The infection risks of JAK inhibition

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ABSTRACT

Introduction: Janus Kinase inhibitors (JAKi) have shown to be highly effective in the treatment of immune-mediated inflammatory diseases. As with all immunomodulatory therapies, careful assessment of any treatment-associated infection risk is essential to inform clinical decision-making.

Areas covered: We summarize current literature on infection rates among the licensed JAKi using published phase II/III trial results, post-licensing and registry data.

Expert opinion: licensed JAKi show increased risk of infection across the class compared to placebo, most commonly affecting respiratory and urinary tracts, nasopharynx and skin. This risk is dose-dependent. Risks are similar at licensed JAKi doses to that seen with biologic therapies. The risk is compounded by other risk factors for infection, such as age and steroid co-prescription. Herpes zoster reactivation is more common with JAKi compared to other targeted immune modulation, making screening for varicella exposure and vaccination in appropriate cohorts an advisable strategy. Crucially, these small risk increases must be balanced against the known harms (including infection) of uncontrolled autoimmune disease. JAKi are a safe and potentially transformative treatment when used for appropriately selected patients.

1. Introduction

The development of small molecule inhibitors of Janus kinases (JAK inhibitors, JAKi) have offered an alternative to biological therapies in immune-mediated inflammatory diseases (IMIDs), demonstrating impressive efficacy in treating conditions mediated by the JAK/signal transducers and activators of transcription (STAT) pathways such as rheumatoid arthritis (RA), psoriatic arthritis, ulcerative colitis, and psoriasis [1].

Janus kinases are members of the tyrosine kinase family that play a key role in transferring extracellular signals into the nucleus, altering DNA transcription, downstream translation, and effector protein manufacture. In humans, four JAKs exist: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Cell surface receptors require a pair of JAKs as either identical homodimers (e.g. JAK2/JAK2) or heterodimers (e.g. JAK1/JAK3) in order to signal [2]. This is in turn activates STAT proteins, which target gene promoters to activate transcription (Figure 1)[3]. The JAK/STAT pathways down regulate more than 50 cytokines and growth factors and are considered a central communication node for the immune system [4].

Human studies on JAK-STAT biology have identified that germline gain or loss of function mutations of different genes encoding JAK-STAT are linked to numerous immunological phenotypes and myeloproliferative disorders [5,6]. For example, loss of function mutations of JAK3 are related to severe combined immunodeficiency (SCID) [7]. Loss of function mutations of JAK 1, TYK2, STAT1, and STAT5B lead to intracellular bacterial infections [6]. STAT5B has an important role T cell differentiation and memory T cell homeostasis. Its deficiency can lead to recurrent pneumonia [8]. STAT1 loss of function mutations can impair interferon (IFN) responses (type 1 IFN and IFNγ) and increase susceptibility to viral infections [8,9]. Gain of function mutations also associate with infection. Patients with STAT1 mutations have recurrent Candida infections, as STAT1 antagonizes STAT3 driven anti-fungal responses mediated by IL-17 [10].

Current Food and Drug Administration (FDA) and European Medical Agency (EMA) licensed JAK inhibitors include two first-generation agents [11]: i) tofacitinib which inhibits JAK3 and JAK1 with some affinity for JAK2 and limited affinity for TYK2 and was licensed in 2012, and ii) baricitinib which inhibits JAK1 and JAK2 (and to a much lesser extent TYK2) and was licensed in 2017. Two second-generation selective JAK1 inhibitors; iii) upadacitinib licensed in 2019 and iv) filgotinib, were licensed in Europe only in 2020 [12,13].

In the management of IMIDs, clinical practice aims to treat the underlying inflammatory condition with immune modulating therapies whilst minimizing the risk of the adverse events, in particular infections. Individuals with IMIDs are at an increased risk of infections due to both their underlying disease and the immunomodulating therapies they are prescribed. There
is a two-fold increase in serious infection risk in patients with rheumatoid arthritis [14], particularly bronchopulmonary and genitourinary infections, which are partially responsible for the increased mortality seen with this condition [15]. When prescribing immune modulating therapies, especially JAK inhibitors, one must not only consider the side effects of the drugs but also an individual’s age, associated comorbidities, and the immunopathogenesis of the disease itself [16].

2. Serious infection risk

JAK inhibition has potential to suppress integral elements of the immune response. The risk of infection, including opportunistic infections, appears increased compared with placebo with all JAK inhibitors. The most frequent serious infections associated with JAK inhibitors include pneumonia, nasopharyngitis, urinary tract infections, cellulitis, and herpes zoster (Figure 2) [17].

Figure 1. JAK signaling pathway.

Figure 2. Serious infections associated with JAK inhibitors.

Based on the summary of product characteristics, the commonest infections associated with Janus Kinases (JAK) inhibitors are: upper respiratory tract infections, pneumonia, Mycobacterium tuberculosis, herpes zoster, urinary tract infections and cellulitis. The right panel shows the licensed clinical uses of JAK inhibitors in Europe according to the European Medicines Agency (EMA) at the time of publication.
Across class, no differences were observed regarding the risk of serious infections in a recent network analysis of clinical trials [18]. However, the individual trials were not powered to examine rare outcomes such as infections. Long-term extension studies (LTE) and registry data are needed to further understand the risks of rarer outcomes [19].

A pooled analysis of clinical trials and LTE studies on tofacitinib found that the incidence of serious infections was 2.7 per 100 patient years (PY) [17]. Similarly, pooled data from phase I to III baricitinib trials found an incidence of 3.2 per 100PY [20]. This risk is comparable to the rates seen with biologic therapies (4.2 per 100PY in real-world data) [21,22]. Of note, the risk of infection in clinical trial data was greater with higher doses of tofacitinib and baricitinib (10 mg, BID, and 4 mg, OD respectively) [23], and did not rise with increasing duration of therapy [17].

Tofacitinib has the largest safety database of the JAKi, since it was the first medication in the class to be licensed [24]. Findings from a US registry of RA patients (n = 21,832) reported higher rates of serious infection in patients prescribed tofacitinib combination therapy with disease-modifying antirheumatic drugs (DMARDs) 3.67(95%CI: 2.21–5.75) versus 2.01 events per 100PY (95% CI: 1.65–2.42) for DMARD therapy alone. For comparison, rates seen with TNFi-DMARD combination therapy were: 2.16 per 100PY (95% CI: 1.98–2.36). Similar hospitalization rates were reported for all strategies [25]. A US multi-database study on RA (n = 130,718) found the risk of serious infection with tofacitinib comparable to that seen with other biologics including adalimumab, certolizumab, golimumab, abatacept, and tocilizumab. Etanercept was the only drug to demonstrate a lower risk of infection [HR tofacitinib versus etanercept: 1.41 (95%CI: 1.15–1.73)] [26].

A pooled analysis from baricitinib trials and LTE study (8 phase 3/2/1b clinical trials and 1 LTE) with 7860 patient exposure years reported an incidence rate of 3.0 per 100 PY (95% CI 2.6 to 3.4), with no increased incidence over time [27]. A Japanese registry of RA patients on baricitinib (n = 138) reported that 1.5% of patients experienced serious infections [28].

Across the selective JAK1 clinical trials, absolute event rates for serious infections were found to be lower with smaller doses [29], and were comparable to nonselective JAKi and biologics [30–34]. An integrated analysis from upadacitinib SELECT trials (SELECT-NEXT [35], SELECT-BEYOND [36], SELECT-EARLY [37], SELECT-MONO [32], and SELECT-COMPARE [38]) reported that event rates of serious infections were higher with the 30 mg dose: 6.2 per 100PY (95%CI: 5.0–7.7) versus 3.8 (CI95%: 3.1–4.7) for the 15 mg dose [39]. An 84-week LTE study (SELECT-SUNRISE) of upadacitinib reported high incidence of serious infections in the 15 mg group (6.7 per 100PY) and at the 30 mg dose (12.7 per 100PY) [40]. Only the 15 mg dose of upadacitinib is currently licensed.

A recent 4 year LTE analysis on patients who completed the filgotinib DARWIN1 and DARWIN2 trials [33,34] reported the number of serious infections on filgotinib 200 mg monotherapy was 1.7 per 100PY versus 0.6 on filgotinib/methotrexate (MTX) combination therapy [41]. Mechanistically this is counternintuitive, and is perhaps a small sample effect, as the differences were not statistically significant.

As upadacitinib and filgotinib are the latest JAKi to be licensed, there are fewer real-world data available, and longer exposure is needed to better understand the safety profile of these agents. A summary of the relative risk of infections across the four licensed JAKi can be seen in Table 1.

Risk factors for serious infections include increasing age, disease duration, comitant glucocorticoid therapy, baseline lymphopenia, line of therapy (3rd line vs 2nd), and geographical region (Asia, Europe and Latin America, versus USA and Canada) [16,49]. The risk of serious infection with increasing JAKi dose may relate to its dose-proportional pharmacokinetic profile with the possibility of off-target effects. For example, tofacitinib selectively inhibits JAKs 1, 3 and 2 at the approved dose but becomes a ‘pan-JAK’ inhibitor at higher doses. JAKi are also subject to hepatic metabolism, renal clearance, and drug interactions. Tofacitinib, upadacitinib and filgotinib all undergo systemic metabolism, and so caution is required with respect to drug interactions [42–44]. In contrast baricitinib undergoes near-complete renal excretion, and so may accumulate with even mild reduction in kidney function [45].

### 2.1. Herpes zoster

Varicella zoster virus (VZV) reactivation, herpes zoster (HZ) or ‘shingles’, is now the most recognized infectious complication with JAKi. This is concerning, as patients with IMIDs, especially those with rheumatoid arthritis have a baseline risk 1.5 to 2-fold higher than healthy individuals [46]. JAKi-associated HZ risk appears to be a class effect. Emerging long-term safety data will continue to clarify this risk and any within-class differences, particularly among the selective JAK1 inhibitors.

Data from tofacitinib and baricitinib safety analyses have reported increased rates compared to placebo, with greater risk in patients prescribed higher doses; HZ incidence per 100 PY: baricitinib 4 mg 4.4 (95%CI: 2.7 – 6.7) and baricitinib 2 mg 3.1 (95% CI: 1.1 to 6.8) and placebo 1.1 (95% CI 0.4–2.5) [47,48]. Baricitinib may confer a greater HZ risk than tofacitinib and upadacitinib in meta-analyses of randomized controlled trial (RCT) data, although more recent meta-analyses have found no statistical difference between drugs at licensed doses [18,49].

Real-world data comparing baricitinib and tofacitinib safety profiles have confirmed HZ as the most frequent adverse event (5.6% tofacitinib, 4.9% baricitinib) but not
confirmed a significant difference between the two drugs [50]. The risk is greatest in older patients, with co-prescription of glucocorticoids or MTX, in Japan and Korea [51]. There are very few cases of multidermatomal or disseminated herpes, and no cases of visceral disease or death [51]. Upadacitinib clinical trials data have confirmed an increased HZ risk compared to individuals prescribed csDMARDs and biologics. As seen with first-generation JAKi, the risk is greatest in individuals prescribed the higher doses, in whom zoster is more likely to be both serious and multidermatomal in nature [32,52,53]. HZ was also reported in filgotinib clinical trials; all HZ infections occurred in patients older than 55 years and were non-complicated [31,33,54]. A recent network analysis on RCT data reported that the risk of HZ is lowest with filgotinib compared to other JAKi [18].

2.2. Tuberculosis

As with biologics, there has been concern around the potential vulnerability to Mycobacterium tuberculosis infection with JAKi. As a result, patients starting treatment are routinely screened for latent tuberculosis. This was a requirement in the phase II and III trials from which much of the safety data for these drugs come and continues in real-world clinical practice. Even accounting for rigorous screening and treatment for previously exposed patients, rates of tuberculosis are low amongst the JAKi population. One large systematic review and meta-analysis of phase II and III RCTs of licensed dose tofacitinib, baricitinib, and upadacitinib confirmed only one case of tuberculosis in a JAKi-treated patient, an individual who had not been fully screened in accordance with the trial protocol [49]. Another meta-analysis of 37 trials found no significant difference between JAKi (tofacitinib, baricitinib, upadacitinib, and filgotinib), MTX, adalimumab, or placebo [18].

Data from tofacitinib LTE studies have demonstrated a low incidence rate (0.21 per 100 PY), particularly in low- and medium-prevalence tuberculosis regions [55]. The vast majority (77%) of patients who developed tuberculosis were prescribed a 10 mg BID dosing regimen. This reflects the previously noted risk of off-target effects at higher doses and highlights the need for careful consideration of dosing in individuals with higher estimated risk of infection. Analysis of 3000 patients receiving baricitinib (7860 PY) showed an incidence rate of 0.1/100 PY, all of which occurred in patients taking the higher (4 mg) dose and living in tuberculosis-endemic areas [27]. Risk of tuberculosis infection is dependent on background population risk in the region of interest; incidence rates with tofacitinib were much higher in endemic regions (0.75 per 100 PY, 95% CI 0.49 to 1.15) than in low-risk areas (0.02 per 100 PY, 95%CI 0.003–0.15) [55]. Given the relatively low cost of screening it remains prudent to test for latent tuberculosis in all patients commencing JAKi therapy.

2.3. Other opportunistic infections

Cytokines downstream of the JAK-STAT pathway such as INFγ and granulocyte-macrophage colony-stimulating factor (GM-CSF) are crucial in host defense against opportunistic pathogens; animal models lacking these immune mediators are more vulnerable to fungal and viral disease [56,57]. Other protein kinases (such as Bruton tyrosine kinase) are crucial in maintaining human innate defense against fungi [58] and their inhibition with small-molecule protein kinase inhibitors such as ibritinib predispose to invasive fungal infections [55]. Despite this, the evidence to date suggests a low incidence of such opportunistic infections amongst patients taking JAKi inhibitors.

Analysis of the pooled safety data across the tofacitinib clinical trials and LTE studies (9,291 patients, 34,223 PY) [55] identified a total of 15 confirmed serious opportunistic infections (excluding tuberculosis and disseminated HZ), with Candida the most common pathogen followed by Cryptococcus, cytomegalovirus, histoplasmosis and Pneumocystis jirovecii. Analysis of infection rates in the LTE data from trials for patients taking baricitinib (2 mg or 4 mg) (3492 patients over 7860 PY) also suggested low risk of opportunistic infection, with only 10 Candida infections, 5 cytomegalovirus and 4 Pneumocystis, each representing an incidence rate of less than 0.15 per 100PY [27]. This small safety signal for Candida infection is also seen for upadacitinib, with significantly more oral candidiasis reported amongst trial patients in the treatment arms [30,35,37,53]. There are no reports of similar infections in the filgotinib trial data published to date [31].

At present, there are no comparative studies between JAKi agents, making accurate assessment of the drugs’ infection risk difficult. There are likely discrepancies in reporting rates and disease definitions between clinical trials, whilst first-generation medications that have been licensed for several years have been investigated across a greater number of studies. What is clear is that incidence rates of opportunistic infection are low across the JAKi class. Large post-licensing surveillance studies and data from registries are required to adequately assess these events when they do arise and provide accurate information on the relative risks of infection by different organisms with each of the drugs studied. While prophylaxis against fungal disease is not warranted given these incidence rates, clinicians should be mindful of the risks of such infections in patients taking JAKi.

2.4. Infection in older patients taking JAK inhibitors

The increased vulnerability to infection with age is well established. This is the result of numerous mechanisms of immunosenescence such as reduced lymphocyte production and altered function, chronic inflammation, and altered cytokine release [59]. Many of these markers of aging, which impact on both innate and adaptive immunity, are noted to be accelerated in IMIDs, and some can be improved or reversed with adequate treatment of the underlying disease [60]. Older patients are less frequently included in clinical trials and as such the data from many of the larger JAKi studies may not be easy to translate into clinical practice for this population.

Analysis of data from RA clinical trials examined the risk of serious infections in individuals over 65 (n = 339) reporting the highest incidence of serious infection with tofacitinib 10 mg,
followed by tofacitinib 5 mg and then adalimumab [61]. The risk of serious infection was significantly greater in over 65s versus under 65s with tofacitinib 10 mg but not with tofacitinib 5 mg or adalimumab, suggesting an effect modification by age for this higher dose, and supporting the globally recommended dose of 5 mg BID.

Other studies of JAKi safety consistently report age as a risk factor for infection but do not indicate that there is a specific JAKi-driven risk for older patients [62]. Clearly, large long-term safety studies using registry data will be required to establish with certainty whether any true difference exists between JAKi and biologic DMARDS in the elderly population. The data currently available do not support withholding JAKi from elderly patients with active inflammatory disease. They may, however, provide a rationale for preferential use of more established therapies in older patients who have not yet failed biologic treatment as well as for careful case-by-case consideration of optimum dosing, consistent with EMA advice for preferential use of the 2 mg baricitinib dose in elderly (>75) patients and to avoid tofacitinib in patients >65 unless no alternative treatment is available [43,45].

3. Vaccination

Vaccination is a crucial mediator in the prevention of infection in individuals considered at risk. Vaccines function by inducing and/or enhancing protective immunity and are associated with a reduction in the rate of serious infection, hospital admission and invasive infectious diseases. Pneumococcal and influenza vaccinations have been recommended by both the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) for rheumatic disease patients, particularly in those receiving immunomodulating agents. These should preferably be administered during quiescent disease or prior to planned immunosuppression. Given the incidence of infections seen with JAKi as well as the inactivated nature of the pneumococcal and influenza vaccinations [63], these should be offered to individuals considering JAK inhibition and are likely to ameliorate some of the excess infection risk. Administration prior to commencing JAK inhibition is preferable in light of the reduced immune response to pneumococcal vaccine amongst some patients taking tofacitinib [64].

Vaccination against VZV is an important, albeit imperfect, means of reducing the impact of HZ infection, and is currently recommended by the ACR and EULAR [63,65]. Both the varicella vaccine (Varivax, for individuals not immune who are <50 years) and zoster vaccine (Zostavax for individuals ≥50 years) are live vaccines, and as such it is recommended to administer at least 3–4 weeks before initiating JAKi therapy in an effort to avoid vaccine-related infection [66]. It is sensible to check VZV serology prior to considering vaccination, and to avoid immunization in individuals found to be VZV-naive, as a live vaccination combined with immunosuppression could be catastrophic and should be avoided (noting that this can seem counterintuitive to specifically avoid vaccination in a patient with no prior immunity – but it is these patients who are most at risk from a live vaccine). The optimum strategy for prophylaxis in such patients remains uncertain, and public health advice on this question is variable region-by-region. Data from two RCTs suggest that HZ vaccination is safe for patients subsequently treated with JAKi [67,68]. Only one patient developed disseminated cutaneous HZ infection (not requiring hospitalization) and was found to be VZV-naive, highlighting the need to assess VZV serology prior to immunization [67]. While a large retrospective study of variably immunosuppressed patients showed no disseminated vaccine-related disease, prior immunity was not assessed and was likely to have been high in the US patient population studied [69]. Cases have been reported of fatal disseminated zoster infection in immunosuppressed patients [70], though none involving patients taking JAK inhibitors.

The efficacy of HZ vaccination has been evaluated in individuals receiving tofacitinib, who mounted a comparable immune response to the vaccine as the placebo group. Further data to show the response with other drugs in this class would be valuable [67]. Follow-up data, however, suggest that as in healthy individuals, the live HZ vaccine may provide inadequate long-term protection, based on humoral and cell-mediated immune responses [71]. The prospect of a new VZV vaccine which is both non-live and more efficacious (zoster recombinant adjuvanted (ZRA) vaccine ‘Shingrix’) is highly anticipated particularly for patients taking JAKi therapy, although not yet widely available [72,73]. Initial data from RA patients is promising: just 3 of 403 (0.7%) participants developed HZ, but the safety, efficacy, and long-term immunogenicity of the ZRA in patients receiving JAKi therapy is so far unknown [74]. Pending availability and study of this vaccine in patients on or starting JAKi, extreme caution should be exercised in administering live vaccines to immunosuppressed individuals. Careful consent, patient education, and early rescue therapy with aciclovir or VZ immunoglobulin is likely to represent a safe and efficacious approach to managing this patient group.

4. Use of JAKi in clinical practice

In view of the incomplete and emerging evidence in this area, no widely established strategy for the use of JAKi currently exists. The currently available data for infection risk suggest a decision to initiate JAK therapy should be taken in view of the patient’s specific clinical circumstances, assessing risk of morbidity (including infection) related to underlying IMID against the estimated vulnerability to infection. This latter evaluation should include assessment of relevant comorbidities and previous infections, medications, age, smoking, leukocyte counts and local infectious disease prevalence. Known susceptibility to serious infection or VZV naivete should prompt consideration of whether other established lines of treatment (including biologics) have been fully exhausted.
5. JAKi therapy in COVID-19

The coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in 2019 has led to significant morbidity and mortality around the world [75]. The clinical spectrum of the disease ranges from being asymptomatic to a severe respiratory distress syndrome. Dysregulated immune responses are one of the important features of COVID-19 resulting in the cytokine release syndrome known as the cytokine storm [76].

Baricitinib and tofacitinib have been studied as therapeutics for severe COVID-19, based on their known ability to reduce proinflammatory cytokine production.

It has been reported that the use of JAKi (mostly baricitinib) in patients with COVID-19 decreased invasive mechanical ventilation usage and increased survival rate [77]. An RCT of baricitinib showed improvements in recovery time from COVID-19 with fewer adverse events compared to placebo [78], while another suggested a significant reduction in 28- and 60-day all-cause mortality with similar rates of adverse events [79].

A smaller CT of tofacitinib showed a reduction in cumulative incidence of death or respiratory failure with tofacitinib therapy but not the 28-day all-cause mortality [80]. These data have led to baricitinib inclusion in the National Institute of Health (NIH) management guideline for use in patients with COVID-19 requiring high-flow oxygen, with tofacitinib recommended if baricitinib is unavailable [81]. A large-scale study of baricitinib is ongoing via the RECOVERY trial [82].

What remains uncertain is whether long-term JAKi use for an autoimmune disease would also offer protection against severe COVID-19.

6. Conclusion

The advent of JAK inhibitors over the last decade has greatly enhanced the treatment options available for individuals with IMIDs. The efficacy of these immunomodulators must be balanced against their potential risks, but also against the known harms of persistent uncontrolled inflammatory disease. While clear evidence exists for increased incidence of infections such as HZ, data are less clear for an increased signal of other infections in comparison to established biologic DMARDs. For the overwhelming majority of patients commencing JAKi, infection risks are far too low to warrant prophylactic antimicrobials. However, vaccinations should be routinely considered, including against herpes zoster. Careful consideration of patient-specific risk factors for infection, previous therapy and disease activity are essential in making judgments about the likely risks and benefits of JAKi. With these caveats, judicious use of JAKi provide a potentially transformative new line of treatment, especially for patients in whom other therapies are not tolerable or efficacious.

7. Expert opinion

JAKi have demonstrated impressive efficacy in treating diseases mediated by the JAK/STAT pathways such as RA, psoriatic arthritis, ulcerative colitis, and psoriasis. These small molecule inhibitors are orally available, providing a more convenient option for patients compared to biologic therapies. However, inhibition of JAK/STAT pathways suppresses the immune response and the efficacy of these immunomodulators must be balanced against potential risks.

JAKi are still a relatively new drug class. First-generation JAKi, tofacitinib, and baricitinib, received licensing in 2012 and 2017, respectively. Second-generation upadacitinib and filgotinib have been licensed in the last two years, with filgotinib currently only licensed in Europe. We are slowly gaining a better understanding of the long-term risk-benefit profiles of these medications. Tofacitinib has the greatest available real-world experience to inform understanding of long-term safety. For the rest of the JAKi, registry data are limited. From the clinical trials, it seems that the risk of infection is increased compared to placebo, but comparable to anti-TNF therapy. The trials demonstrate a dose response relationship with infection, with higher doses associated with greater risk. Whilst overall infection rates are reassuring, a specific signal does exist for shingles, a risk that appears to be a class effect. The risk of shingles is between 1 and 4% per year, of which approximately 1 in 10 cases will be severe. Tuberculosis rates are low, although dependent on background population risk with higher rates seen in endemic regions.

The decision to initiate JAK therapy should be a shared decision with a patient, taking into account comorbidity, infection risk, and severity of the underlying autoimmune disease. It may be possible to mitigate infection risks with vaccination. Pneumococcal and influenza vaccines should be offered. Shingles vaccination is advisable in patients over 50, ideally using the non-live vaccine.

Further research is required to delineate the long-term safety of JAKi, particularly for second generation selective JAK-1 inhibitors. Registry data will be important to offer insights into comparisons between JAKi and other biologics in high-risk populations, including the elderly, who are generally not represented in the trial programs. Over the next five years, the use of JAKi in clinical practice will undoubtedly increase and alongside this our knowledge and experience will advance. We anticipate this will allow us to offer more tailored personalized medicine.

Declaration of interest

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