Selectivity of Janus Kinase Inhibitors in Rheumatoid Arthritis and Other Immune-Mediated Inflammatory Diseases: Is Expectation the Root of All Headache?

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Abstract
Janus kinase (JAK) is a signal transducer and activator of a protein transcription system that transduces signals from cell surface cytokine and growth factor receptors to the nucleus. Recently developed JAK inhibitors (JAKinibs) inhibit JAKs non-selectively or selectively and down-regulate the effects of corresponding ligands (i.e. cytokines and growth factors). JAKinibs are efficacious against rheumatoid arthritis and other immune-mediated inflammatory diseases and are being increasingly prescribed clinically. Regarding safety, JAKinib use is associated with common or unique changes in laboratory parameters; however, incidence rates of serious adverse drug reactions (ADRs) associated with these changes are low. Opportunistic and other infections, including tuberculosis, are the most critical ADRs of treatment with JAKinibs, and screening and monitoring of patients should be carefully performed. Incidence rates of herpes zoster (HZ) in patients receiving JAKinibs are high in Japan and Korea, and modestly high in other countries. Filgotinib may not be associated with an elevated risk for HZ, but long-term safety data are lacking. Data from clinical development programmes and post-marketing surveillance have indicated no increased risk for malignancy or serious cardiac events; however, long-term observational studies are necessary. Despite the non-elevated risk of gastrointestinal perforations, patients with older age and/or a history of diverticulitis or receiving non-steroidal anti-inflammatory drugs should be carefully evaluated to determine the risk-benefit balance. The incidence rates of venous thromboembolism with all approved doses are similar to that expected in the population, although there are discrepancies in the placebo-controlled portion of the baricitinib clinical development programmes. Regulatory agencies in the USA and Europe suggested a higher risk for thrombotic events in patients receiving JAKinibs. Pharmacokinetic studies demonstrated that dose adjustment should be considered for JAKinib use in patients with moderate-to-severe renal or hepatic dysfunction, depending on the metabolism of each drug. Long-term observational studies enrolling patients with diverse clinical backgrounds are required to strike a risk-benefit balance in clinical settings.

Key Points
The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) system plays an essential role in the pathogenesis of rheumatoid arthritis (RA) and other immune-mediated inflammatory diseases.

JAK inhibitors (JAKinibs) are efficacious for RA with various treatment backgrounds; four JAKinibs have been approved and one is under review.

JAK inhibitors with different selectivity to JAK family proteins have similar efficacy and safety profiles in RA patients with some minor differences.
1 The Roles of the Janus Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) System in Health and Diseases

1.1 JAK-STAT System

JAK and STAT proteins are key components of the JAK-STAT systems in mammalian cells. They specifically transmit signals from type I and type II cytokine receptors to the nucleus in response to stimuli of ligands of these receptors, but are not involved in the signalling of tumour necrosis factor (TNF) receptor family, IL-1 receptor family, and G protein-coupled receptors [1, 2]. Four members of the JAK family, namely JAK1, JAK2, JAK3, and Tyk2, and seven of the STAT family, namely STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, have been identified. A JAK homodimer or heterodimer comprises a complex with a cytokine/growth factor receptor. Binding of a ligand to a receptor stimulates the dimerisation of its receptors, which activates associated JAKs, leading to auto-phosphorylation of JAKs and phosphorylation of the receptor. STATs in the cytoplasm are recruited to the phosphorylated tyrosine of the receptors via their SH-domains, are phosphorylated by JAK to form dimers, and are transferred to the nucleus to regulate the transcription of DNA [1] (Fig. 1). Each receptor utilises a specific pair of JAKs, and this fact has relevant therapeutic implications for targeting JAKs in various immune-mediated inflammatory diseases (IMIDs). Supplementary Table 1 summarises the combinatorial use of JAKs and STATs in cytokine/growth factor signalling [2].

Binding of ligands (i.e. cytokines or growth factors) to specific receptors triggers conformational changes in the receptors and initiates signal transduction. Subsequently, JAKs are activated and phosphorylate STATs. The phosphorylated STATs form a dimer, which is translocated into the nucleus to regulate transcription. See 1.1 JAK-STAT system for details.

1.2 Germline Mutations in the JAK-STAT System and Clinical Manifestations

Germline loss-of-function and gain-of-function mutations observed in the JAK-STAT system are summarised in Supplementary Table 2 [1, 3]. In addition to these mutations, genome-wide association studies (GWAS) identified associations between the JAK-STAT system and several diseases as follows: JAK1 and diabetic kidney disease; JAK2 and myeloproliferative neoplasms, inflammatory bowel disease (IBD), and paediatric autoimmune diseases (PADs); Tyk2 and IBD, systemic lupus erythematosus (SLE), multiple sclerosis (MS), psoriasis, rheumatoid arthritis (RA), primary biliary cholangitis (PBC), and PADs; STAT1 and IBD, SLE, and PBC; STAT2 and psoriasis; STAT3 and IBD, MS, atopic dermatitis, and psoriasis; STAT4 and IBD, SLE, RA, Behçet’s disease, PBC, Sjögren’s syndrome, and systemic sclerosis; and STAT6 and atopy, bronchial asthma, and eosinophilic esophagitis [1].

Most of the reported mutations are associated with susceptibility to various types of infections, suggesting their cardinal roles in host defence against these pathogens. A homozygous mutation of JAK3 is one of the causes of severe combined immunodeficiency (SCID). Patients with SCID are susceptible to severe infectious diseases, including opportunistic infections in early life, and require bone marrow transplantation to save their lives. Patients with JAK3 deficiency show impairments in T-cell development and proliferation, interferon-γ production, and interleukin (IL)-4 signalling as well as a decreased number of CD11c+ dendritic cells [3]. In a recent case study, a Tyk2 frame-shift deletion rendered a patient susceptible to severe or opportunistic infections and caused severe atopic dermatitis and elevation of immunoglobulin E levels. The patient had decreased IL-12 and IL-23 production in response to toll-like receptor 4 or 9 activation and impaired IL-12 and interferon-γ signalling [3]. JAK2 mutations are frequently noted in patients

IBM, SLE, and PBC; STAT2 and psoriasis; STAT3 and IBD, MS, atopic dermatitis, and psoriasis; STAT4 and IBD, SLE, RA, Behçet’s disease, PBC, Sjögren’s syndrome, and systemic sclerosis; and STAT6 and atopy, bronchial asthma, and eosinophilic esophagitis [1].

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with myeloproliferative disorders and leukaemia, whereas JAK mutations are seldom observed in patients with solid tumours [1, 3]. Patients with a loss-of-function mutation in STAT5B develop autoimmune complications resulting from defects in Treg cells [4].

2 Profiles and Efficacy of JAKinibs in Rheumatoid Arthritis (RA)

2.1 Indications for JAKinibs in RA Treatment

As of March 2020, tofacitinib, baricitinib, and upadacitinib have been approved for treating RA in the USA, EU, Japan, and other countries. Filgotinib is under review by regulatory agencies of these countries. Japan, Korea, and Taiwan approved peficitinib for RA treatment as of May 2020. Indications of JAKinibs for RA differ slightly with countries or regions. For example, the US Food and Drug administration (FDA) states that tofacitinib and upadacitinib may be used to treat adult patients with moderately to severely active RA who have shown an inadequate response or intolerance to methotrexate (MTX) [5, 6]; a maximum dose of 2 mg baricitinib is indicated for those who have shown an inadequate response to one or more tumour necrosis factor inhibitors (TNFi) therapies [7]. Peficitinib is indicated for patients with active RA who have shown an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs) [8]. The approved JAKinibs can be used both in monotherapies and in combined therapies with MTX or other non-biologic DMARDs, but their combination with other JAKinibs, biological DMARDs, or potent immunosuppressants is not approved for safety concerns. Approved dosages of JAKinibs for treating RA are shown in Table 1.

The 2019 updated European League Against Rheumatism (EULAR) RA management recommendations state that a biological DMARD or targeted synthetic DMARD (i.e. JAKinib) should be added if the treatment target is not achieved with the first conventional synthetic DMARD (csDMARD) strategy in patients with poor prognostic factors [9–11]. The EULAR recommendations strongly suggest that biological DMARDs and targeted synthetic DMARDs should be combined with a csDMARD. Primary indications of JAKinib use for RA are clearly defined in these recommendations by EULAR. Available JAKinibs and their dosages differ across regions or countries as described above.

2.2 Characteristics of JAKinibs

The characteristics of JAKinibs are summarised in Table 1. JAKinibs are classified by their selectivity to JAKs, which is based on preclinical data from enzymatic or biochemical assays. These assays can be impacted by substrate and their results may differ depending on clinical drug concentration. All JAKinibs presented in Table 1 inhibit JAK1. Tofacitinib has additional selectivity for JAK3; baricitinib for JAK2; and peficitinib for JAK2, JAK3, and Tyk2. All JAKinibs target the conserved adenosine triphosphate (ATP)-binding pocket of JAKs [12]. Plasma protein binding varies widely with each JAKinib, ranging from 20.4% for tofacitinib to 75.2% for peficitinib. Approximately 30% of tofacitinib is metabolised by the kidneys and 70% by the liver. The enzymes responsible for drug metabolism and the routes of excretion of JAKinibs are summarised in Table 1. According to characteristics of metabolism and excretion of tofacitinib and baricitinib, dose adjustment of these drugs is recommended in patients with liver dysfunction or renal impairment. Dose adjustment for peficitinib and upadacitinib is recommended in patients with liver dysfunction. These two JAKinibs need no dose adjustment for renal function, as their renal excretion is negligible, while filgotinib is mainly excreted in urine, and its dosage is currently under review.

2.3 Efficacy of JAKinibs in Patients with RA

Tofacitinib, baricitinib, upadacitinib, and peficitinib were reported to be clinically, functionally, and radiologically efficacious at their approved dosages in patients who had inadequate responses to MTX (MTX-IR), those who had inadequate response to a TNFi or other biological DMARDs (biological DMARD-IR), and in MTX-naïve patients (Figs. 2, 3, and 4 and Supplementary Figs 1, 2, and 3). Since each drug used different study populations, the absolute numbers in the clinical metrics of different molecules (i.e. absolute proportions of ACR20/50/70 response) cannot be compared; yet it is still possible to interpret whether or not a given molecule achieved a specific threshold (i.e. statistical difference in ACR20/50/70 responses from the control group).

In MTX-IR patients, a significantly higher proportion of patients reached ACR20, ACR50, and ACR70 response criteria after receiving JAKinibs with MTX compared to placebo plus MTX at Week 12 (Fig. 2a and Supplementary Fig. 2a) and 24 (Supplementary Figs 1a and 3a), [22–26]. The efficacy of 2 mg baricitinib once daily, which is not shown in Fig. 2a, has been investigated in another randomised controlled trial (RCT) that enrolled patients with RA who showed inadequate response to csDMARDs [27]. Patients received placebo, 2 mg baricitinib once daily, or 4 mg baricitinib once daily with a stable dose of csDMARD. The proportion of patients who met ACR20 response criteria at Week 12, the primary endpoint of the study, was significantly higher in baricitinib groups (65.9% for the 2-mg group and 61.7% for the 4-mg group) versus
Table 1 Characteristics of JAKinibs approved or under review for rheumatoid arthritis

|                     | Tofacitinib [13]       | Baricitinib [14, 15]      | Upadacitinib [16, 17]     | Peficitinib [8, 18]     | Filgotinib [19–21]        |
|---------------------|------------------------|--------------------------|---------------------------|------------------------|--------------------------|
| **Selectivity to JAK** | JAK1/3                 | JAK1/2                   | JAK1                      | Pan JAK                | JAK 1                    |
| **Molecular weight** | 312.4                  | 371.4                    | 380.4                     | 326.4                  | 541.6                    |
| **Dosage for RA**    | 5 mg (twice daily)     | 2 or 4 mg* (once daily)  | 15 mg (once daily)        | 100–150 mg (once daily) | Under review             |
|                     | 11 mg (once daily) for extended release tablets | Only 2 mg is approved in US | 7.5 mg (twice daily) is approved only in Japan | Approved only in Japan and South Korea |
| **Plasma protein binding** | 39%                    | 44–56%                   | 52%                       | 72.83–75.2%           | 20.4%                    |
| **Metabolism**       | Kidney, 30%            | Mediated by CYP3A4       | Mediated by CYP3A4, CYP3A5, and CYP2D6 | Mediated by NNMT and SULT2A1 | Mediated by CES2 and weakly by CES1 |
|                     | Liver, 70%             |                          |                           |                        |                          |
|                     | Mediated by CYP3A4 and CYP2C19 |                          |                           |                        |                          |
| **Excretion**        | Urine 80%              | Urine 75.2%              | Urine 43%                 | Urine 36.8%            | Urine >80%               |
|                     | Faeces 14%             | Faeces 19.9%             | Faeces 53%                | Faeces 56.6%           |                          |
| **Factors related to drug interaction** | Substrate of Pgp and MDR1 | Substrate of OAT3, Pgp, BCRP, and MATE2-K | Substrate of Pgp and BCRP | Substrate of Pgp and BCRP | Substrate of Pgp and BCRP. Weak inhibitor of UGT1A1, OATP1B1, and OATP1B3 |
|                     | Increase exposure: ketoconazole, tacrolimus, cyclosporin due to inhibition of CYP3A4, and fluconazole due to inhibition of CYP3A4 and CYP2C19 | Decrease exposure: rifampicin due to inducing CYP3A4 | Decrease exposure: rifampicin due to inducing CYP3A4 | Decrease exposure: rifampicin due to inducing CYP3A4 | |
| **Drugs affecting plasma concentration of JAKinibs** | None                    | Increase exposure: probenecid and leflunomide due to inhibition of OAT3 | None                     | Increase exposure: ketoconazole, tacrolimus, cyclosporin due to inhibition of CYP3A4, and fluconazole due to inhibition of CYP3A4 and CYP2C19 | None |
| **Dose adjustment** | Reduced dose in patients with moderate liver dysfunction or severe renal impairment | Reduced dose in patients with moderate renal impairment or severe renal impainment and severe liver dysfunction | Not recommended for patients with severe renal impairment and severe liver dysfunction | Reduced dose in patients with moderate liver dysfunction | Under review |

ND not done, JPN Japan, USA United State of America, BCRP breast cancer resistance protein, CES carboxylesterase, CYP cytochrome P450, GI gastrointestinal, JAK Janus kinase, MATE multidrug and toxic extrusion protein, MDR multidrug resistance protein, NNMT nicotinamide N-methyltransferase, OAT organic anionic transporter, OATP organic anion transporting polypeptide, OCT organic cation transporter, Pgp P-glycoprotein, PK pharmacokinetics, RA rheumatoid arthritis, SULT sulfotransferase; UGT uridine 5'-diphospho-glucuronosyltransferase

*The dose of baricitinib is limited to 2 mg in the USA
placebo group (39.5%) ($p \leq 0.001$). The differences in the responses to placebo across the five trials (Fig. 2) may stem from differences in the countries and regions where they were implemented. Notably, the onset of their efficacy was rapid, usually approximately 1–2 weeks after starting the therapy, and almost all responders had an ACR20 response by Weeks 8–12. In addition, JAKinibs improved physical functions of MTX-IR patients, which was measured with health assessment questionnaires-disability index (HAQ-DI, Fig. 3a).

JAKinibs were also efficacious in biological DMARD-IR patients, who are more difficult to treat than MTX-IR.
A significantly higher proportion of patients reached ACR20 and ACR50 response criteria at Week 12 after treatment with all JAKinibs plus MTX or csDMARDs than after treatment with placebo plus MTX or csDMARD, and the efficacy did not change at Week 24 (Fig. 2b, Supplementary Fig. 1b, 2b, and 3b). ACR 70 response at Week 12 was also significant to 5 mg tofacitinib twice daily, 2 mg and 4 mg baricitinib once daily, and 200 mg filgotinib once daily versus placebo. HAQ-DI decreased significantly after treatment with JAKinibs in these patient populations (Fig. 3b). RCTs were implemented in MTX-naïve patients with RA [32–35]. While comparator arms were placebo + MTX in all four clinical trials, test arms were different; 5 mg tofacitinib twice daily + MTX; 4 mg baricitinib once daily + placebo and 4 mg baricitinib once daily + MTX; 15 mg upadacitinib once daily + placebo; 100 mg filgotinib once daily + MTX, 200 mg filgotinib once daily + placebo, and 200 mg filgotinib once daily + MTX. All JAKinibs plus MTX significantly suppressed the progression of structural changes in the joints at Weeks 24 (Fig. 3c and Supplementary Figs 1c, 2c, and 3c).
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24–28 (depending on JAKinibs tested) compared with placebo plus MTX in MTX-IR patients with RA except for 5 mg tofacitinib twice daily [22, 24–27] (Fig. 4a). However, tofacitinib plus MTX significantly inhibited the progression of structural changes at Week 24 in MTX-naïve patients with RA as well as 4 mg baricitinib plus MTX, 15 mg upadacitinib plus MTX, and 200 mg filgotinib plus placebo (Fig. 4b). The progression of joint destruction in the placebo group was higher in the clinical trial of peficitinib, which may have been due to ethnic differences in the susceptibility to joint destruction by RA.

Clinical efficacy of JAKinibs and adalimumab was compared in RCTs of tofacitinib, baricitinib, and upadacitinib. Adalimumab was used as a standard-of-care biologic DMARD for RA with moderate-to-severe disease activity. The results were summarised in Table 2. In MTX-IR patients with RA, tofacitinib+MTX effects were non-inferior to adalimumab+MTX at Month 6 for ACR50 response, while superiority could not be significantly proven. Baricitinib+MTX was superior as well as non-inferior to adalimumab+MTX in MTX-IR patients with RA at Week 12 for ACR20 response. Upadacitinib + MTX was superior as well as non-inferior to adalimumab + MTX in MTX-IR patients with RA at Week 12 for ACR50 response and DAS28-CRP < 3.2.

### 3 JAKinibs in Other IMIDs

The efficacy and safety of JAKinibs have been evaluated in various IMIDs [37] (Table 3). Of these, tofacitinib is approved to treat ulcerative colitis (UC) in the USA, the EU and Japan and psoriatic arthritis (PsA) in the USA as of May 2020 [5, 13, 38]. According to the USA FDA, tofacitinib is indicated for adult patients with moderately to severely active UC who have showed inadequate response or who are intolerant to TNFi. The recommended dose of tofacitinib is 10 mg (twice daily) as an induction therapy for 8 weeks and for a maximum of 16 weeks if needed. This is followed by 5 mg (twice daily) for maintenance therapy. In addition, tofacitinib is indicated for the treatment of adult patients with PsA who showed inadequate response or intolerance to MTX or other DMARDs. The recommended doses for PsA are the same as those for RA, but tofacitinib is not
approved as a monotherapy. A Phase III RCT demonstrated superior efficacy of tofacitinib versus placebo in csDMARD-IR patients with PsA [39]. There were significant improvements for tofacitinib versus placebo in ACR20 response at Month 3 (5 mg twice daily 50%, 10 mg twice daily 61%, and placebo 33%; \(p = 0.01\) for 5 mg vs placebo, \(p < 0.001\) for 10 mg vs placebo) and change in HAQ-DI at Month 3 (5 mg twice daily −0.35, 10 mg twice daily −0.40, and placebo −0.18; \(p = 0.006\) for 5 mg vs placebo, \(p < 0.001\) for 10 mg vs placebo). Tofacitinib was also efficacious in patients with PsA who showed inadequate response to a TNF inhibitor. Significantly larger proportions of patients achieved ACR20 response at Month 3, the primary endpoint, in the tofacitinib group versus placebo group (5 mg twice daily 50%, 10 mg twice daily 47%, placebo 24%; \(p < 0.001\) for both tofacitinib groups vs placebo) [40]. A Phase II RCT demonstrated the efficacy of filgotinib in csDMARD-IR patients with PsA. There was a significant improvement in

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Table 3 Phase II and Phase III studies of JAKinibs in other immune-mediated inflammatory diseases registered in ClinicalTrials.gov [37]

| IMID                | Tofacitinib                      | Baricitinib                      | Upadacitinib                      | Peficitinib                      | Filgotinib                      |
|---------------------|----------------------------------|----------------------------------|-----------------------------------|---------------------------------|---------------------------------|
| SLE/DLE             | Phase II (03288324, 03159936)     | Phase III (03843125, 03616964, 03616912) | Phase II (03978520)               | Phase II (03285711, 03134222)   |
| IIM                 |                                   | Phase II (03274076)              |                                   |                                 |                                 |
| SSc                 |                                   |                                   |                                   |                                 |                                 |
| SpA                 | Phase II (03738956)               |                                   |                                   |                                 |                                 |
| AS                  | Phase II (03502616)               |                                   |                                   |                                 |                                 |
| PsA                 | Approved (USA)                    |                                   |                                   |                                 |                                 |
| Psoriasis           | Phase II (01163253, 01815424, 01309737, 01276639, 01519089, 01186744, 01241591) | Phase II (01490632)               |                                   | Phase II (01096862)             |
| JIA                 | Phase III (02592434, 01500551)    | Phase III (03773965, 03773978)    |                                   |                                 |                                 |
| sJIA                | Phase III (03000439)              | Phase III (04088396)              |                                   |                                 |                                 |
| PMR                 | Phase II                          | Phase II (04027101)               |                                   |                                 |                                 |
| Takayasu arteritis  | Phase II                          |                                   | Phase III (03162983)              |                                 |                                 |
| GCA                 | Approved (USA, EU, JPN)           |                                   | Phase II (03026504)               |                                 |                                 |
| UC                  |                                   |                                   | Phase III (03006068, 03653026, 02819635) | Phase II (01959282) | Phase III (02914535, 02914522) |
| CD                  | Phase II (01393899, 01393626, 01470599, 00615199) | Phase III (03345836, 03345823, 03345849) | Phase III (03742973) | Phase II (03742973) | Phase III (03207815) |
| PBC                 | Phase II (03580343)               | Phase III (04088409)              |                                   |                                 |                                 |
| Non-infectious uveitis | Phase II (02299297, 02812342, 02197455) | Phase III (03899259)             |                                   |                                 |                                 |
| Alopecia            | Phase II (02001181)               | Phase III (03559270, 03344422, 03952559, 03334396, 03435081, 01733301, 03334435, 03428100) | Phase III (04195698, 03569293, 03568318, 03607422, 03661138, 03738397) |                                 |                                 |
| Atopic dermatitis   | Phase II (02001181)               |                                   |                                   | Phase III (03559270, 03344422, 03952559, 03334396, 03435081, 01733301, 03334435, 03428100) |                                 |

NTC number is shown in the parenthesis
Data were obtained from the website of ClinicalTrials.gov at https://clinicaltrials.gov/
Ruxolitinib, a JAK1 and JAK2 inhibitor, is approved for myeloproliferative neoplasms but is not included in this table.

CD Crohn’s disease, DLE discoid lupus erythematosus, EU European Union, GCA giant cell arteritis, GVH graft versus host disease, IIM idiopathic inflammatory myositis, IMID immune-mediated inflammatory disease, JIA juvenile idiopathic arthritis, JPN Japan, PBC primary biliary cholangitis, PMR polymyalgia rheumatica, sJIA systemic juvenile idiopathic arthritis, SLE systemic lupus erythematosus, SpA spondyloarthritis, SS systemic sclerosis, SSC systemic sclerosis, UC ulcerative colitis.

a proportion of patients who achieved ACR20 response at Week 16 for 200 mg filgotinib versus placebo (80% vs 33%; treatment difference 47%; 95% confidence interval (95% CI) 30.2–59.6) [41].

While tofacitinib failed in the Phase II clinical trials for Crohn’s disease [42], a Phase II clinical trial of filgotinib with active Crohn’s disease met its primary endpoint [43]. Patients (n = 174) were randomly assigned (3:1) to receive 200 mg filgotinib or placebo once daily for 10 weeks. Intention-to-treat analysis revealed that 60 (47%) of 128 patients treated with 200 mg filgotinib achieved clinical remission at Week 10 versus ten (23%) of 44 patients treated with placebo (difference 24 percentage points [95% CI 9–39], p = 0.0077). Upadacitinib was also investigated in patients with Crohn’s disease. A Phase II clinical trial enrolling 220 patients with moderate-to-severe Crohn’s disease demonstrated that
upadacitinib induced endoscopic remission in a significant proportion of patients, compared with placebo [44]. Phase III clinical trials are being implemented with these JAKinibs. Discordance of the results of clinical trials for Crohn’s disease may stem from study design or selectivity of JAKinibs, but we should wait for results from ongoing Phase III clinical trials to draw a conclusion.

Efficacy and safety of four JAKinibs (tofacitinib, baricitinib, upadacitinib, and filgotinib) have been investigated in patients with systemic lupus erythematosus (SLE). Phase II study of baricitinib enrolled 314 patients with SLE who had SLEDAI-2 K score ≥ 4 based on clinical symptoms and had active arthritis and/or active rash as defined by the SLEDAI-2 K at randomisation. Patients were allocated to one of the three arms: placebo, 2 mg baricitinib, or 4 mg baricitinib. At Week 24, the proportion of the patients in the 4-mg baricitinib group who achieved the primary endpoint (defined as the resolution of SLEDAI-2 K arthritis or rash) was significantly higher than that in placebo group (odds ratio [OR] vs placebo 1.8, 95% CI 1.0–3.3; p = 0.0414) [45]. A Phase III study on baricitinib in patients with active SLE is currently being implemented. A Phase II study on filgotinib in cutaneous lupus erythematosus (NTC#03134222) did not meet its primary endpoint and another study in lupus membranous nephropathy (NTC#03285711) was stopped because of low enrolment. Two Phase II studies on tofacitinib in discoid lupus erythematosus and SLE with cutaneous disease and one Phase II study with upadacitinib in moderately to severely active SLE are recruiting participants (Table 3 and https://clinicaltrials.gov/).

Clinical trials in patients with ankylosing spondylitis (AS) are also promising. A randomised, placebo-controlled, Phase II trial compared placebo, 2 mg tofacitinib twice daily, 5 mg twice daily, and 10 mg twice daily. The primary efficacy endpoint was the response rate at Week 12 analysed by Assessment of SpondyloArthritis International Society for 20% improvement (ASAS20) with the Bayesian EMAX model. Administering 5 and 10 mg tofacitinib twice daily demonstrated greater clinical efficacy than placebo in reducing signs, symptoms and objective endpoints of active AS in adult patients [46]. In the Phase II RCT of filgotinib, patients with active AS (n = 116) were randomly allocated to 200 mg filgotinib once daily or to placebo (1:1 ratio) [47]. The change in the mean AS disease activity score (ASDAS) from baseline to Week 12, the primary endpoint, was − 1.47 in the filgotinib group vs − 0.57 in the placebo group (least squares mean difference − 0.85; 95% CI − 0.17 to − 0.53; p < 0.0001). Decrease in ASDAS was already significant at Week 1. In the Phase II/III RCT of upadacitinib, 93 patients with active AS received upadacitinib and 94 received placebo [48]. Significantly more patients in the upadacitinib group versus the placebo group had an ASAS40 response at Week 14, the primary endpoint of the study (52% vs 26%; treatment difference 26%; 95% CI 13–40; p = 0.0003).

4 Safety Profiles of JAKinibs

4.1 Changes in Laboratory Parameters

The safety data for JAKinibs have been extensively collected and analysed in clinical development programs (CDPs) and post-marketing surveillance studies for RA and other IMIDs. Changes in laboratory parameters of patients with RA treated with JAKinib that were obtained from CDPs are summarised in Table 4 [24, 30, 31, 49–55]. Some differences were observed in the levels of haemoglobin, lymphocyte counts, and platelet counts. The net effect of JAKinibs on haemoglobin levels and platelet counts is complex because of the effect of RA-associated inflammation on these laboratory parameters and different selectivity of JAKinibs to JAK2, which is used by erythropoietin receptors and thrombopoietin receptors (Supplementary Table 1). Haemoglobin levels increase after treatment with all JAKinibs except upadacitinib. Partial inhibition of JAK2 could be responsible for the decrease in haemoglobin levels in patients treated with upadacitinib. Platelet counts decrease following treatment with all JAKinibs except baricitinib, which showed transient increase in platelet counts before returning to normal levels. Lymphocyte counts remain stable following filgotinib treatment but decreased after other JAKinibs therapies. Increased levels of serum liver transaminases, creatine kinase, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and creatinine are common across all JAKinibs therapies. Incidence rates of serious adverse events (AEs) associated with these changes in laboratory parameters are low and seldom lead to the cessation of treatment with a JAKinib.

4.2 AEs of Interest Associated with JAKinib Treatment

The incidence rates of AEs of interest associated with tofacitinib, baricitinib, peficitinib, upadacitinib, and filgotinib treatment in patients with RA are summarised in Table 5 [18, 56–63]. It is important to note that patient-years (PYs) for tofacitinib and baricitinib are larger than those of other three JAKinibs. Overall, safety profiles of JAKinibs are quite similar irrespective of their selectivity to JAKs. Incidence rates of serious infection and herpes zoster (HZ) with filgotinib might be lower than with other JAKinibs, but more data are required to discuss the difference. Details of each AE are discussed in the following sections.
Because JAKinibs simultaneously inhibit signal transduction pathways of several cytokines and growth factors that are relevant to host defence mechanisms, the risk of serious infection is a significant concern for patients treated with these drugs. The incidence rates of serious infections in the CDPs were similar for all JAKinibs except for filgotinib and ranged from 2.5 to 3.8 per 100 PYs [18, 56–58] (Table 5). These values were higher than those of hospitalised infections in the cohorts of patients with RA (1.1–1.6 per 100 PYs) [64] (Supplementary Fig. 4) and similar to those of patients treated with biological DMARDs [11, 65]. Of note, patients’ background of these cohort studies was different from that of clinical trials with JAKinibs. The incidence rates of serious infections in the CDPs of filgotinib was 3.3 per 100 PYs for 100 mg and 1.7 for 200 mg [59], which was within the range of the five RA cohorts (i.e. 1.1–1.6/100 PYs). Integrated data analyses of JAKinibs indicated that the incidence rates of serious infections remained constant with long exposures to these drugs [18, 56–59]. Age is a significant risk factor for serious infections in patients with RA receiving a biological DMARD, but odds ratio of serious infections for biological DMARD use versus non-use are similar between patients under and over 65 years [66]. Taking these results into consideration, announcement of an increased risk of serious and fatal infections in patients aged > 65 years by The European Medical Agency should be carefully interpreted [67]. The incidence rates of serious infection in the Japanese post-marketing surveillance was 5.38 (4.68–6.15) per 100 PYs [68].

Independent risks of serious infections during treatment with JAKinibs were age, diabetes mellitus, corticosteroid use (> = 7.5 mg/day of prednisolone), and tofacitinib dosage (10 mg twice daily vs 5 mg twice daily) for tofacitinib [69] and age, non-normal body mass index (vs normal, 18–24 kg/m²), enrolment in the Asian region excluding Japan, and concomitant use of corticosteroids for baricitinib [70].

Rheumatologists should also pay attention to tuberculosis during RA treatment. It is widely recognised that tuberculosis incidence rates are higher in patients with RA compared to the general population [71–73], and these rates (95% CI) in the five large registries ranged from 0.02 (0.01–0.03) to 0.35 (0.17–0.67) [64] (Supplementary Fig. 4). The incidence rate for tuberculosis was 0.2 for tofacitinib and baricitinib and 0 for peficitinib, and three patients receiving upadacitinib were reported to have tuberculosis in the CDP (Table 5). All patients in the RCTs were screened for tuberculosis and excluded from trials if necessary, but probably not all were screened in the registries. Two important observations should be noted. First, incidence rates for tuberculosis during treatment with JAKinibs are strongly associated with the background incidence rates for tuberculosis in a given country or a region [74]. Second, extrapulmonary tuberculosis is more common in patients treated with JAKinibs than in the general population [57, 74], which is similar to characteristics of tuberculosis in patients treated

Table 4 Effects of JAKinibs on laboratory parameters

| Laboratory parameters | Tofacitinib [49, 50] | Baricitinib [51] | Upadacitinib [30, 53] | Peficitinib [24, 52] | Filgotinib [31, 54, 55] |
|-----------------------|---------------------|-----------------|----------------------|---------------------|----------------------|
| Haemoglobin           | Gradual increase    | Gradual increase| Gradual increase     | Decreasea            | Gradual increase      |
| Lymphocyte count      | Gradual decrease    | Gradual decrease| Transient increase   | Instant decrease     | Decreasea            |
| Platelet count        | Instant decrease followed by stabilisation | Instant increase followed by stabilisation | Transient increase | Decreasea            | Decreasea            |
| Liver transaminases   | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Increasea            | Increasea            |
| Creatinine kinase     | Increasea            | Increasea       | Instant increase followed by stabilisation | Increasea            | Increasea            |
| HDL cholesterol       | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Increasea            | Increasea            |
| LDL cholesterol       | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Increasea            | Increasea            |
| Creatinine            | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Instant increase followed by stabilisation | Increasea            | Increasea            |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; ND, not determined

aDetailed changes over the first weeks of treatment with the corresponding drugs were not published
A Phase III study of tofacitinib utilised this approach, and of the 286 patients with untreated LTBI, none developed active tuberculosis [74]. A wide range of opportunistic infections has been reported in patients receiving JAKinibs; these include non-tuberculous mycobacterium infections, Cryptococcus infections, Cytomegalovirus infections, Epstein–Barr virus infections, BK virus infections, Pneumocystis pneumonia, aspergillosis, candidiasis, histoplasmosis, paracoccidioidomycosis and toxoplasmosis [75]. Reactivation of hepatitis B virus (HBV) was reported during treatment with JAKinibs [76]. An integrated analysis of tofacitinib with 5671 patients reported 60 opportunistic infections including 34 non-TB infections in Phase II, Phase III, and LTE studies [74] with crude IR (95% CI) of 0.46 (0.36–0.59) per 100 PYs.

### 4.2.2 Herpes Zoster

Risks for HZ in patients with RA receiving tofacitinib, baricitinib, and upadacitinib ranged from 3.3 to 3.9 per 100 PYs [56–58] (Table 5) and were higher than those previously reported in patients with RA (0.66–1.9 per 100 PYs) [64] (Supplementary Fig. 4). Peficitinib showed a higher incidence rate (95% CI) of HZ [6.5 (5.5–7.7)] than other JAKinibs because most patients analysed were Japanese [18] who also had a significantly higher incidence of HZ in association with other JAKinibs [60]. The integrated safety analysis of filgotinib reported an incidence rate of 1.1 per 100 PYs for 100 mg and 1.7 for 200 mg [59]. The risk for HZ in RA patients administered with filgotinib seems to be lower than that of other JAKinibs, but the analysis of a larger database with a more extended observation period is required to draw a conclusion and interpret the differences between filgotinib and other JAKinibs. Risk for HZ in patients receiving a biological DMARD has been reported with hazard ratio (HR) ranging from 1.0 to 1.7 [77].

Asian countries, especially Japan and Korea, had consistently higher incidence rates of HZ in patients with RA who received JAKinibs in CDPs. The incidence rate (per 100 PYs) of HZ in Japanese and Korean patients who received tofacitinib was 8.0 (6.6–9.6); in Asian patients who received baricitinib it was 5.6, and for peficitinib it was 6.5 (5.5–7.7) [18, 60, 61]. The high incidence rates were confirmed by

### Table 5 Safety profiles of JAKinibs

| Adverse events | Tofacitinib [56, 62] | Baricitinib [57, 63] | Upadacitinib [58] | Peficitinib [18] | Filgotinib [59] |
|---------------|---------------------|---------------------|-------------------|-----------------|----------------|
| Serious infection | 2.7 (2.5–3.0) | 2.8 | 3.8 (3.1–4.7) | 2.5 (1.9–3.2) | 100 mg 3.3, 200 mg 1.7 |
| Herpes zoster | 3.9 (3.6–4.2) | 3.3 | 3.7 (3.0–4.5) | 6.5 (5.5–7.7) | 100 mg 1.1, 200 mg 1.7 |
| TB | 0.2 (0.1–0.3) | 0.2 | 0.1 | 0 | ND |
| Malignancies excluding NMSC | 0.9 (0.8–1.0) | 0.8 | 0.9 (0.5–1.3) | 0.9 (0.6–1.3) | 100 mg 0.5, 200 mg 0.5 |
| Lymphoma | 0.1 (0.1–0.2) | 0.1 | < 0.1 | 3 cases out of 1052 patients | ND |
| GI perforation | 0.11 (0.07–0.17) | 0.04 (0.01–0.13) | 0.2 | 0.2 (0.1–0.5) | ND |
| Serious cardiac events | 0.58a (0.39–0.88) | 0.5a | 0.6a (0.4–1.0) | 0.5 (0.3–0.9) | 100 mg 0.6a, 200 mg 0.3a |
| VTE | ND | 0.5 | 0.6 (0.3–1.0) | 0 | ND |
| DVT | 0.1 (0–0.3) | 0.4 | ND | 0 | ND |
| PE | 0.1 (0–0.4)b | 0.2 | ND | 0 | ND |

These data show the incidence rates per 100 patient-years (PYs; 95% CI) except GI perforation (per 1000 PYs). Note that some of the incidence rates of AEs in recently developed JAKinibs are not yet reported in literature. Data are from the integrated safety analyses of each drug. Venous thrombotic events were reported as VTE in upadacitinib and filgotinib, as DVT/PE in tofacitinib, and as VTE/DVT/PE in baricitinib and peficitinib.

For upadacitinib, the safety data of patients tested for dosages other than 15 mg (once daily) are not included.

DVT deep vein thrombosis, GI gastrointestinal, ND not described, NMSC non-melanoma skin cancer, PE pulmonary embolism, TB tuberculosis, VTE venous thromboembolism

a Major adverse cardiovascular event

b 0.1 for 5 mg (twice daily) and 0.2 for 10 mg (twice daily)

c Each case of diffuse large B-cell lymphoma, lymphoma, and lymphoproliferative disorder with TNFi. Screening and treatment of latent tuberculosis infections (LTBIs) before starting treatment with a biological DMARD is strongly recommended in clinical settings. A Phase III study of tofacitinib utilised this approach, and of the 286 patients with untreated LTBI, none developed active tuberculosis [74].

A wide range of opportunistic infections has been reported in patients receiving JAKinibs; these include non-tuberculous mycobacterium infections, Cryptococcus infections, Cytomegalovirus infections, Epstein–Barr virus infections, BK virus infections, Pneumocystis pneumonia, aspergillosis, candidiasis, histoplasmosis, paracoccidioidomycosis and toxoplasmosis [75]. Reactivation of hepatitis B virus (HBV) was reported during treatment with JAKinibs [76]. An integrated analysis of tofacitinib with 5671 patients reported 60 opportunistic infections including 34 non-TB infections in Phase II, Phase III, and LTE studies [74] with crude IR (95% CI) of 0.46 (0.36–0.59) per 100 PYs.

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Asian countries, especially Japan and Korea, had consistently higher incidence rates of HZ in patients with RA who received JAKinibs in CDPs. The incidence rate (per 100 PYs) of HZ in Japanese and Korean patients who received tofacitinib was 8.0 (6.6–9.6); in Asian patients who received baricitinib it was 5.6, and for peficitinib it was 6.5 (5.5–7.7) [18, 60, 61]. The high incidence rates were confirmed by
the PMS study of tofacitinib in Japan. The incidence rate of HZ over 36 months of treatment with tofacitinib in the all-case PMS programme implemented in Japan was 6.81 (6.01–7.68) per 100 PYs [68]. Despite elaborate genetic and epidemiological studies, reasons for this geographic difference are still unknown and require further investigation.

In CDPs, the significant risk factors of developing HZ were age at baseline [per 10-year increment; HR, 1.41 (95% CI 1.31–1.52)], corticosteroid dose at baseline [>0 to ≤ 5 mg/day vs 0 mg/day, 1.49 (1.22–1.82); > 5 mg/day vs 0 mg/day, 1.41 (1.12–1.77)], regions of recruitment [Asia vs Western Europe, 2.52 (1.80–3.53); Latin America vs Western Europe, 1.49 (1.03–2.15); and US/Canada/Australia vs Western Europe, 1.43 (1.02–2.02)], smoking status [former smoker or non-smoker vs smoker, 1.32 (1.04–1.69)], and tofacitinib dose during treatment [per 5 mg increment, 1.33 (1.14–1.54)] for tofacitinib [78]. The risk factors of HZ for baricitinib were old age (HR 1.3, 95% CI 1.17–1.43) and Asian population, especially from Japan, Taiwan, and South Korea (HR 1.82, 95% CI 1.28–2.58), but the risk of HZ was not increased in the baricitinib programme with the use of corticosteroids [79].

### 4.2.3 Malignancy

Cohort studies demonstrated that patients with RA have a slightly higher risk for overall malignancies than the general population [80]. Patients with RA have an increased standardised incidence rate (95% CI) for lymphoma [2.46 (2.05–2.96)] and lung cancer [1.64 (1.51–1.79)] than the general population, whereas a decreased risk of colorectal [0.78 (0.71–0.86)] and breast [0.86 (0.73–1.01)] cancer was reported [80]. Analyses of integrated databases from CDPs indicated no significant effects of JAKinibs on the risk of overall malignancies, excluding non-melanoma skin cancer, in patients with RA compared with the analyses of the five representative cohorts of patients with RA (Table 5 and Supplementary Fig. 4). The incidence rates of overall malignancies were 0.46–0.87 for the five RA cohorts and 0.5–0.9 for CDPs of JAKinibs [18, 56–61, 81]. No skewed proportion of site-specific malignancies have been reported. Long-term observation in a clinical setting is required to conclude if associations exist between the use of JAKinibs and malignancies.

Two- to three-fold higher risks of lymphoma have been reported in patients with RA, and the risk is associated with accumulated levels of inflammation [82]. In addition, patients with RA sometimes develop iatrogenic immunodeficiency-associated LPDs during treatment with JAKinibs. Some patients developed LPDs during treatment with JAKinibs. Crude incidence rates (95% CI) for lymphoma in patients treated with tofacitinib and baricitinib were 0.10 (0.06–0.15) [56] and 0.10 (95% CI not reported) [57], respectively. No patients were reported to develop lymphoma in the CDP of peficitinib. The numbers of reported cases with LPDs are few for each JAKinibs. Further accumulation of cases is required to evaluate the risk for LPD precisely.

#### 4.2.4 Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

A series of epidemiological studies showed that patients with RA generally have a higher risk for DVT, PE, and venous thromboembolism (VTE) than a control population with risk ratios of 2.08 (95% CI 1.75–2.47), 2.17 (2.05–2.31), and 1.96 (1.81–2.11), respectively, according to a meta-analysis [84].

In the analysis of the data from Phase II and Phase III randomised clinical studies of tofacitinib for RA, psoriasis, PsA, and UC [62], the number of reported DVT events was two in patients with RA (1 each for 5 mg twice daily and 10 mg twice daily) and one in patients with PsA (10 mg twice daily). There were 5 reported PE events in patients with RA (5 mg twice daily, n = 2; 10 mg twice daily, n = 3). The incidence rates (95% CI) of DVT were 0.1 (0.0–0.3) for both tofacitinib doses in RA and 0.5 (0.0–2.8) for 10 mg (twice daily) in PsA, whereas those of PE were 0.1 (0.0–0.4) for 5 mg (twice daily) and 0.2 (0.0–0.4) for 10 mg (twice daily). In the placebo-controlled period of clinical trials of baricitinib, five DVT/PE cases, including two serious cases, were reported in the 4 mg baricitinib group, and incidence rates of DVT/PE were 1.2 per 100 PYs in the 4 mg baricitinib group and none in the placebo group [85]. The incidence rates of overall DVT and PE in a combined dataset from the CDP of baricitinib were 0.4 and 0.2 per 100 PYs, respectively [63]. The incidence rates (95% CI) of VTE were 0.6 (0.3–1.0) per 100 PYs for upadacitinib [58], 0.1 for 100 mg filgotinib, and 0.2 for 200 mg filgotinib [59]. No VTE/DVT/PE were reported in the CDP of peficitinib. Venous thrombotic events were reported as VTE in upadacitinib and filgotinib, as DVT/PE in tofacitinib, and as VTE/DVT/PE in baricitinib and peficitinib.

A randomised safety endpoint study to compare tofacitinib (CP-690,550-10) at two doses (5 mg and 10 mg twice daily) and TNFi has been implemented (A3921133, NCT02092467), and patients with moderate-to-severe MTX-IR RA having at least one cardiovascular risk factor were enrolled. The primary outcome measures were malignancies, excluding NMSC, and incidence of major adverse cardiovascular events (MACE). The FDA found a higher risk of pulmonary embolism in patients with RA treated with 10 mg
tofacitinib (twice daily) than in patients treated with TNFi, and a higher all-cause mortality in 10 mg tofacitinib (twice daily) versus 5 mg tofacitinib (twice daily) and TNFi groups; thus, a warning for thrombosis was added in the package insert in 2019 [5, 86]. The FDA also stipulated that the drug labelling for baricitinib and upadacitinib mentions the risk for thrombosis [6, 87]. Similarly, the European Medical Agency announced that tofacitinib could increase the risk of blood clots in the lungs and deep veins in patients who are already at high risk [67]. The results of this study have been monitored by an external Rheumatology Drug Safety Monitoring Board, but the events are not yet adjudicated. Appropriateness of incident rates of events in the control arm (i.e. TNFi arm) should be evaluated carefully and precisely. A3921133 is currently still underway, and its final data should frame the results correctly. Continued pharmacovigilance is strongly recommended for JAKinib-related risk of blood clots, since risk for VTE/DVT/PE may be a class effect of JAKinibs.

4.2.5 Gastrointestinal (GI) Tract Perforation

A higher risk of GI tract perforation has been described in patients receiving tocilizumab [88–91]. As all JAKinibs inhibit JAK1 and IL-6 signal transduction pathways, the risk of GI tract perforation has been investigated. The incidence rates per 1000 PYs (95% CI) of GI tract perforation in CDPs for RA treated using JAKinibs were 0.11 (0.07–0.17) for tofacitinib [56], 0.04 (0.01–0.13) for baricitinib [57], and 0.2 (not reported) for peficitinib [18]. Older age, diverticulitis, other gastrointestinal conditions, and prednisone use (> 7.5 mg/day) have been reported as independent risk factors for lower GI tract perforation [91]. These factors, as well as risk factors of acute diverticulitis in general, including presence of diverticulosis, obesity, smoking, diet, lifestyle factors, and use of non-steroidal anti-inflammatory drugs [92] should be carefully evaluated for the risk-benefit balance of treatment before starting treatment with JAKinibs.

4.2.6 Pregnancy and Breastfeeding

JAKinibs have been demonstrated to have teratogenic effects in preclinical animal studies [6, 18, 87, 93]. The following pregnancy outcomes in 47 patients who received tofacitinib during RCTs were reported: 25 healthy new-borns, one congenital pulmonary valve stenosis, seven spontaneous abortions, eight medical terminations, and six pending or lost to follow-up [94]. JAKinibs are contraindicated during pregnancy, and women of child-bearing age should use effective contraception during and at least 1 week after treatment. Breastfeeding mothers should not use JAKinibs because of the risks to new-borns and infants [6, 18, 87, 93].

5 Discussion

5.1 Implications of Inhibiting JAKs in the Pathogenesis of RA

All JAKinibs showed good efficacy in MTX-IR patients with moderate-to-severe RA disease activity. In addition, clinical trials of tofacitinib, baricitinib, upadacitinib, and filgotinib demonstrated significant efficacy in biological DMARD-IR and MTX-naïve patients with RA (Figs. 2, 3, and 4, Supplementary Figs 1, 2, and 3). The selectivity to JAKs of each JAKinib differ, but all JAKinibs inhibit JAK1. The selective JAK1 inhibitors, upadacitinib and filgotinib, showed similar efficacy to the other three JAKinibs. These data indicate that JAK1 plays an essential role in RA pathogenesis among the four JAK family members. A novel functional module of the cytokine network, which includes TNF, IL-6, and GM-CSF, has been proposed to explain RA synovitis [95]. Hence, the main targeted pathway of JAKinibs in RA appears to be that of IL-6. The similar efficacy of JAKinibs and tocilizumab reported in MTX-naïve patients with RA [96, 97] may support this hypothesis.

Clinical trials of TNF inhibitors in MTX-naïve patients with RA demonstrated a similar range of efficacy to those of JAKinibs [98, 99]. Considering that the TNF signal transduction system mainly utilises the NFκB pathway and does not utilise JAK family proteins [100], the pathogenesis of RA synovitis is heterogeneous and includes at least the IL-6-JAK1 pathway-dominant type and TNF-NFκB pathway-dominant type, and some patients may present these two types of synovitis simultaneously.

5.2 Head-to-Head Comparison of JAKinibs and Adalimumab

Tofacitinib was non-inferior to adalimumab, while baricitinib and upadacitinib were superior as well as non-inferior to adalimumab in MTX-IR patients with RA (Table 2). Biological DMARDs and JAKinib are recommended without preference by the EULAR for RA patients with poor prognostic factors in whom the treatment target could not be achieved with the first csDMARD strategy [9]. The results of head-to-head comparison of JAKinibs and adalimumab in MTX-IR patients with RA indicate possible preference of JAKinibs in terms of clinical efficacy, but long-term safety and pharmacoeconomic consideration are indispensable. Long-term safety data are still in short for upadacitinib and filgotinib, and the results from observational studies using database of regional or national cohorts of patients with RA and claims database may provide further insights. Although baricitinib and upadacitinib showed a better clinical efficacy than adalimumab...
by several measures, pharmacoeconomic implication of the difference is not clear. Accumulation of evidence is still needed for appropriate positioning of JAKinibs in RA treatment strategies.

5.3 Difference in the Incidence Rates of HZ Following JAKinib Treatment

The increased risk of HZ has been recognised as a common adverse drug reaction in patients administered JAKinibs. Although PY are still few, the incidence rate of HZ in the CDP of filgotinib was 1.1 per 100 PYs for 100 mg and 1.7 per 100PYs for 200 mg [59] and was within the range of incidence rates from the three representative RA cohorts (i.e. CORRNA, IORRA, and CORRONA International) (Table 5 and Supplementary Fig. 4). Furthermore, another JAK1 inhibitor, upadacitinib, exhibited an incidence rate of 3.7 (95% CI 3.0–4.5), which is very close to the value associated with tofacitinib (JAK1/3 inhibitor) or baricitinib (JAK1/2 inhibitor) (Table 5). Because all JAKinibs target the conserved ATP-binding pockets of JAKs, JAKinibs are relatively but not absolutely selective to JAK family proteins and may exert unintended inhibition depending on drug concentrations in vivo. Effects of JAKinibs at clinical doses on IL-15-induced NK cell proliferation, which is mediated via JAK3, have been reported [101]. Filgotinib showed less inhibition than other JAKinibs on the JAK1-mediated signaling of IFN-gamma and IL-2, 4 and 15 [102]. Lower calculated inhibition of IL-15-induced NK cell proliferation and of interferon-gamma signaling with filgotinib versus other JAKinibs may explain the differences in the incidence rates of HZ observed with these JAKinibs, but results from long-term observational studies are required to discuss and confirm the differences.

5.4 Safety Management of JAKinibs in Patients with RA and Other IMIDs

During the past two decades, evidence on the safety of biological DMARDs has been accumulated, and proper screening and monitoring methods are established in accordance with recommendations or guidelines of countries or regions [9, 103]. Considering the mechanism of action of JAKinibs, it is reasonable and highly recommended to follow the screening and monitoring methods for biological DMARDs when a physician prescribes JAKinibs to patients.

Before starting treatment with a JAKinib, risks of serious infection, HZ, tuberculosis, malignancy, GI perforation, serious cardiac events, and thromboembolic events should be evaluated by obtaining data from history, physical examination, laboratory tests, and imaging tests. History of malignancy, diverticulitis and thromboembolic events will be useful for evaluating the risks of a JAKinib in each patient. Regarding the risks associated with serious infections; age, comorbidities including diabetes mellitus and chronic respiratory diseases, the use of glucocorticoids, and recent hospitalised infection or serious infection are especially important [104–107]. In addition to complete blood counts and laboratory tests for liver and kidney function, hepatitis B (HBs) antigen, HBc antibody, HBs antibody, HCV antibody, and β-D-glucan should be evaluated. In HBs antigen-positive patients or HBs antigen-negative and HBc or HBs antibody-positive patients (i.e. patients with previous HBV infections), measuring levels of HBV-DNA and adhering to local guidelines are recommended [76]. History of exposure to Mycobacterium tuberculosis, chest X-rays, and interferon-γ-releasing assays are required to identify patients with LTBI.

After starting treatment with a JAKinib, complete blood count and laboratory tests for liver and kidney function should be performed regularly, and doses should be adjusted if necessary. Effectiveness of treatment is evaluated using composite measures, such as simplified disease activity index and clinical disease activity index, health assessment questionnaires, and imaging tests such as X-rays and sonography of affected joints [9]. The monitoring of signs and symptoms of AEs of special interest, as listed in Table 5, is strongly recommended.

In conclusion, JAKinibs are efficacious for RA and other immune-mediated inflammatory diseases. Selectivity of JAKinibs to JAK family protein depends on drug concentration in vivo. JAK inhibitors with different selectivity to JAK family proteins have similar efficacy and safety profiles, with some minor differences in patients with RA. Long-term observational studies enrolling patients with diverse clinical backgrounds are required to strike a risk-benefit balance in clinical settings.

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Compliance with Ethical Standards

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