabilized over time, and subsequently returned to baseline after treatment discontinuation. In patients with RA who participated in three phase II and three phase III studies of baricitinib, 9.5% of the placebo group, 16.9% of the baricitinib 2-mg group, and 24.9% of the baricitinib 4-mg group had a maximum on-treatment platelet level that is greater than the upper limit of the normal. During the

placebo-controlled period (baseline to week 24) of a merged dataset including three phase II and three phase III studies, 23 patients (2.3%) in the baricitinib 4-mg group ($n = 983$), seven patients (1.5%) in the baricitinib 2-mg group ($n = 472$), and 14 patients (1.3%) in the placebo group ($n = 1055$) had maximum platelet counts $\geqslant 600 \times 10^9$/l. The proportion of patients with high post-baseline platelet levels was comparable between those with and those without deep venous thromboembolism (DVT) or pulmonary embolism (PE). During the placebo-controlled period (baseline to week 24) of the three phase II and three phase III studies of baricitinib, five DVT/PE cases (1.2 per 100 PY), including two serious ones, were reported in the baricitinib 4-mg group and none in the placebo group [5, 15]. The IRs of overall and serious DVT/PE in a combined dataset of one phase I, three phase II, four phase III and LTE studies were 0.5 and 0.3 per 100 PY, respectively.

Risks of DVT/PE in patients treated with tofacitinib were analysed using the data from phase II and phase III randomized clinical studies for RA, psoriasis, psoriatic arthritis (PsA) and ulcerative colitis [47]. In the placebo-controlled cohort, DVT and PE were reported in two patients (RA, $n = 1$ and ulcerative colitis, $n = 1$) receiving placebo for each and no patients receiving tofacitinib 5 mg or 10 mg bid had DVT or PE. In the dose-comparison cohort, there were two DVT events in tofacitinib treated patients with RA (5 mg bid, $n = 1$; 10 mg bid $n = 1$) and one DVT event in a patient with PsA (tofacitinib 10 mg bid). IRs (95% CI) were 0.1 (0.0, 0.3) for both tofacitinib doses in RA, and 0.5 (0.0, 2.8) for tofacitinib 10 mg bid in PsA. Five PE events were reported in patients with RA (5 mg BID, $n = 2$; 10 mg BID, $n = 3$) in the dose-comparison cohort. IRs (95% CI) of PE were 0.1 (0.0, 0.4) and 0.2 (95% CI: 0.0, 0.4) for 5 and 10 mg bid, respectively.

Because the observation period of the placebo group was relatively short because of the nature of RCTs, the risk of DVT/PE should be interpreted in the context of the risk in the general population and patients with RA in general. The estimated annual IRs of DVT/PE range from 0.104–0.183 per 100 PY among people of European ancestry and could be higher in the African-American and lower in the Asian population [48]. A meta-analysis showed elevated risk ratios of DVT, PE and venous thromboembolism in patients with RA versus controls: 2.08 (95% CI 1.75, 2.47) for DVT, 2.17 (95% CI 2.05, 2.31) for PE, and 1.96 (95% CI 1.81, 2.11) for venous thromboembolism [49]. Although the data from the placebo-controlled period may indicate a safety signal for baricitinib, the IR of DVT and PE were similar between the two JAK inhibitors. A long-term observation in the real world is necessary to precisely evaluate the risk of DVT/PE in patients receiving these drugs.

GI perforation

Concerns about increased risk of lower GI tract perforation have been reported in patients treated with tocilizumab [50–52]. As JAK inhibitors also block IL-6 signalling, risk of GI perforation was investigated in RA patients using health plan data in the USA. Most perforation cases (62%) occurred in the lower GI tract and the IR per 1000 PY (95% CI) was 1.26 (0.73, 2.18) for tocilizumab, 0.86 for tofacitinib (0.10, 3.60), 0.76 for abatacept (0.53, 1.09), 0.48 for rituximab (0.06, 1.75) and 0.46 for TNF inhibitor (0.35, 0.58). A multivariable analysis using Cox proportional hazard models revealed a significantly elevated risk of lower GI tract perforation among tocilizumab users (hazard ratio 2.51, 95% CI 1.31, 4.80). A numerically elevated risk among tofacitinib users was identified (hazard ratio 1.94, 95% CI 0.49, 7.65); however, the rate was based on only two events. Other significant predictors of lower GI tract perforation were older age, diverticulitis and other GI conditions, and the use of prednisone $\geqslant 7.5$ mg/day. A high mortality rate was noted: 28% of the patients with lower GI perforation died in the hospital or within 90 days after discharge [53]. Of 6194 patients treated with tofacitinib, GI perforation was reported in 22 patients with IR (95% CI) of 0.11 (0.07, 0.17) [12]. In a combined dataset of the clinical development programme of baricitinib for RA (data cutoff: 1 September 2016), three cases of lower GI tract perforation were reported in patients who received $\geqslant 1$ dose of baricitinib, with an IR (95% CI) of 0.5 per 1000 PY (0.01–0.13) [15, 32]. These data suggest that the benefit-risk balance of JAK inhibitors should be deliberately considered in RA patients with intestinal diverticulum or history of intestinal diverticulitis.

Interstitial lung disease

ILD was reported in RA patients treated with bDMARDs and csDMARDs, such as MTX and leflunomide. In an RA clinical development programme of tofacitinib and baricitinib, 0.1% of the patients developed ILD and some of them were *de novo* ILD [54, 55]. An interim analysis of the Japanese post-marketing surveillance programme of tofacitinib identified 14 cases (0.5%) with serious ILD, of which three died [21]. ILD in patients treated with JAK inhibitors and other antirheumatic drugs was predominantly reported in Japan [56, 57], and some genetic factors providing susceptibility to drug-induced ILD possibly exist [58].

Pregnancy and breastfeeding

Pre-clinical animal studies demonstrated teratogenic effects of tofacitinib, including membranous ventricular septal defects and skeletal/cranial malformation or variations, after 10- to 100-fold exposures compared with the human dosage [59]. Of 1309 patients with RA and 512 with psoriasis enroled in RCTs of tofacitinib, 31 and 16 women, respectively, reported pregnancy. Majority of the patients with RA (58.1%) and all patients with psoriasis received tofacitinib monotherapy, and the rest of the patients with RA received tofacitinib plus MTX. The pregnancy outcomes were as follows: 25 healthy newborns, one congenital pulmonary valve stenosis, seven spontaneous abortions, eight medical terminations, and six pending/lost to follow-up [60]. Baricitinib also has teratogenic effects in animals, reduces fetal growth/weight and

produces skeletal malformations [61]. Data on pregnancy outcomes in patients exposed to baricitinib remain to be established. Both tofacitinib and baricitinib are excreted into the milk of lactating rats. Decreased pup weights and decreased postnatal survival were observed at exposures 4 and 21 times greater, respectively, than the typical human baricitinib exposure. JAK inhibitors are contraindicated during pregnancy, and women of child-bearing age should use effective contraception during and at least 1 week after treatment. JAK inhibitors poses risks to newborns/infants and thus should not be used during breastfeeding.

Acknowledgements

Tokyo Women's Medical University (TWMU), particularly the Division of Epidemiology and Pharmacoepidemiology of Rheumatic Diseases, has received unrestricted research grants from Ayumi Pharmaceutical Co.; Bristol Myers Squib, Chugai Pharmaceutical Co., Ltd; Eisai Co., Ltd, Nippon Kayaku Co., Ltd; Taisho Toyama Pharmaceutical Co., Ltd; Takeda Pharmaceutical Co., Ltd; Mitsubishi Tanabe Pharma Co.; and Teijin Pharma Ltd, with which TWMU paid the salary of M.H.

Supplement: This supplement is supported by a grant from Gilead Sciences, Inc.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: M.H. has received research grants and/or honoraria from Abbvie Japan Co., Ltd, Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd, Eisai Co., Ltd, Mitsubishi Tanabe Pharma Co., Ono Pharmaceutical Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd, Santen Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Teijin Pharma, Ltd and Pfizer Japan Inc. and serves as a consultant for Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd and Pfizer Japan Inc.

References

1 Smolen JS, Landewé R, Bijlsma J *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

2 Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol 2017;13:234–43.

3 Wollenhaupt J, Silverfield J, Lee EB *et al*. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. J Rheumatol 2014;41:837–52.

4 Wollenhaupt J, Silverfield J, Lee EB *et al*. Tofacitinib, an oral Janus kinase inhibitor, in the treatment of rheumatoid arthritis: safety and efficacy in open-label, long-term extension studies over 9 years (Abstract 1647). Arthritis Rheumatol 2017;69:Abstract 1647.

5 Kremer J, Huizinga TWJ, Chen L *et al*. Analysis of neutrophils, lymphocytes, and platelets in pooled phase 2 and phase 3 studies of baricitinib for rheumatoid arthritis (FRI0090). Ann Rheum Dis 2017;76:512.

6 Kay J, Harigai M, Rancourt J *et al*. Effects of baricitinib on haemoglobin and related laboratory parameters in rheumatoid arthritis patients (FRI0092). Ann Rheum Dis 2017;76:513.

7 Tanaka Y, Yamaoka K, Ishida M *et al*. Characterization of changes in lymphocyte (LYM) subsets in baricitinib (Bari)-treated patients (pts) with rheumatoid arthritis (RA) in a phase 3 study (RA-BEAM). Mod Rheumatol 2017;27:S357.

8 Isaacs JD, Zuckerman A, Krishnaswami S *et al*. Changes in serum creatinine in patients with active rheumatoid arthritis treated with tofacitinib: results from clinical trials. Arthritis Res Ther 2014;16:R158.

9 Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287–93.

10 Crowson CS, Hoganson DD, Fitz-Gibbon PD, Matteson EL. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. Arthritis Rheum 2012;64:2847–55.

11 Yamanaka H, Askling J, Berglind N *et al*. Infection rates in patients from five rheumatoid arthritis (RA) registries: contextualising an RA clinical trial programme. RMD Open 2017;3:e000498.

12 Cohen SB, Tanaka Y, Mariette X *et al*. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 2017;76:1253–62.

13 Winthrop K, Genovese M, Harigai M *et al*. Serious infection and associated risk factors in patients with moderate to severe rheumatoid arthritis treated with baricitinib (OP0248). Ann Rheum Dis 2017;76:158.

14 Atsumi T, Takeuchi T, Ishii T *et al*. Herpes zoster in patients including Japanese with moderate to severe active rheumatoid arthritis treated with baricitinib, an oral JAK 1/JAK 2 inhibitor (Abstract W13-6). Mod Rheumatol 2017;27:S98.

15 Genovese MC, Smolen JS, Takeuchi T *et al*. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 5.5 years: an updated integrated safety analysis (Abstract #511). Arthritis Rheumatol 2017;69:Abstract 511.

16 Askling J, Berglind N, Franzen S *et al*. How comparable are rates of malignancies in patients with rheumatoid arthritis across the world? A comparison of cancer rates, and means to optimise their comparability, in five RA registries. Ann Rheum Dis 2016;75:1789–96.

17 Curtis JR, Lee EB, Kaplan IV *et al*. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann Rheum Dis 2016;75:831–41.

18 Ramiro S, Sepriano A, Chatzidionysiou K *et al*. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR

recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2017;76:1101–36.

19 Fleischmann R, Wollenhaupt J, Takiya L *et al*. Safety and maintenance of response for tofacitinib monotherapy and combination therapy in rheumatoid arthritis: an analysis of pooled data from open-label long-term extension studies. RMD Open 2017;3:e000491.

20 Cohen S, Radominski SC, Gomez-Reino JJ *et al*. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66:2924–37.

21 Mimori T, Harigai M, Atsumi T *et al*. Post-marketing surveillance of tofacitinib in Japanese patients with rheumatoid arthritis: an interim report of safety data (Abstract 431). Arthritis Rheumatol 2017;69(Suppl 10):Abstract 431.

22 Smitten AL, Choi HK, Hochberg MC *et al*. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007;57:1431–8.

23 Winthrop KL, Curtis JR, Lindsey S *et al*. Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. Arthritis Rheumatol 2017;69:1960–8.

24 Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1843–7.

25 Yamada T, Nakajima A, Inoue E *et al*. Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. Ann Rheum Dis 2006;65:1661–3.

26 Askling J, Fored CM, Brandt L *et al*. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005;52:1986–92.

27 Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. Nat Clin Pract Rheumatol 2006;2:602–10.

28 Chiu YM, Lang HC, Lin HY *et al*. Risk of tuberculosis, serious infection and lymphoma with disease-modifying biologic drugs in rheumatoid arthritis patients in Taiwan. Int J Rheum Dis 2014;17(Suppl 3):9–19.

29 Ke WM, Chen LS, Parng IM, Chen WW, On AW. Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan. Int J Tuberc Lung Dis 2013;17:1590–5.

30 Baddley JW, Winthrop KL, Chen L *et al*. Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) study. Ann Rheum Dis 2014;73:1942–8.

31 Winthrop KL, Park SH, Gul A *et al*. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1133–8.

32 Harigai M, Takeuchi T, Ishii T *et al*. Long-term safety of baricitinib, an oral JAK1/JAK2 inhibitor, in patients with moderate to severe active rheumatoid arthritis: an integrated analysis (Abstract W13-1). Mod Rheumatol 2017;27:S97.

33 Dixon WG, Watson K, Lunt M *et al*. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti--tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:2368–76.

34 Harigai M, Koike R, Miyasaka N. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med 2007;357:1874–6.

35 Komano Y, Harigai M, Koike R *et al*. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheum 2009;61:305–12.

36 Winthrop KL, Novosad SA, Baddley JW *et al*. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015;74:2107–16.

37 Winthrop KL, Lindsey S, Harigai M *et al*. Potential opportunistic infections, and other infections of interest in patients with moderate to severe rheumatoid arthritis in the baricitinib program (Abstract 2787). Arthritis Rheumatol 2017;69:Abstract 2787.

38 Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 2015;17:212.

39 Harigai M, Nanki T, Koike R *et al*. Risk for malignancy in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs compared to the general population: a nationwide cohort study in Japan. Mod Rheumatol 2016;26:642–50.

40 Wu CY, Chen DY, Shen JL *et al*. The risk of cancer in patients with rheumatoid arthritis taking tumor necrosis factor antagonists: a nationwide cohort study. Arthritis Res Ther 2014;16:449.

41 Mercer LK, Lunt M, Low AL *et al*. Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis 2015;74:1087–93.

42 Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA *et al*. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA 2012;308:898–908.

43 Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011;331:1565–70.

44 Shimaoka H, Takeno S, Maki K *et al*. A cytokine signal inhibitor for rheumatoid arthritis enhances cancer metastasis via depletion of NK cells in an experimental lung metastasis mouse model of colon cancer. Oncol Lett 2017;14:3019–27.

45 Mariette X, Chen C, Biswas P, Kwok K, Boy MG. Lymphoma in the tofacitinib rheumatoid arthritis clinical development program. Arthritis Care Res 2018;70:685–94.

46 Maneiro JR, Souto A, Gomez-Reino JJ. Risks of malignancies related to tofacitinib and biological drugs in rheumatoid arthritis: systematic review, meta-analysis,

and network meta-analysis. Semin Arthritis Rheum 2017;47:149–56.

47 Mease PJ, Kremer J, Cohen S *et al*. Thromboembolic events in the tofacitinib rheumatoid arthritis, psoriasis, psoriatic arthritis and ulcerative colitis development programs (Abstract 16L). Arthritis Rheumatol 2017;69:Abstract 16L.

48 Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015;12:464–74.

49 Ungprasert P, Srivali N, Spanuchart I, Thongprayoon C, Knight EL. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol 2014;33:297–304.

50 Schiff MH, Kremer JM, Jahreis A *et al*. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther 2011;13:R141.

51 Koike T, Harigai M, Inokuma S *et al*. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol 2014;41:15–23.

52 Yamamoto K, Goto H, Hirao K *et al*. Longterm safety of tocilizumab: results from 3 years of followup postmarketing surveillance of 5573 patients with rheumatoid arthritis in Japan. J Rheumatol 2015;42:1368–75.

53 Xie F, Yun H, Bernatsky S, Curtis JR. Risk of gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, tocilizumab, or other biologic treatments. Arthritis Rheumatol 2016;68:2612–7.

54 Elli_Lilly_and_Company. Japanese Package Inserts of Baricitinib [in Japanese]. http://www.info.pmda.go.jp/go/pack/3999043F1020_1_02/ (16 July 2018, date last accessed).

55 Pfizer. Japanese Package Inserts of Tofacitinib [in Japanese]. http://www.info.pmda.go.jp/go/pack/3999034F1020_1_09/ (16 July 2018, date last accessed).

56 Sawada T, Inokuma S, Sato T *et al*. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. Rheumatology 2009;48:1069–72.

57 Sato T, Inokuma S, Sagawa A *et al*. Factors associated with fatal outcome of leflunomide-induced lung injury in Japanese patients with rheumatoid arthritis. Rheumatology 2009;48:1265–8.

58 Furukawa H, Oka S, Shimada K, Tsuchiya N, Tohma S. Rheumatoid_Arthritis_Interstitial_Lung_Disease_Study_Consortium. HLA-A*31: 01 and methotrexate-induced interstitial lung disease in Japanese rheumatoid arthritis patients: a multidrug hypersensitivity marker? Ann Rheum Dis 2013;72:153–5.

59 Pfizer_Inc. Xeljanz, Highlights of Prescribing Information. 2018. http://labeling.pfizer.com/ShowLabeling.aspx?id=959#section-8.1 (16 July 2018, date last accessed).

60 Clowse ME, Feldman SR, Isaacs JD *et al*. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. Drug Saf 2016;39:755–62.

61 Elli_Lilly_and_company_Limited. Summary of Product Characteristics, Olumiant 2 mg and 4 mg Film-coated Tablets. 2018. https://www.medicines.org.uk/emc/medicine/32997 (16 July 2018, date last accessed).

62 Charles-Schoeman C, Wicker P, Gonzalez-Gay MA *et al*. Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. Semin Arthritis Rheum 2016;46:261–71.