JAK inhibitors and black box warnings: what is the future for JAK inhibitors?

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Abstract

Introduction: Janus kinase inhibitors (JAKi) have dramatically improved the treatment of various autoimmune, and myeloproliferative disorders. Recently concern has arisen regarding their safety in patients with rheumatoid arthritis.

Areas covered: Here we provide a comprehensive summary of the major current and emerging JAKi and their indications, address recent studies on comparative safety, and provide insight into their future and use. We emphasize that the application of the research findings on a case-by-case basis should consider a patient's age, comorbidities, disease for which JAKi is being considered, disease activity, the JAKi target(s), alternate treatment options available for the patient, and the planned duration of JAKi.

Expert opinion: Rheumatologists are used to prescribing therapies in which a risk to benefit assessment is required as well as with screening and monitoring for safety of medications. Thus, rheumatologists are already practiced in applying specific criteria to effectively screen and monitor patients who are candidates for JAKi therapy. Ongoing research will help to clarify

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any mechanisms underlying differential safety signals between JAK and other therapies, what the balance between risk and efficacy is, who the susceptible subpopulations are, and whether safety signals are shared between different JAKis and across indications.

Keywords

Cancer; comparative safety; JAK inhibitors; MACE; rheumatoid arthritis; shared decision making; TNFi

1. Introduction

Janus kinase inhibitors (JAKI) are a family of targeted synthetic drugs that have dramatically improved the treatment of various inflammatory, autoimmune, and myeloproliferative disorders. Janus kinases (JAKs) are cytokine receptors that facilitate intracellular signaling and modulate gene expression. The JAK family in humans consists of four tyrosine kinases: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).(1, 2) Each intracellular JAK receptor has a varying degree of specificity and selectivity for extracellular cytokine receptors, although there is a significant overlap. JAK3 is considered the most specific, while JAK2 associates with a wider variety of cytokine receptors including erythropoietin, thrombopoietin, interferon (IFN)-γ, interleukin IL)-3, IL-5, growth hormone, and granulocyte/macrophage colony stimulating factor (GM-CSF).(3) Upon cytokine receptor engagement, JAKs auto-phosphorylate and activate the signal transducers and activators of transcription (STAT) pathway which results in dissociation, dimerization, and translocation of DNA binding proteins into the nucleus.(4)

Specific JAK proteins and pairs are implicated in regulating inflammation, hematopoiesis, and immune homeostasis to varying degrees. JAK1 plays a role in various disease processes, including rheumatoid arthritis (RA), atopic dermatitis (AD), and inflammatory bowel disease (IBD).(5) JAK2 is essential for erythropoiesis, myelopoiesis, and platelet production. JAK3 is critical for lymphocyte proliferation and homeostasis, and similarly to JAK1, has been implicated in RA.(4) Dual-JAK inhibition has also demonstrated therapeutic benefits, highlighting the significant overlap between the effects of these proteins in treating autoimmune and inflammatory conditions.(5)

Current Food and Drug Administration (FDA)-approved JAKis include abrocitinib, baricitinib, fedratinib, pacritinib, ruxolitinib, tofacitinib, and upadacitinib.(5) Other JAKis approved outside of the United States include delgocitinib and peficitinib, which are approved in Japan, and fligotinib, which is approved by the European Medicines Agency (EMA).(5) JAKis differ in their selectivity for specific JAK proteins (Table 1) and are classified as first- or second-generation. First-generation JAKis are non-selective and include baricitinib and tofacitinib. Second-generation JAKis are selective and comprise the majority of currently approved JAKis, such as upadacitinib (JAK1 selective) and ruxolitinib (JAK1/JAK2 selective).(5)

These differences in selectivity are implicated in the varying degrees of efficacy and differences in safety profiles of these drugs (6). Tofacitinib, a non-selective JAKi widely used for conventional synthetic- and biologic-refractory rheumatoid arthritis, has

demonstrated efficacy in disease management, but has also been noted to have increased cardiovascular risk compared to tumor necrosis factor inhibitors (TNFi).(7) Upadacitinib, a JAK1 selective inhibitor, has shown efficacy in treating both RA and AD, with a similar safety profile for RA and no major safety concerns identified for AD, although clinical trials are still currently underway.(8)

The goals of this review on JAKis are to provide a comprehensive summary of the major current and emerging drugs and their indications, address recent studies on comparative safety, and provide insight and guidance into their future and use.

2.   Rationale for the FDA mandate

Tofacitinib's clinical development program demonstrated its efficacy in patients with RA, but some concern arose regarding elevations in low-density lipoprotein cholesterol levels, as well as the incidence of 11 solid cancers and one lymphoma in 3328 patients treated with tofacitinib.(9–13) These effects were more pronounced at the higher 10 mg twice daily dose. Subsequently, in 2012, the FDA approved tofacitinib 5 mg twice daily for treating patients with RA who did not respond adequately to methotrexate. However, in light of the potential safety signals, this approval was accompanied by the requirement for a post-marketing trial to be conducted by the manufacturer to further explore the safety of tofacitinib.

2.2.   ORAL Surveillance Trial

Oral Rheumatoid Arthritis Trial (ORAL) Surveillance trial was a randomized, open-label, noninferiority, phase 3b/4 trial with the primary objective of comparing rates of major adverse cardiovascular events (MACE) and malignancy, excluding non-melanoma skin cancer (NMSC).(7) The studied population comprised RA patients aged 50 years or older who had active RA while on methotrexate and at least one additional cardiovascular risk factor, namely active smoking, hypertension, low high-density lipoprotein cholesterol levels, diabetes, family history of premature coronary heart disease, extraarticular RA, or a personal history of coronary heart disease. While continuing background methotrexate, patients were randomized to tofacitinib 5 mg or 10 mg twice daily or a TNF inhibitor, either adalimumab or etanercept. An upper bound of 1.8 for the hazard ratio (HR) confidence interval (CI) for MACE and malignancy ratios was set, which would determine noninferiority. During the course of the study in 2019, patients on the 10 mg dose of tofacitinib were changed to 5 mg after a statistically significant higher risk of pulmonary embolism was observed by the data and safety monitoring board, but subsequent analyses were conducted in the originally assigned groups.

The trial concluded with a total of 4362 patients and a median follow-up time of 4.0 years. Noninferiority for MACE, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, was not met for both doses of tofacitinib. An incidence rate of 0.98 per 100 patient-years for tofacitinib combined doses was seen, compared with 0.73 per 100 patient-years for TNF inhibitors. This represented a HR of 1.33 (95% CI 0.91–1.94), with the upper bound of the 95% CI exceeding the predetermined threshold of 1.8. A subgroup analysis among patients 65 years of age or older found a higher risk with combined

tofacitinib doses in this group (HR 1.36, 0.76–2.45) compared to those who were younger than 65 (HR 0.95, 0.55–1.64).

The noninferiority of the combined tofacitinib group for malignancy was similarly not demonstrated (HR 1.48, 1.04–2.09), with an incidence rate of 1.13 per 100 patient-years versus 0.77 per 100 patient-years in the TNF inhibitor group. Stratified by age, cancer risk was higher in those over the age of 65 (HR 1.70, 1.00–2.90) than their younger counterparts (HR 1.36, 0.85–2.17). At the FDA-approved dose of 5 mg twice daily, the number needed to harm was 567 patient-years for MACE and 276 patient-years for malignancy, translating to one additional MACE and cancer for every 113 and 55 patients, respectively, treated with tofacitinib instead of a TNF inhibitor over a five-year period. Besides an open label design, a key limitation of this trial is the lack of a group in the trial that was not JAKi or TNFi. At this time, it is open to interpretation whether the use of adalimumab or etanercept in the trial lowered the risk of MACE and cancer events or in fact, there is increased risk of these events on use of Tofacitinib.

2.3.   Post hoc analyses and observational studies on comparative safety of JAKi

Taking into consideration the age-related effects seen in ORAL Surveillance, a post hoc analysis further separated patients into a high-risk group of patients aged 65 years or older with a history of smoking or low-risk group.(14) In the high-risk subset, an increase in risk was observed with tofacitinib compared to TNF inhibitors for both MACE (HR 1.41, 0.92–2.15 vs. HR 0.98, 0.42–2.31) and malignancy (excluding NMSC) (HR 1.55, 1.05–2.30 vs. HR 1.16, 0.53–2.55). In contrast, no discernible difference was detected in the low-risk cohort. Another post hoc analysis of ORAL Surveillance discriminated between patients with or without a pre-existing history of atherosclerotic cardiovascular disease and found higher MACE risk in the former with tofacitinib use (HR 1.98, 0.95–4.14 vs. HR 1.14, 0.73–1.78).(15) Similarly, ORAL Surveillance patients with known atherosclerotic cardiovascular disease had an increased risk of malignancy (excluding NMSC) when taking tofacitinib, evident after 18 months of treatment (HR 1.93, 1.22–3.06).(16) These findings in concert may indicate that MACE and cancer risk are predominantly seen in risk-enriched populations, such as that of ORAL Surveillance.

Molander et al found an increased risk of pulmonary embolism (HR = 3.21 [2.11, 4.88]), but a non-significant lower risk of deep vein thrombosis (HR = 0.83 [0.47, 1.45]) for those treated with JAKis relative to TNFis in an observational study of Swedish patients with RA(17), a pattern which was replicated when applying similar inclusion and exclusion criteria as the ORAL surveillance trial (HR for PE = 2.86 [1.46, 5.61], HR for DVT = 0.72 [0.30–1.74]). This suggests that the cardiovascular risks from JAKis may be limited to PE, and not all MACE events. In addition, this study population was older and had high rates of smoking and cardiovascular disease, making it difficult to know whether these risks would extend to younger, healthier patients without CVD risk factors, and differed in exposure (inclusion of all JAKi and TNFi) compared to the RCT.

Khosrow-Khavar et al replicated the RCT eligibility criteria pertaining to CVD risk factors in an observational study of US claims data and compared that with a real-world evidence (RWE) cohort with relaxed inclusion and exclusion criteria.(18) They found similar elevated

CV risks for patients treated with tofacitinib in the RCT-duplicate cohort (HR =1.24 [0.90, 1.69]) but not in the RWE cohort (HR = 1.01 [0.83, 1.23]). They further compared CV risks for patients with and without baseline CV risk factors and found CV risks to be elevated only among patients with existing risk factors, suggesting that patients' CV risk profile may be an important consideration in determining the safety of tofacitinib or other JAKis for RA.

In their STAR-RA study, Khosrow-Khavar et al (2022) further examined the increased risk of malignancies with tofacitinib use compared to TNFi use in patients with RA that was found in the ORAL Surveillance safety trial.(18) As above, they designed an observational study with two cohorts, a RWE cohort including RA patients from routine care and a RCT-duplicate cohort which replicated the eligibility criteria from the ORAL trial. In contrast to those prior results, they found no evidence of increased malignancy risk associated with tofacitinib use in either cohort, although the RCT-duplicate cohort showed a numerically higher estimate of risk (HR of 1.17 [0.85, 1.62]) compared to the RWE cohort (HR of 1.01 [0.83, 1.22]), potentially indicating increased risk in older patients with cardiovascular risk factors. These results held across individual types of malignancy outcomes and across a variety of subgroup and sensitivity analyses, including restricting the TNFi exposure group to patients treated with adalimumab and etanercept, in accordance with the treatments from the ORAL trial.

Despite attempts to control for differences in the sampled populations and in treatments, there remain other factors that could explain the conflicting conclusions between the ORAL RCT and the STAR-RA observational study. For one, the follow-up time for the STAR-RA study was substantially shorter, with a mean follow-up of less than one year and only 11.1% of the study population followed for more than two years compared to a mean follow-up time of over three years in the ORAL trial. It remains possible that any increased effects of tofacitinib on malignancies may not manifest within the first year and longer follow-up may have discovered this. Also, due to the nature of an observational study, there could still be unmeasured confounders affecting the risk estimates in the STAR-RA study that were randomized out in the ORAL trial.

Huss et al (2022) instead compared risks of cancer for patients with RA who were treated with biologic and targeted synthetic DMARDs (b/tsDMARDs) relative to both b/tsDMARD-naïve RA patients and a matched cohort from the general population.(19) This exposure class of b/tsDMARDs encompasses TNFis and Janus Kinase inhibitors (JAKis), including tofacitinib, as well as other b/tsDMARDs. They found no evidence of increased cancer risk associated with use of TNFis (HR of 1.0 [0.9,1.0]), rituximab (HR of 1.0 [0.9, 1.1]), abatacept (HR of 1.15 [0.98, 1.34]), or tocilizumab (HR of 1.0 [0.8, 1.2]) relative to the b/tsDMARD-naïve cohort.(19) Since only five cancers were observed in the JAKi exposure group, relative risks were not estimated. The b/tsDMARD-naïve cohort was found to have increased risk of cancer relative to the general population (HR of 1.15 [1.11, 1.19]) with the other b/tsDMARD exposure groups showing similarly elevated estimates of risk.(19) Compared to STAR-RA, this study had over three years of mean follow-up time for most exposure groups, with the TNFi group having over six years. Unfortunately, with a mean follow-up time of only 0.7 years and only five observed cancers, evidence regarding JAKis

was scant, so the results from this study are not directly comparable to the ORAL trial of the STAR-RA study regarding tofacitinib.

Westermann et al. investigated the risk of incident cancer in patients with RA treated with JAKi compared to those on bDMARDs using the Danish register (DANBIO) from January 2017 to December 2020.(20) There were 19 cancers observed per 1315 person-years in the JAKi group compared to 111 cancers over 8597 person-years in the bDMARD group. Even though numerically increased risk estimates were detected, they did not observe statistically significant increased risk of cancer in JAKi group compared to bDMARd group.

3.   Comparative safety of different JAKi across various indications

Although the ORAL surveillance trial specifically studied the safety of tofacitinib relative to TNFi (etanercept or adalimumab), the trial led to issuance of new black box warnings to all JAKi by the FDA. Similarly, the EMA released revised recommendations for the use of JAKi in March 2023. However, there are no studies evaluating the comparative safety of various JAKi drugs to each other. Does the safety signal observed in the ORAL surveillance trial with tofacitinib (compared to TNFi) also apply to other drugs in the JAKi class remains less studied to date although investigations are ongoing.

Baricitinib is a selective JAK1/2 inhibitor approved for use in RA and severe alopecia areata (AA). The two clinical trials leading to approval in alopecia areata for baricitinib were: BRAVE-AA1 and BRAVE-AA2 (21). In an integrated safety analysis in 1303 patients with severe AA treated with baricitinib, results were consistent with the overall safety profile of baricitinib (22). In their posthoc analyses of baricitinib with data pooled from clinical trials and long term extension studies for RA, AA and atopic dermatitis (AD), Taylor et al found that patients who were younger than 65 years and without any of the risk factors pre-specified (prior atherosclerotic heart disease, smoker, hypertension, low HDL, diabetes mellitus, BMI> 30 kg/m2, history of malignancy and severe mobility impairment) had relatively low incidence of the adverse events of special interest (MACE, VTE, malignancy, serious infections, and mortality) examined, particularly compared with the incidence reported in literature for these patient populations (23). Among dermatologic indications, the risk for these adverse events was low even among patients with high risk factors. But, among patients with RA, the risk of the adverse events was increased among the high-risk group relative to the low-risk group. Further data from trials such as RA-BRIDGE and RA-BRANCH will help shed light on the question of whether the safety signals seen in ORAL-surveillance are really a class effect or uniquely related to tofacitinib (24).

Upadacatinib is a relatively newer JAKi with selectivity of JAK1. Fleischmann et al conducted a post hoc analysis of six clinic trials of upadacitinib in patients with RA to assess its safety, focusing on patients similar to those enrolled in ORAL Surveillance . The study found that the incidence of MACE, malignancy (excluding NMSC), VTE and mortality was typically higher in patients at increased CV risk compared with the overall RA population, but the rates remained generally similar between upadacitinib 15mg and adalimumab. However, higher rates of herpes zoster and NMSC in all populations in the higher CV risk population were observed with upadacitinib versus comparators. These

results need to be interpreted with caution though given the post hoc design, short follow-up of clinical trials while it takes years to develop events like cancer, and small number of events.

Upadacatinib is also approved for other indications besides RA such as psoriatic arthritis and atopic dermatitis. Burmester et al evaluated the safety profile of Upa over 15,000 patient-years and across indications: RA (six trials), psoriatic arthritis (two trials), ankylosing spondylitis (one trials) and AD (three trials) (25). Study observed that malignancy excluding non-melanoma skin cancer (NMSC), MACE and venous thromboembolism were observed at similar rates between upadacitinib and the active comparators adalimumab and methotrexate. Authors report that known differences in the adverse event (AE) profile of JAK inhibitors, such as increased rates of herpes zoster, CPK elevations, and NMSC, were observed.

Interestingly, although concerns have been raised for MACE, VTE and malignancy risks with JAKi in RA, in their large systematic literature review and meta-analysis evaluating the efficacy and safety of JAKi use in trials of ulcerative colitis (UC) or Crohn's disease, Solitano et al did not observe differences in rates of these adverse events in patients with IBD on JAKi, either selective or non-selective therapies, compared to placebo (26). Further, Sandborn et al conducted an updated integrated summary of tofacitinib safety using cumulative experience throughout the global tofacitinib UC clinical programme with up to 7.8 years [2999.7 PY] of tofacitinib treatment exposure (27). The incidence rates (IRs) of most adverse events, except herpes zoster, were similar to IRs reported for other UC treatments, including biologic therapies.

The risk of herpes zoster with JAKi is now well accepted as a class effect based on several studies (28–30). In their review, Wang et al included RCTs of tofacitinib (5 and 10 mg twice daily), baricitinib (2 and 4 mg daily), and upadacatinib (15 and 30 mg daily) to assess efficacy and safety of these different JAKi in RA (30). A statistically higher risk for herpes zoster infection was observed only with baricitinib, 4 mg, daily (RR, 3.81; p=01) compared with placebo. The risk was numerically higher but not statistically significant for baricitinib, 2 mg, daily (RR, 2.32; p=.44); tofacitinib (RR, 1.66; p=.63 [5 mg] and RR, 6.94; p=.06 [10 mg]); or upadacitinib (RR, 1.41; p=.09 [15 mg] and RR, 2.96; p=.09 [30 mg] showing a potential dose effect.

Several systematic reviews and meta-analyses have been published on the safety of JAK inhibitors. A select few such reviews published in past 12 months are highlighted in Table 2. Maqsood et al meta-analyzed data from 66 RCTs of various JAKI across different indications. They observed interesting results when stratified the data by the period of follow-up. Compared to placebo, JAKi use was not associated with risk of VTE. However, compared to biologic comparators, JAKi had statistically significant higher risk of VTE OR 2.38 (95% CI 1.24–4.57) in trials with >12 months follow-up; but this association was not seen in shorter (<12 months) duration trials (OR 0.30, 95% CI 0.07–1.26). These results underscore the need for longer term studies when assessing drug safety. In the same meta-analysis, they observed higher rates of MACE in users of JAKi compared to control

groups (OR 1.19, 95% CI 0.86–1.64) although the association was non-significant and results did not differ by duration of use.

4. Needs & opportunities for improving clinical practice and understanding.

Despite the growing body of literature dedicated to assessing the true risks of JAKis, there is yet to be clear and well-delineated guidance for practicing rheumatology providers and their patients. First, as aforementioned, this concern for risk of JAKi really arose from the initial results of ORAL Surveillance which did not meet non-inferiority, indicating that safety profile of tofacitinib *may be* "inferior" to that of TNFi. And again, this was based on a pre-determined upper bound of 1.8 for reported hazard ratio (HR) confidence intervals for MACE and malignancy incident rate comparisons. To apply the findings of the ORAL Surveillance trial results, its post hoc analyses and subsequent studies, a clinician must consider the statistical methodology of the different comparisons, respective statistical implications, generalizability of the results and, most importantly, contextualization of these findings to the individual patient to facilitate informed decision making.

4.1 Statistical nuances

Understanding clinical study design and the "hazard of hazard ratios" is vital to apply the aforementioned research results to clinical practice. While the ORAL Surveillance trial was powered to measure for non-inferiority,(7) the subsequent studies compared populations and reported HRs without denoting a "cut off" upper or lower number for the HR confidence intervals.(17–20) For these latter studies, beyond considering the population of study (real world versus ORAL replication), the HR 95% confidence intervals are important because the inclusion of 1 in this interval means that if the respective study is conducted many times, there is a possibility that the true population mean can include no difference between the populations (a HR of 1). In addition, HRs are an average of the hazard over time so HRs are impacted by the duration of follow up time; the hazard of a drug may change over time, but an overall average HR will not reflect these variations through the course of the study. Future study should report on series of average hazard ratios or survival curves in order for providers to comprehend the resulting data in a more comprehensive way. Finally, interpretation of HRs should also recognize the importance of which confounders were incorporated in the regression model by the study investigators. Leaving out important covariates and/or including irrelevant covariates in the model can dramatically change the results.

4.2 Discussions in the clinic need to be individualized.

The application of the research findings on a case-by-case basis should consider a patient's age, comorbidities, disease for which JAKi is being considered, disease activity, the JAKi target(s), alternate treatment options available for the patient, and the potentially planned duration of JAKi (31). The in-clinic conversation with a 30-year-old male without other comorbidities considering tofacitinib for severely active, seropositive, erosive rheumatoid arthritis regarding risks and benefits of JAKi will likely differ from the conversation with a 70-year-old patient with long standing history of smoking along with hypertension,

hyperlipidemia and chronic kidney disease considering upadacitinib for mildly active, non-radiographic axial spondylarthritis. One of the greatest takeaways from all the aforementioned studies is that the comparator populations are not untreated.(7) Treatment decisions in the clinic are not about choosing a JAKi versus no treatment at all, but between JAKi or another DMARD (the latter varies depending on the disease). So, if there is a patient with high disease activity and the patient has either exhausted other options and/or does not have an alternative DMARD available, a provider should not withhold JAKi solely based on the currently available literature.

4.3 "MACE" and "malignancy"

Regarding the risk of MACE, the clinical provider and the patient need to appreciate the varied implications of the different entities that are encompassed within the umbrella of the "MACE" terminology and that one type of MACE is not equal in danger to another. Similarly, for malignancy, the diagnosis of local nonmelanoma skin cancer is not the same as the ramifications of a metastatic non-small cell lung carcinoma diagnosis. Finally, many other modifiable factors aside from control of primary rheumatic disease and choice of DMARD can contribute to the risk of cardiovascular disease and/or cancer: smoking, diet, exercise, other lifestyle choices, use of steroids, non-steroidal anti-inflammatory drugs (NSAIDs) etc.

All in all, the clinician needs to determine level of risk "beyond reasonable doubt" and evaluate whether or not there is a better alternative available for the patient in the context of the patient's comorbidities, rheumatic disease, other modifiable risks, and patient preference.

4.4 Future study

Future study needs to be conducted in well-powered, large populations of patients with long follow up where the results report on hazard ratios but also survival curves to reflect the potential variation of risk over time. Confounding variables need to be carefully determined and controlled for to the best of the investigators' abilities to meaningfully apply the results in clinical practice. While prospective study with each different JAKi for particular rheumatic diseases and specific patient populations may not be imminently feasible, well-conducted meta-analyses may be able to inform clinical decision making in the more near future.

5. The ever-expanding indications for JAKi

While JAKi safety has primarily been explored in the context of rheumatoid arthritis, its pluripotency for inflammatory pathway inhibition has led to its consideration and use in a broad spectrum of different indications, in which their relative potential and market competitiveness vary.

1. Similarly to TNFi and their broad efficacy, tofacitinib and upadacitinib are FDA approved for use in a variety of spondyloarthritis-spectrum disorders, including psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis; upadactinib is also approved for Crohn's disease and non-radiographic axial spondyloarthropathy. Tofacitinib is also approved for juvenile idiopathic arthritis,

another disease where TNFi options exist. For all of these indications, a broad array of choices exist at a similar line of therapy within a crowded therapeutic landscape. While demonstrating some potential benefits, particularly with respect to fatigue, JAKi largely demonstrate comparable efficacy to TNFi at the approved doses in these diseases.(32, 33) Nevertheless, benefits regarding oral administration are likely to remain appealing for clinicians,(34) although it remains to be seen how clinicians will manage safety risks in these patients,(35) and whether such concerns will impact drug utilization.

2. JAKi are now approved for a number of different dermatological indications, most notably atopic dermatitis (abrocitinib, baricitinib, upadacitinib, and topical ruxolitinib), where JAKi can effectively suppress key pathogenic cytokines, including IL-4, IL-13, and IL-31 (36). In a largely young and mobile patient population, oral agents not only have advantages regarding administration, but faster time to action and slightly higher early efficacy remain highly appealing. (37) Furthermore, in clinical trials, no new safety signals were identified (38), and it remains highly debatable as to whether concerns from ORAL Surveillance relevant to an older population are of any substantive concern in this younger population.(37, 39, 40) Similarly, IL-2, IL-7, and IL-15 are also known to be important in the pathogenesis of alopecia areata via their effect on cytotoxic T cells (38) supplementing the critical role of interferon-γ (41). JAKi are capable of suppressing all of these effectively and the subsequent approval of baricitinib for alopecia areata has revolutionized therapy for this indication, particularly given the absence of other comparable therapies.(42, 43) Its use has, however, been overshadowed by an absence of longer-term data, despite favorable safety analyses from registration trials,(22) and safety concerns are likely to stratify on the basis of background cardiovascular risk. Nevertheless, baricitinib's approval for this indication has been followed by a substantive pipeline of JAKi clinical trials for alopecia areata and within alopecia more broadly.(44)

3. Exploration of new indications for JAKi has particularly increased following the onset of COVID-19, where baricitinib had proven useful in hospitalized adults not on mechanical ventilation.(45) Ruxolitinib, however, failed to demonstrate efficacy in the same indication,(46) and this mirrors the somewhat speculative drug development pipeline that currently exists for JAKi. Over 20 different indications have currently been subject to phase II/III clinical trials of JAKi,(44) including currently ongoing trials in type 1 diabetes mellitus (baricitinib(47)), hypereosinophilic syndrome (ruxolitinib(48)), Sjogren's syndrome (tofacitinib(49)), and vitiligo (baricitinib(50)) (Table 3). Furthermore, in some diseases like Sjogren's syndrome, translational data has supported a role for JAKi in modulating disease activity in target tissues (51). This enthusiasm stands to reason, given the relevance of cytokines highly dependent on JAK signaling in the pathogenesis of these diseases (51). Nevertheless, despite this broad promise, on some occasions some JAKi have failed to prove themselves in comparison to existing therapeutic options. Notably, for chronic plaque psoriasis, a number of JAKi including tofacitinib,

(52) have failed to perform adequately in clinical trials as to justify approval, although the selective Tyk2 inhibitor deucravacitinib has demonstrated modest efficacy and has subsequently been FDA approved. JAKi will continue to be trialed for a variety of different underserved conditions, both within clinical trials and in off-label use, and the latter is likely to escalate with tofacitinib's impending patent expiry.

In the next section, we specifically examine the potential for JAKi in three promising areas where substantive therapeutic unmet need exists: large vessel vasculitis and polymyalgia rheumatica (PMR), dermatomyositis, and systemic lupus erythematosus (SLE).

6.1 Large vessel vasculitis and polymyalgia rheumatica

It has also been noted that a number of qualities of JAKi portend well for their use in large vessel vasculitis, such as giant cell arteritis (GCA) and Takayasu's arteritis (TAK), and may also address unmet inadequacies within the existing therapeutic armamentarium. The pathogenesis of large vessel vasculitis may involve both Th17 cells promoted by the IL-6-IL-17 axis, which are though relevant to inflammation suppressed early by glucocorticoids, and Th1 cells promoted by the IL-12-IFN-ɣ axis thought responsible for chronic intravascular inflammatory changes, reminiscent of graft atherosclerosis.(53)

Other therapeutics approved or in late-stage trials for GCA, such as tocilizumab and secukinumab, focus primarily on the former axis, and may be imperfect in managing chronic intravascular inflammatory changes. It has been noted that tocilizumab treatment for GCA may still permit continuing large vessel inflammation at autopsy,(54) similar to what has been seen in glucocorticoid-treated patients, and only partially abrogates FDG-PET large vessel avidity in the first year.(55) Ongoing tocilizumab therapy may also not prevent visual loss(56) or aortic dilatation.(57) As a consequence, there remains a desire for other non-glucocorticoid therapies that might affect change on Th1 cells.

In contrast, JAK1 plausibly modulates both axes and has been hypothesized to better prevent such feared complications.(58, 59) JAK-STAT pathway upregulation has been demonstrated in both GCA lesions(60, 61) and TAK patients.(62) A mounting body of clinical data supports the potential benefit of JAKi in large vessel vasculitis,(63) although larger clinical trials are currently only being undertaken for upadacitinib in GCA (SELECT-GCA)(64) and, in TAK, for upadacitinib (SELECT-TAK)(65) and tofacitinib (TACTIC-MM)(66), and at the time of writing had not yet reported. Outside of this, some studies do support further investigation. Notably, in a prospective TAK cohort, tofacitinib was associated with a higher remission rate than methotrexate after 12 months, although no difference in radiographic progression was noted during that period of therapy.(67) In an open-label proof-of-concept study of baricitinib in relapsing GCA, with baseline prednisolone requirement distributed between 10–30mg, 13 out of 14 treated patients were able to cease prednisolone completely after 12 months. These data add encouragement to further clinical study of JAKi in both GCA and TAK.

PMR is also a therapeutically underserved disease,(68) despite being the most common inflammatory rheumatic disease in patients over the age of 50.(69) While recent data have

supported the use of IL-6R inhibitors in PMR)(70, 71) leading to a first FDA registration for sarilumab, it appears not all patients will obtain a response from such therapy, and there remains an imperative to find alternative therapies. Given the intrinsic pathophysiological commonalities between PMR and GCA,(72) it stands to reason that JAKi might be considered in PMR.(73) Two recent studies have looked at tofacitinib in patients with PMR: an open-label cohort where the tofacitinib was well tolerated and facilitated a prednisolone wean to a mean dose of 1.3mg after 48 weeks,(74) and a small randomized controlled trial where tofacitinib monotherapy performed similarly to a standard glucocorticoid wean over 24 weeks.(75) Median prednisolone duration in PMR extends beyond two years,(76) and is associated with substantial morbidity,(77) supporting a substantial imperative to further investigate JAKi in PMR.

Despite this, the questions from ORAL Surveillance around the safety of JAKi use in RA regarding older patients might be heightened in both GCA and PMR, given that both diseases almost exclusively affect people over the age of 50. The current standard of care for both, however, permits substantial exposure to glucocorticoids for longer durations and at higher doses than are commonly seen in RA. This reduction in glucocorticoids alone mean the comparative safety of JAKi for general infection, herpes zoster, cardiovascular disease, and incident cancer might be more favorable for both GCA and PMR patients than for RA patients with similar traditional cardiovascular risk factors. It also remains possible that JAKi may affect a reduction in disease-related cardiovascular complications in GCA, representing a further potential benefit of JAK inhibitors over the standard of care, specific to these diseases. As a consequence, the age of GCA and PMR patients should not prevent investigation of JAKi efficacy in these diseases, but appropriate pharmacovigilance approaches will be required.

6.2 Dermatomyositis

The recent escalating appreciation of the role of interferon in idiopathic inflammatory myopathies (IIM) has increased the impetus for JAKi as a therapy for them.(78, 79) In particular, transcriptomics has demonstrated how interferon defines and sustains dermatomyositis, particularly for the anti-MDA5 associated subtype compared to other dermatomyositis; in this subtype, disease severity has been associated with the strength of interferon signature.(80) As a consequence of this, and the substantial unmet clinical need for steroid-sparing therapies, dermatomyositis has become the focus of investigation into JAKi efficacy in IIM.(81) Early data has outlined the benefit of JAKi, particularly in disease refractory to glucocorticoids, intravenous immunoglobulin, and other current early-line therapies such as methotrexate, mycophenolate, and azathioprine.(81) Baricitinib is currently subject to a phase 3 trial in dermatomyositis (the BIRD trial)(82) and a small phase 2 trial in adult IIM,(83) brepocitinib is subject to a phase 3 trial in dermatomyositis (VALOR),(84) and further open-label investigation into tofacitinib for anti-MDA5(85) associated disease is also underway.(86)

Pleasingly, JAKi appear to have potential benefit across disease manifestations. While refractory skin disease, with its high interferon signature, was the focus of early reports of JAKi efficacy, substantial benefit appears to exist for muscle too. A small

open-label study of tofacitinib demonstrated improvement in muscle strength in all ten refractory dermatomyositis patients after 12 weeks, and within a series of refractory juvenile dermatomyositis patients, a patient with serial muscle biopsies showed a complete restoration of the endomysial microvascular bed.(87) In fact, benefit appears to exist even early in therapy across difficult-to-treat manifestations of dermatomyositis including interstitial lung disease(88) and calcinosis.(89)

Dermatomyositis is associated with an increased risk of malignancy in many patients, and in the context of ORAL Surveillance, JAKi may raise questions about increased incident cancer risk.(90) At present, JAKi are being primarily considered in refractory disease and in high-risk disease, such as that associated with anti-MDA5. Enhanced cancer screening remains a priority for many patients, and clearly should be maintained in this patient population. Notably, however, the relative risk of relevant toxicity associated with tofacitinib compared to other proposed therapies, such as tacrolimus and glucocorticoids, remains uncertain, and in the absence of further pharmacovigilance data, warrants consideration.

6.3 Systemic lupus erythematosus

Another relatively common rheumatic disease with substantial culpability from interferon is SLE. In animal models of SLE, tofactinib has not only demonstrated the capacity for interferon suppression but also the potential to repair endothelial damage and dysfunction. (91) This benefit was reflected in parameters from early phase clinical trials in tofacitinib, (92) although tofacitinib does appear to be being pursued in later-stage clinical trials in SLE, perhaps reflecting the challenging landscape of SLE clinical trials. Nevertheless, given the inherent pathophysiological advantages, it is understandable that JAKi are being actively pursued for SLE.(93)

Notably, baricitinib at 4mg daily reported a positive phase 2 result in SLE with skin and joint involvement, where it was well tolerated,(94) albeit with relatively modest clinical impact. (95) Unfortunately, in paired randomized controlled trials designed for registration, only one study (SLE-BRAVE-1) met its primary endpoint of SRI-4 response,(96) although just like its counterpart SLE-BRAVE-2, it did not meet any of it major secondary endpoints, including glucocorticoid tapering and time to first flare.(97) SLE trials have been fraught in the past, possibly representing the complex disease paradigm, but also high levels of background glucocorticoid exposure and unresolved endpoint science.(98) A dose-dependent effect was noted between baricitinib 2mg daily and 4mg daily, and with this in mind upadacitinib is being pursued at a higher dose than is approved in RA, with a successful phase 2 result leading to plans for phase 3 clinical trials(66).(99)

Given the dose-dependent safety concerns of baricitinib, it was notable that, despite the enhanced pro-thrombotic nature of SLE, risk of venous thromboembolism related to baricitinib in SLE-BRAVE-1 and SLE-BRAVE-2 was similar to RA. Given the relationship between glucocorticoid exposure and cardiovascular events in SLE, the potential for any glucocorticoid reduction provides continuing appeal for further investigation. With this in mind, deucravacitinib remains a promising option; a phase 2 study(100) demonstrating arguably a clearer effect over placebo than baricitinib did at an equivalent stage provides further optimism of a further addition to the therapeutic armamentarium. Paired phase 3

studies in SLE(101, 102) and a phase 2 in discoid and subacute cutaneous lupus(103) will further explore the potential nature of this benefit. Nevertheless, for both upadacitinib and deucravacitinib, enthusiasm on the basis of phase 2 data in SLE should be tempered, and further ways to enrich treatment patients in SLE for JAKi response will need to be further pursued.(98)

7. Conclusion

In summary, JAKi currently have indications across several autoimmune, hematologic conditions. Compared to biologic DMARDs, their faster onset of action and oral dosing make them very attractive options for patients. Rheumatologists will need to risk stratify patients and make decisions based on patient and disease-specific factors. The future might see more and more indications for which JAKi will be approved. Several gaps in current knowledge remain on this topic such as the comparative safety of different drugs within the JAKi class; how do their safety compare with other biologic DMARDs, is there a dose-response association where the longer someone has been on a JAKi, the higher they are at risk of adverse events.

8. Expert opinion

Rheumatologists are used to prescribing therapies in which a risk to benefit assessment is required. High dose glucocorticoids and cyclophosphamide are among the most potentially toxic of rheumatic disease therapies used, and their risks (i.e. infection, CVD, malignancy) overlap those in the ORAL Surveillance Trial. Rheumatologists are also familiar with the side effect profile of therapies changing over time. The potential for TNF inhibitors to increase malignancy risk was a major concern in the early days of use. Now, with the benefit of decades of experience and broad evidence from registry studies, they are now safely used in patients with most prior malignancies. Even the safety perception of methotrexate has changed over time, with the practice of liver biopsy after a specific cumulative dose no longer considered necessary.

Screening and monitoring for safety are also a routine aspect of rheumatologic care. Latent tuberculosis and hepatitis B infection are a well-accepted step in the prescription of TNF inhibitors, and concerns for infections, demyelinating disease, and worsening of heart failure are part of the shared decision making for each prescription. Thus, rheumatologists are already practiced in applying specific criteria to effectively screen and monitor patients who are candidates for JAKi therapy. Ongoing research will help to clarify any mechanisms underlying differential safety signals between JAK and other therapies, what the balance between risk and efficacy is, who the susceptible subpopulations are, and whether safety signals are shared between different JAKis and across indications. Undoubtedly, like prior concerns with therapies in the past, research and experience will provide more clarity on current concerns. The safety assessment is not complete, and further research will help to fill in the gaps.

The French Society of Rheumatology have published 11 recommendations to provide practical assessment of CVD and VTE risk before considering JAKi therapies in patients

with chronic inflammatory rheumatic diseases (104). A few of these recommendations include decreasing the inflammatory disease burden, encouraging smoking cessation, and minimizing exposure to NSAIDs and glucocorticoids. Besides these, referring for appropriate vaccinations to minimize infection burden prior to starting these drugs is crucial. If a patient already has history of CVD or VTE or malignancy, engaging in a multidisciplinary discussion with the involved specialists and ultimately, prioritizing patient priorities by shared decision making is central in this scenario. Periodic assessment of overall CVD risk using risk calculators appropriate to the background population is already recommended for people with RA and other forms of inflammatory arthritis (105). Applying this recommendation prior to JAKi prescription will assist in the discussion of whether the patient falls in a high CVD risk group and provide an opportunity to implement strategies to reduce risk, if identified. A signal for lung cancer, particularly among smokers, was also identified in ORAL Surveillance. Yearly screening for lung cancer using low-dose chest computed tomography is already recommended for all individuals 50–80 years of age who are current or former smokers with a 20 pack-year history of smoking (106). In this context, discussion of JAKi safety with current or former smokers provides an opportunity to implement this already recommended screening.

Perhaps the most important issue raised by the ORAL Surveillance trial is how to effectively communicate risk to patient in a way that balances the risks and benefits of alternate therapies and the risk of undertreating disease. Many providers have felt inadequacies in how to effectively frame risks and benefits to their patients in the context of an incomplete evidence base. A burgeoning field of research in risk communication is emerging, one in which the controversies arising from the ORAL Surveillance trial could easily be a case study. In future, as the full assessment of JAKi efficacy and safety will be elucidated across rheumatic diseases, similar issues will uncertainly arise as newer therapies are introduced.

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Article highlights

- Recently several studies have been published on the comparative safety of Janus kinase inhibitors (JAKi) including the ORAL surveillance clinical trial.

- Much of the evidence to date points to an increased risk of herpes zoster from use of JAKi relative to other comparators and the risk can be minimized with vaccinations.

- There is an urgent need of long term comparative safety studies evaluating the risk of MACE and malignancy among users of various JAKi drugs.

- Other important considerations in managing MACE, VTE or cancer risks need to include minimizing inflammatory disease burden, decreasing exposure to glucocorticoids or NSAIDs, smoking cessation.

- One of the most important issue raised by the ORAL Surveillance trial is how to effectively communicate risk to patient in a way that balances the risks and benefits of alternate therapies and the risk of undertreating disease.

Table 1.

Currently approved Janus kinase inhibitors, their selectivity, and indications

Drug	Initial approval year	Inhibition selectivity	Indication(s)	
FDA approved				
Abrocitinib	2022	JAK1	**1**	Atopic dermatitis
Baricitinib	2018 2022	JAK1/JAK2	**1**	Rheumatoid arthritis
			2	Severe Alopecia areata
Fedratinib	2019	JAK2	**1**	Myelofibrosis
Pacritinib	2022	JAK2	**1**	Myelofibrosis
Ruxolitinib	2011	JAK1/JAK2	**1**	Myelofibrosis
			2	Polycythemia vera
			3	Acute/chronic GVHD
Tofacitinib	2012	JAK3 > JAK1 > JAK2	**1**	Rheumatoid arthritis
			2	Psoriatic arthritis
			3	Ulcerative colitis
			4	Juvenile idiopathic arthritis
			5	Ankylosing spondylitis
Upadacitinib	2019 2022 2023	JAK1	**1**	Rheumatoid arthritis
			2	Psoriatic arthritis
			3	Atopic dermatitis
			4	UC
			5	CD
Approved in Japan, South Korea, Taiwan				
Delgocitinib	2020	Non-selective (pan-JAK)	**1**	Atopic dermatitis
Peficitinib	2019	Non-selective (pan-JAK)	**1**	Rheumatoid arthritis
EMA approved				
Filgotinib	2020	JAK1	**1**	Rheumatoid arthritis

Table 2.

Select few systematic reviews and meta-analyses published in the last 12 months on the safety of JAKi across different indications

Author, year	Study design	Number of studies included	Study population and JAKi studied	Drug dosage	Effect estimate (95% CI)
JAKi and VTE risk					
Maqsood et al., 2022 (107)	Meta-analysis of RCTs through January 28, 2022	66 RCT's included; 38,574 patients with mean age 48.8 years and mean follow up 10.5 months	Abrocitinib, Baricitinib, Filgotinib, Tofacitinib, Upadacatinib; Disease indications: AD, AS, CD, PsA, PsO, RA, SLE, UC	N/A	Pooled risk ratio for overall VTE 1.65 (0.97–2.79)*
Chen et al, 2022 (108)	Meta-analysis of cohort studies and RCTs through February 2022	2 cohort studies and 15 RCTs in Atopic Dermatitis of JAKi versus placebo or dupilumab	Abrocitinib Baricitinib Upadacatinib SHR0302	N/A	Mantel-Haenszel risk difference, 0 (95% CI, 0–0); $I2$ = 0%
JAKi and risk of MACE					
Maqsood et al., 2022 (107)	Meta-analysis of RCTs through January 28, 2022	66 RCTS included; 38,574 patients with mean age 48.8 years and mean follow up 10.5 months	Abrocitinib, Baricitinib, Filgotinib, Tofacitinib, Upadacatinib; Disease indications: AD, AS, CD, PsA, PsO, RA, SLE, UC	N/A	Pooled risk ratio for overall MACE 1.19 (0.86–1.64)
JAKi versus TNFi studies using administrative health databases					
De Quieroz et al, 2022 (109)	Meta-analysis of observational studies through October 2021	2 studies included comparing safety of TNFi vs JAKi	JAKi versus TNFi in RA	N/A	Pooled RR: 3.54 (0.30–42.09)
Tofacitinib and malignancy risk					
Russell et al., 2023 (110)	Meta-analysis of studies through December 9, 2022	Patients on tofacitinib versus placebo in eligible RCTs		5 or 10 mg/d	Pooled incidence rate ratio (IRR) 0.63 (0.24–1.62) Pairwise meta-analysis of individual JAKi medications did not show significant differences in malignancy incidence, compared with placebo, in eligible RCTs; however, there was considerable uncertainty in estimates.
Baricitinib and malignancy risk					
Russell et al, 2023 (110)	Meta-analysis	Patients on baricitinib versus placebo in eligible RCTs		2 or 4mg	Pooled incidence rate ratio 0.41 (0.13–1.29)
Upadacatinib and malignancy risk					
Russell et al, 2023 (110)	Meta-analysis	Patients on upadacatinib versus placebo in eligible RCTs		15 or 30 mg	IRR 1.42 (0.56–3.56)
Filgotinib and Malignancy risk					

Author, year	Study design	Number of studies included	Study population and JAKi studied	Drug dosage	Effect estimate (95% CI)
Russell et al, 2023 (110)	Meta-analysis	Patients on filgotinib versus placebo in eligible RCTs			IRR 0.54 (0.19–1.58)
Peficitinib and malignancy risk					
Russell et al, 2023 (110)	Meta-analysis	Patients on peficitinib versus placebo in eligible RCTs			IRR 0.39 (0.08–1.88)

Abbreviations: AD: atopic dermatitis; AS: ankylosing spondylitis; CD: Crohn's disease; UC: ulcerative colitis; RA: rheumatoid arthritis; CI: confidence interval; PsO: Psoriasis; PsA: Psoriatic arthritis; IRR: incident rate ratio; JAKi: Janus kinase inhibitor; RCT: Randomized controlled trial; N/A: not available; SLE: systemic lupus erythematosus; MACE: Major acute cardiovascular event; VTE: venous thromboembolism

Table 3:

Clinical Trials underway with Janus kinase inhibitors

Drug	Indication	Clinical trials underway
RUXOLITINIB	Hematologic	• Myelofibrosis: NCT02251821, NCT04370301, NCT02784496, NCT05371964, NCT02917096, NCT04384692 • Myeloproliferative disorders: NCT04282187, NCT05592015, NCT03801434, NCT03874052, NCT03878199, NCT03654768, NCT02723994 • GVHD: NCT03954236
	Dermatologic	• Vitiligo: NCT05247489, NCT04896385 • Atopic dermatitis: NCT05456529
TOFACITINIB	Rheumatologic	• Sjogren: NCT04496960 • RA: NCT04512573
	Dermatologic	• Various: NCT04246372
FEDRATINIB	Hematologic	• Myelofibrosis: NCT04370301 • Myeloproliferative disorders: NCT04282187, NCT04955938
BARICITINIB	Rheumatologic	• RA: NCT04512573
UPADACITINIB	Rheumatologic	• RA: NCT04512573, NCT05814627, NCT02629159, NCT03086343 • SLE: NCT05843643, • NCT04451772, Spondyloarthritis: NCT04169373 • Giant cell arteritis: NCT03725202 • JIA: NCT03725007 • Psoriatic arthritis: NCT03104374, NCT03104400
	Dermatologic	• Atopic dermatitis: NCT05601882, NCT04195698, NCT03646604, NCT03607422, NCT03569293, NCT03568318 • Vitiligo: NCT04927975
	Gastroenterological	• Crohn's: NCT03345823, NCT02782663 • UC: NCT05782907, NCT03006068
ABROCITINIB	Rheumatologic	• Sarcoidosis: NCT05696795
	Dermatologic	• Granuloma annulare: NCT05650736