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THERAPY IN PRACTICE

Managing Cardiovascular and Cancer Risk Associated with JAK Inhibitors

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Abstract

Janus kinase inhibitors (JAKi) have enormous appeal as immune-modulating therapies across many chronic inflammatory diseases, but recently this promise has been overshadowed by questions regarding associated cardiovascular and cancer risk emerging from the ORAL Surveillance phase 3b/4 post-marketing requirement randomized controlled trial. In that study of patients with rheumatoid arthritis with existing cardiovascular risk, tofacitinib, the first JAKi registered for chronic inflammatory disease, failed to meet non-inferiority thresholds when compared with tumor necrosis factor inhibitors for both incident major adverse cardiovascular events and incident cancer. While this result was unexpected by many, subsequently published observational data have also supported this finding. Notably, however, such a risk has largely not yet been demonstrated in patients outside the specific clinical situation examined in the trial, even in the face of many studies examining this. Nevertheless, this signal has practically re-aligned approaches to both tofacitinib and other JAKi to varying extents, in other patient populations and contexts: within rheumatoid arthritis, but also in psoriatic arthritis, axial spondyloarthritis, inflammatory bowel disease, atopic dermatitis, and beyond. Application to individual patients can be more challenging but remains important to harness the substantive potential of JAKi to the maximum extent safely possible. This review not only explores the evolution of the regulatory response to the signal, its informing data, biological plausibility, and its impact on guidelines, but also the many factors that clinicians must consider in navigating cardiovascular and cancer risk for their patients considering JAKi as immune-modulating therapy.

Key Points

JAK inhibitor therapeutic benefit must be balanced against the potential for harm in the clinical context in which it is being prescribed.

Cardiovascular and cancer risk from JAK inhibitors appears subject to effect modification dependent on baseline cardiovascular risk.

Clinical risk for individual patients is dependent on multiple factors, including indication, baseline cardiovascular risk, previous response to therapy, alternative therapies available, type and dose of JAK inhibitor chosen, and other risk–benefit considerations.

1 Introduction

JAK inhibitors (JAKi) are a novel class of immune-modulating therapies that convey great therapeutic promise [1]. While they were first registered for rheumatoid arthritis (RA) where multiple equally efficacious therapies exist, their potential utility extends across a number of different chronic inflammatory diseases. These not only include other registered indications including psoriatic arthritis (PsA), axial spondyloarthritis, atopic dermatitis, inflammatory bowel diseases (IBD), and alopecia areata, but also diseases with substantive unmet need including systemic lupus erythematosus (SLE), giant cell arteritis, polymyalgia rheumatica, and inflammatory myopathies [2]. Even within RA, while other therapies have similar efficacy, JAKi confer logistical advantages over them, including oral administration and a rapid onset of action.

However, throughout their drug development for chronic inflammatory disease indications, some questions have remained about JAKi safety. The first registered JAKi, tofacitinib, has been subject to enhanced

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post-marketing surveillance since its registration, culminating in a post-marketing requirement for a phase 4 randomized controlled trial (RCT) identifying safety signals within a patient population with existing cardiovascular risk. Foremost amongst these risks was a potential for increased cardiovascular and cancer events when compared with tumor necrosis factor inhibitors (TNFi), the co-primary endpoints of this study. Safety studies of this fidelity are rare in this therapeutic field, but nevertheless these results have proven challenging to apply in practice.

Clinicians have had to consider multiple different complex interacting factors when applying these results to individual patients, and the implications have differed across the highly varied clinical scenarios where JAKi might be used. In practice, at this point in time, substantial diversity in approach exists between individual clinicians in how these risks are interpreted and to how this might change their prescribing. Among changing data and regulation, and the pharmaceutical industry's substantial interest in influencing clinical decision-making, it is important to encourage rational decision-making through comprehensive assessment of all factors at play.

In this review, we seek to capture the full complexity of considerations that clinicians face in deriving their clinical approach, as it currently stands. We summarize the current landscape of JAKi for providers, in particular addressing cardiovascular and cancer risk and all factors pertinent to informing clinical decision-making: the history of this safety signal, the broader data informing it, the plausibility behind it, other pertinent individual-level factors, and existing guidance. This information may serve to guide clinicians in managing their patients, as we aim to encapsulate the unique challenges faced by this patient group and detail our approach to managing this risk in practice, acknowledging the inherent associated uncertainty.

2 A Signal Correctly Identified, But with Uncertain Clinical Implications for Patients

Alongside the first US Food and Drug Administration (FDA) approval of tofacitinib in 2012, which was for use in RA, an additional post-marketing clinical trial was mandated due to dyslipidemia observed in the drug's clinical development program and the extrapolated concern of an increased risk of cardiovascular adverse events [3–7]. Similarly, there was a need to further investigate the incidence of serious infections and malignancy, having seen 11 solid cancers and one lymphoma diagnosed in 3328 patients compared with zero in placebo-receiving patients [8]. These concerns were identified on the background of other known safety signals from tofacitinib's registration trials, including most notably an increased risk of herpes zoster [4]. Shortly after this time, the European Medicines Agency (EMA) similarly released a notification in 2013 for the refusal of the marketing authorization for tofacitinib [9].

In response to these regulatory actions, the manufacturer of tofacitinib undertook the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance trial, a phase 3b/4, randomized, open-label, non-inferiority, post-marketing study, whose first patient was enrolled in March 2014 [10]. Patients included were those with RA with an inadequate response to methotrexate, aged 50 years or older and with at least one additional cardiovascular risk factor (current cigarette smoker, hypertension, dyslipidemia, diabetes mellitus, family history of premature coronary heart disease, extra-articular RA, or history of coronary artery disease). Included patients were randomized to receive tofacitinib 5 mg BID or 10 mg BID or a TNFi (adalimumab or etanercept), with the trial's primary endpoints being non-inferiority of tofacitinib compared with TNFi relating to major adverse cardiovascular events (MACE) and malignancies [excluding non-melanoma skin cancer (NMSC)].

Further concerns about tofacitinib's safety were raised in February 2019 when higher rates of pulmonary embolism and mortality were noted in the 10 mg BID arm in comparison with TNFi but not the 5 mg BID arm. At that time, the other JAKi in clinical use for RA, baricitinib, had similarly shown a signal for increased venous thromboembolism (VTE) risk in the higher 4 mg daily dose, but not the 2 mg daily dose [11], leading the FDA to only register the latter dose for baricitinib's RA indication the year prior. This combination of events led the ORAL Surveillance study investigators to switch these patients to the lower 5 mg BID dose [10]. In addition, the EMA issued a series of warnings in March 2019 regarding the increased risk of VTE and subsequent restrictions of the use of tofacitinib while this was further assessed [12]. The FDA, too, announced a boxed warning for the 10 mg BID dose in July 2019, with this dose approved only in limited cases of ulcerative colitis (UC) but not RA or PsA [13].

January 2021 saw the announcement of primary endpoint results for ORAL Surveillance, namely the failure to meet prespecified non-inferiority criteria for MACE and malignancy [14]. This prompted further FDA updates to the boxed warning in February 2021 to describe increased risk of cardiovascular disease and cancer with tofacitinib [15], before ultimately placing a broader black box warning to the other JAKi in use for immune-mediated inflammatory diseases—baricitinib and upadacitinib—in September 2021, citing a similar mechanism of action and restricting the class of medications to patients failing TNFi [16].

Following the publication of final results from ORAL Surveillance in January 2022, safety concerns about cardiovascular and cancer risk from JAKi were highly debated

among clinicians attempting to evolve their practice to incorporate these new data. Cautionary warnings and advisory statements were evoked by professional organizations, including a statement by the American College of Rheumatology (ACR) recommending shared decision-making between patients and providers about the risks versus benefits of JAKi [17]. Among other actions by key regulatory bodies (Table 1), the EMA issued a direct healthcare professional communication advising against first-line use of JAKi across all approved indications in inflammatory and dermatologic diseases in patients aged 65 or older with smoking history and other cardiovascular or cancer risk factors, explicitly describing MACE and malignancy as class effects [18].

For many clinicians, the implications are still being fully understood. Although rheumatologists frequently manage uncertainty in clinical practice, many remain unclear as to how to best incorporate JAKi into the treatment paradigm of RA and other rheumatologic diseases. For some, these warnings may deter the use of JAKi in a majority of patients, while on the other end of the spectrum, JAKi may endure as a valuable option in the armamentarium for patients without risk factors. For non-rheumatological prescribers who might consider JAKi for autoimmune disease indications, interpreting this safety signal remains even more challenging and currently may not be directly addressed in counseling all patients [19].

The reality is that, while this post-marketing requirement study successfully built on concerns from a signal correctly noted by regulators within registration studies and added certainty within the scope that the research question was asking, its application in clinical practice for individual practice is still subject to multiple factors (Table 2). In this review, we try to address the importance of each of these factors and discuss how this might influence clinical decision-making for individual prescribers.

3 Clinical Data that Inform the Nature and Extent of Risk

Analyses of ORAL Surveillance, registration studies, and real-world data have all informed our understanding of the cardiovascular and cancer risks associated with JAKi (Table 3). To this end, we performed a search of the literature using MEDLINE to capture a broad mix of evidence that might help elucidate these risks in different cohorts. The search strategy is presented in Online Resource 1.

3.1 ORAL Surveillance

Within ORAL Surveillance, there was a trend toward increased incident MACE (HR 1.33, 95% CI 0.91–1.94) and a significant increase in incident cancer (HR 1.48, 1.04–2.09), although neither met the pre-determined non-inferiority threshold [10]. These figures equated to a number needed to harm for tofacitinib 5 mg BID of 567 patient-years for MACE and 276 patient-years for cancer, translating to an additional event for every 113 and 55 patients who were treated within the study, respectively.

3.2 Post Hoc Analyses of ORAL Surveillance

Notably, this effect was enriched in patients aged 65 years or older and was the focus of a post hoc analysis that separated patients into either a high-risk group, defined by age 65 years or older and history of long-term smoking, or low-risk group [20]. Observed in the former was a greater risk of serious adverse events, namely cancer (HR 1.55, 1.05–2.30 versus HR 1.16, 0.53–2.55), MACE (HR 1.41, 0.93–2.15 versus HR 0.98, 0.42–2.31), myocardial infarction (HR 1.92, 0.92–4.00 versus HR 0.78, 0.13–4.65), and all-cause mortality (HR 2.24, 1.20–4.19 versus HR 1.05, 0.36–3.07).

Other post hoc analyses have similarly analyzed the importance of these risk factors. Charles-Schoeman et al. highlighted an increased risk of MACE in patients with a baseline history of atherosclerotic cardiovascular disease (ASCVD) (HR 1.98, 0.95–4.14) compared with those without (HR 1.14, 0.73–1.78), even in association with a high 10-year cardiovascular risk score [21]. A similar post hoc analysis evaluated cancer risk and found a trend to higher incidence in patients with a history of ASCVD or higher cardiovascular risk scores, perhaps reflecting overlapping risk factors for cardiovascular disease and cancer [22]. Interestingly, this study observed similar malignancy risk between tofacitinib and TNFi groups until month 18 (HR 0.93, 0.53–1.62), after which this diverged (HR 1.93, 1.22–3.06), suggesting a possible time-dependent risk with tofacitinib use. It should be noted that ORAL Surveillance demonstrated a greater risk of infections, including opportunistic infections and herpes zoster with tofacitinib [10]. This factor has been consistently demonstrated amongst JAKi to date [23] and may have influenced clinical practice.

These post hoc analyses, while potentially providing important clarity that might help clinicians apply this study in practice, might also be selective and may not be as fair as the pre-specified analysis. Similar to the similar provisos that surround subsequent real-world data analyses, this should be considered when weighing the conclusions that might be drawn from such analyses.

3.3 Tofacitinib Clinical Program

Excessive MACE risk was not originally identified in tofacitinib's clinical trial program that consisted of 21 phase 1–3b/4 and two long-term extension studies [24]. However,

Table 1 Summary of actions taken by key international regulatory bodies regarding JAKi use

Jurisdiction	Regulatory body	Date	Relevant JAKi	Action
United States	Food and Drug Administration	February 2021 [16]	Tofacitinib, baricitinib, upadacitinib	Boxed warning for MACE, malignancy, and mortality with recommendation for the use of JAKi in moderately to severely active RA with an inadequate response or intolerance to TNF blockers
European Union	European Medicines Agency	March 2023 [18]	Tofacitinib, baricitinib, upadacitinib, filgotinib, abrocitinib	Recommendation for the use of JAKi across all approved indications in inflammatory and dermatologic diseases only if no suitable alternative treatments available for patients with the following risk factors: Age ≥ 65 Increased risk of cardiovascular disease Current or past long-time smoking Increased risk of cancer
United Kingdom	Medicines and Healthcare products Regulatory Agency	April 2023 [148]	Tofacitinib, baricitinib, upadacitinib, filgotinib, abrocitinib	Recommendation for the use of JAKi only if no suitable alternative treatments available for patients with the following risk factors: Age ≥ 65 Current or past long-time smoking Other risk factors for cardiovascular disease or malignancy
Canada	Health Canada	October 2022 [157]	Tofacitinib, baricitinib, upadacitinib, filgotinib, abrocitinib	Recommendation to consider the benefits and risks of JAKi for the individual patient, particularly for patients with the following risk factors: Above 65 years of age Current or past smokers Other cardiovascular or malignancy risk factors Underlying malignancy or those who develop a malignancy Increased risk of thrombosis
Australia	Therapeutic Goods Administration	May 2023 [158]	Tofacitinib, baricitinib, upadacitinib	Boxed warning and recommendation for the use of JAKi only if no suitable treatment alternatives are available for patients with the following risk factors: History of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers) Malignancy risk factors (such as currently malignancy or history of malignancy) Age ≥ 65

JAKi JAK (Janus kinase) inhibitors, *MACE* major adverse cardiovascular events, *RA* rheumatoid arthritis

Table 2 Factors influencing the interpretation of cardiovascular and cancer risk for individual patients starting JAKi

Factor	Feature within the post-marketing requirement study (ORAL Surveillance)	Factors influencing interpretation for individual patients	Importance
Disease indication	RA as indication	Indications apart from RA (rheumatological and non-rheumatological)	Underlying disease may influence CV and cancer risk
Baseline CV risk	Patients had at least one CV risk factor, including age	Lesser or greater patient baseline CV risk	Current data might imply risk represents effect modification
Previous response to therapy	Patients had not previously responded to either JAKi or TNFi	Variable clinical response to either JAKi or TNFi	Disease activity and adjunct therapies (glucocorticosteroids, non-steroidal antiinflammatories) may both separately also confer risk
Alternative therapies	Comparison with TNFi	Alternative not a TNFi (other therapy or no therapy)	Many alternative therapies may confer greater risk than TNFi, either directly or in interacting with other factors
JAKi choice	Tofacitinib used	JAKi apart from tofacitinib	Lack of clear mechanism-related plausibility means uncertain whether represents class effect, and whether JAK selectivity is of any importance
JAKi dose	Some patients 5 mg BID, other patients 10 mg BID to 5 mg BID	Variable doses of tofacitinib and other JAKi in use	Dose-dependent effect plausible, and JAK selectivity functionally abrogated at higher doses
Follow-up duration	Relatively short follow-up in context of double-blind randomized controlled trial	Indefinite use from chronic inflammatory diseases	CV and cancer risk may be incurred over longer durations of therapy
Risk-benefit consideration	Limited magnitude of absolute risk of harm	Patient preference for other advantages (perceived rapid onset, mode of administration)	Patients may not decline non-JAKi therapies in practice, or be happy to offset CV and cancer risk against other advantages

CV cardiovascular, *JAKi* JAK (Janus kinase) inhibitor, *JAK1* Janus kinase 1 protein, *TNFi* TNF (tumor necrosis factor) inhibitors, *RA* rheumatoid arthritis

Table 3 Summary of MACE and malignancy risk from select studies

Study	Study design	Population restrictions	Medication	Outcome	95% CI
Risk of MACE					
Ytterberg et al. 2002 (ORAL Surveillance) [10]	RCT	RA; age ≥ 50 + ≥ 1 additional CV risk factor	Tofacitinib 5 mg BID and 10 mg BID versus TNFi (adalimumab, etanercept)	HR 1.33	0.91–1.94
Charles-Schoeman et al. 2023 (ORAL Surveillance post hoc analysis) [21]	RCT	RA; age ≥ 50 + ≥ 1 additional CV risk factor + no history of ASCVD	Tofacitinib 5 mg BID and 10 mg BID versus TNFi (adalimumab, etanercept)	HR 1.14	0.73–1.78
		RA; age ≥ 50 + ≥ 1 additional CV risk factor + history of ASCVD		HR 1.98	0.95–4.14
Khosrow-Khavar et al. 2022 (STAR-RA) [32]	Cohort study	RA; age ≥ 18 (MarketScan, Optum) or age ≥ 65 (Medicare)	Tofacitinib versus TNFi (infliximab, adalimumab, certolizumab pegol, etanercept, golimumab)	HR 1.01	0.83–1.23
		RA; age ≥ 50 (MarketScan, Optum) or age ≥ 65 (Medicare) (ORAL Surveillance duplicate)		HR 1.24	0.90–1.69
Fang et al. 2022 [42]	Cohort study	RA	Tofacitinib versus TNFi	HR 1.03[a]	0.45–2.36
				HR 0.75[b]	0.29–1.94
Kremer et al. 2021 [34]	Cohort study	RA; age ≥ 18	Tofacitinib 5 mg BID and 10 mg BID versus bDMARDs	HR 0.61	0.34–1.06
Hoisnard et al. 2023 [35]	Cohort study	RA; age ≥ 18	JAKi (tofacitinib 5 mg BID and 10 mg BID, baricitinib 2 mg and 4 mg) versus adalimumab	HR 1.0	0.7–1.5
		RA; age ≥ 65 + ≥ 1 additional CV risk factor		HR 1.0	0.5–1.9
Bilgin et al. 2022 [39]	Cohort study	RA	Tofacitinib 5 mg BID versus etanercept	IRR 0.8	0.2–4.1
Cohen et al. 2020 [26]	RCTs + extension studies	RA	Tofacitinib 5 mg BID and 10 mg BID	IR 0.4	0.3–0.5
Sandborn et al. 2022 [43]	RCTs + extension study	UC; age < 65	Tofacitinib 5 mg BID and 10 mg BID	IR 0.20	0.07–0.47
		UC; age ≥ 65		IR 1.06	0.13–3.81
Risk of malignancy					
Ytterberg et al. 2002 (ORAL Surveillance)[c] [10]	RCT	RA; age ≥ 50 + ≥ 1 additional CV risk factor	Tofacitinib 5 mg BID and 10 mg BID versus TNFi (adalimumab, etanercept)	HR 1.48	1.04–2.09
Curtis et al. 2023 (ORAL Surveillance post hoc analysis)[c] [22]	RCT	RA; age ≥ 50 + ≥ 1 additional CV risk factor (until month 18)	Tofacitinib 5 mg BID and 10 mg BID versus TNFi (adalimumab, etanercept)	HR 0.93	0.53–1.62
		RA; age ≥ 50 + ≥ 1 additional CV risk factor (from month 18 onwards)		HR 1.93	1.22–3.06
		RA; age ≥ 50 + ≥ 1 additional CV risk factor + history of ASCVD		HR 1.23	0.60–2.49
		RA; age ≥ 50 + ≥ 1 additional CV risk factor + no history of ASCVD + high ASCVD risk score		HR 1.79	0.91–3.49

Table 3 (continued)

Study	Study design	Population restrictions	Medication	Outcome	95% CI
		RA; age ≥ 50 + ≥ 1 additional CV risk factor + no history of ASCVD + intermediate ASCVD risk score		HR 1.90	0.95–3.82
		RA; age ≥ 50 + ≥ 1 additional CV risk factor + no history of ASCVD + borderline ASCVD risk score		HR 0.50	0.17–1.50
		RA; age ≥ 50 + ≥ 1 additional CV risk factor + no history of ASCVD + low ASCVD risk score		HR 1.71	0.56–5.24
Khosrow-Khavar et al. 2022 (STAR-RA)[d] [33]	Cohort study	RA; age ≥ 18 (MarketScan, Optum) or age ≥ 65 (Medicare)	Tofacitinib versus TNFi (infliximab, adalimumab, certolizumab pegol, etanercept, golimumab)	HR 1.01	0.83–1.22
		RA; age ≥ 50 (MarketScan, Optum) or age ≥ 65 (Medicare) (ORAL Surveillance duplicate)		HR 1.17	0.85–1.62
Huss et al. 2023[c] [37]	Cohort study	RA; age ≥ 18	JAKi (baricitinib, tofacitinib 5 mg BID, upadacitinib) versus bDMARDs	HR 0.94	0.65–1.38
		RA; age ≥ 18 + ≥ 1 CV risk factor		HR 1.03	0.58–1.82
Fang et al. 2022[d] [42]	Cohort study	RA	Tofacitinib versus TNFi	HR 1.10	0.44–2.78
Kremer et al. 2021[c] [34]	Cohort study	RA; age ≥ 18	Tofacitinib 5 mg BID and 10 mg BID versus bDMARDs	HR 1.04	0.68–1.61
Bilgin et al. 2022[c] [39]	Cohort study	RA; age ≥ 18	Tofacitinib 5 mg BID versus etanercept	IRR 3.5	0.4–92.2
Cohen et al. 2020[c] [26]	RCTs + extension studies	RA	Tofacitinib 5 mg BID and 10 mg BID	IR 0.8	0.7–0.9
Sandborn et al. 2022[c] [43]	RCTs + extension study	UC; age < 65	Tofacitinib 5 mg BID and 10 mg BID	IR 0.65	0.37–1.06
		UC; age ≥ 65		IR 2.05	0.56–5.25

[a]Coronary heart disease

[b]Stroke

[c]Excluding NMSC

[d]Any malignancy

ASCVD atherosclerotic cardiovascular disease, *bDMARDs* biologic disease-modifying antirheumatic drugs, *CV* cardiovascular, *HR* hazard ratio, *IR* incidence rate (per 100 patient-years), *IRR* incidence rate ratio (per 1000 patient-years), *JAKi* JAK (Janus kinase) inhibitors, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *TNFi* tumor necrosis factor (TNF) inhibitors, *UC* ulcerative colitis, *95% CI* 95% confidence interval

a notable difference between registration studies and ORAL Surveillance was the lower proportion of patients with a history of ASCVD (4% versus 15%), and this was explored in a study that emulated the risk-enriched cohort of ORAL Surveillance using 3125 patients from the clinical trial program [25]. Compared with ORAL Surveillance, the MACE IRs were lower overall but comparable in patients without a history of ASCVD.

Integrated safety summaries of prior RCTs and extension studies of tofacitinib have reported similar long-term rates of safety events compared with biologic disease-modifying antirheumatic drugs (bDMARDs). Of these, the largest, longest clinical dataset accrued 22,875 patient-years of exposure pooled from phase 1–3b/4 and long-term extension studies and reported an incidence rate (IR, per 100 patient-years) of 0.4 (0.3–0.5) for MACE and 0.8 (0.7–0.9), 0.6 (0.5–0.7), and 0.1 (0.0–0.1) for malignancies (excluding NMSC), NMSC, and lymphomas, respectively [26]. These figures appeared to be consistent with previous analyses of both MACE and malignancy with tofacitinib treatment [27–30]. To put these Irs into perspective, long-term safety data for adalimumab in RA with 37,106 patient-years reported an IR of 0.7 for malignancies (excluding lymphoma, skin cancer, leukemia, and hepatosplenic T-cell lymphoma), although such risk was likely historically higher at the time many of these data were collected [31].

All these findings raise the question as to whether the signals seen in ORAL Surveillance arose due to the studied population having a higher risk for cardiovascular events at baseline. Whatever the case, the importance of addressing traditional cardiovascular risk factors in patients with RA has never been clearer, and clinicians should take this as a reminder that risk stratification is a key component of the shared decision-making process.

3.4 Real-World Evidence for Tofacitinib Safety in RA

One must be prudent in generalizing the results of ORAL Surveillance as this population was not inclusive of all patients with RA. The RCT selected older, higher-risk individuals; as a consequence, the external validity and generalizability of the trial needs to be taken into consideration. Real-world evidence serves as an important, complementary form of evidence which may differently represent the effectiveness and safety of therapeutics. One such example is a large observational study (STAR-RA) using US commercial and Medicare claims data that, in a cohort of routine care patients (n = 102,263), did not identify an increased risk of a composite outcome of myocardial infarction and stroke with tofacitinib versus TNFi (pooled weighted HR 1.01, 0.83–1.23) [32]. Meanwhile, a sub-cohort within this study that was designed to mimic the inclusion and exclusion criteria of ORAL Surveillance (n = 35,070) did demonstrate a cardiovascular signal similar to that seen in the reference trial (pooled weighted HR 1.24, 0.90–1.69). While the STAR-RA study served purely for an exploratory analysis and was not powered to compare individual MACE risk factors across each treatment group, the findings seem to support the proposition that increased risk of MACE is particularly strong within the cardiovascular risk-enriched population captured in ORAL Surveillance. The latter group also puts forward the implication that the cardiovascular observations in ORAL Surveillance may have been influenced by effect modification, in that the effect of having a baseline history of increased cardiovascular risk led to a higher risk of developing incident MACE.

The STAR-RA study also investigated malignancy risk in both real-world evidence (n = 83,295) and ORAL Surveillance duplicate (n = 27,035) groups [33]. There was no significant difference between tofacitinib versus TNFi amongst all patients with RA in the real-world setting, but a numerically higher pooled weighted HR was observed in the ORAL Surveillance-matched group (1.01, 0.83–1.22 versus 1.17, 0.85–1.62), again suggesting older patients with cardiovascular risk factors may be at higher risk. However, with a mean follow-up time of just over 10 months and the knowledge that cumulative VTE risk from JAKi increases over time, there are insufficient data to comment on any effect on cardiovascular and cancer risk that a longer duration of tofacitinib use may incur.

The safety profile of tofacitinib observed in real-world settings across the world is also compatible with what has been described during its clinical development program. Cardiovascular and malignancy outcomes from select studies are summarized in Table 2.

Kremer et al. performed a registry study comparing tofacitinib (n = 1999) and biologic DMARD (n = 8358) initiation and found similar MACE and malignancy rates over 5 years [34]. In Europe, a French national health data cohort study of 15,835 patients compared patients with RA who started a JAKi (40% tofacitinib including 5 mg and 10 mg BID, 60% baricitinib) versus adalimumab and found no difference in MACE risk between the groups, even at the higher 10 mg BID dose of tofacitinib, although this dose was only observed in 21 patients [35]. Interestingly, the same outcome was delineated in a risk-enriched subset of patients aged 65 years or older with at least one cardiovascular risk factor, although the study was not powered for this subgroup analysis. Another French registry study of 100 patients reported one patient with SLE who had recurrence of cutaneous T-cell lymphoma after 6 months of tofacitinib but no MACE over the 9-month follow-up period [36]. A prospective Swedish cohort study of 10,447 patients with RA and 4443 patients with PsA compared cancer risk with JAKi (78% baricitinib, 18% tofacitinib, 4% upadacitinib),

TNFi, and non-TNFi bDMARDs [37]. After less than 3 years of treatment, increased rates of NMSC were observed in the combined JAKi group in patients with RA (HR 1.39, 1.01–1.91), but the same was not seen for other malignancies (HR 0.94, 0.65–1.38). Of note, analysis of a cardiovascular-enriched subset demonstrated higher incidences but a similar HR of 1.03 (0.58–1.82), in keeping with the main analysis. In a Swiss cohort of 144 patients with RA receiving tofacitinib, no MACE or malignancy was reported after a mean follow-up of 1.22 years [38]. British registry data from a single center comparing tofacitinib 5 mg BID ($n = 145$) and etanercept ($n = 114$) identified three and four cases of MACE in the respective groups [IR ratio (IRR) 0.8, 0.2–4.1], with all affected patients having pre-existing cardiovascular risk factors [39]. The number of cancer events were three and one, respectively (IRR 3.5, 0.4–92.2). Notably, patients in the tofacitinib group were older, exposed more to active smoking, had higher odds of hypertension and family history of early coronary heart disease, and had lower odds of cancer history, but still had similar event rates compared with etanercept.

Studies in Asia include a 1-year multicenter study consisting of 370 patients with RA across 12 Japanese sites that compared adverse events with tofacitinib and abatacept and discovered comparable rates of MACE and malignancy [40]. In contrast, a Japanese cohort of 242 patients with RA treated with tofacitinib ($n = 161$) or baricitinib ($n = 81$) reported three cases of malignancy (colon, skin, and lung cancer) in the tofacitinib group and one (breast cancer) with baricitinib over a relatively short 24-week period [41]. In a Taiwanese insurance database study of patients with RA treated with tofacitinib ($n = 822$) with a mean follow-up of 2.02 years versus TNFi ($n = 2357$) with a mean follow-up of 2.10 years, there was no statistically significant difference in rates of coronary heart disease (HR 1.03, 0.45–2.36), stroke (HR 0.75, 0.29–1.94), or malignancy (HR 1.10, 0.44–2.78) [42].

These real-world experiences are reassuring of similar MACE and malignancy risk from JAKi compared with bDMARD therapy in a general RA population. Simultaneously, they suggest that specific patient populations with RA do hold increased odds of cardiovascular events, namely those who are older or have a pre-existing history of cardiovascular disease, and that caution should be exercised to balance these risks with the potential benefits of tofacitinib in these patients.

3.5 Tofacitinib in the Treatment of Other Diseases

While the present discussion revolves around RA, it would be sensible to explore whether the safety signals seen in ORAL Surveillance extend to tofacitinib use in other diseases, such as UC, where the more routine use of the higher 10 mg BID dose as part of induction therapy is also of note. The underlying molecular targets in different immune-mediated diseases may affect the efficacy and safety of each JAKi, so potential MACE and malignancy risks of tofacitinib may not necessarily be reflected when treating other conditions. An integrated summary of major trials in UC consisting of a total of 1157 patients treated with tofacitinib, predominantly at a dose of 10 mg BID (83%), found IRs of 0.29 (0.13–0.55) for MACE, 0.84 (0.55–1.24) for malignancies excluding NMSC, and 0.73 (0.45–1.10) for NMSC [43], figures not dissimilar to those seen in comparable RA analyses. Interestingly, the signal for VTE at the higher dose seen in ORAL Surveillance was not demonstrated in this UC group, with IRs of 0.03 (0.00–0.18) for deep vein thrombosis and 0.19 (0.07–0.42) for pulmonary embolism, and it is known that RA itself confers an increased risk of VTE [44–47]. Analysis of the same cohort stratified by age found that those aged 65 years or older had a significantly higher risk of adverse events than those younger than 65: MACE, IR 1.06, 0.13–3.81 versus 0.20, 0.07–0.47; malignancies excluding NMSC, IR 2.05, 0.56–5.25 versus 0.65, 0.37–1.06; and NMSC, IR 3.97, 1.60-8.19 versus 0.37, 0.17–0.70 [48]. These were reminiscent of age being recognized as a risk factor in ORAL Surveillance and STAR-RA, albeit without enrichment for cardiovascular history. These data do not appear to indicate an increased risk of MACE or malignancy with tofacitinib in patients with UC; discrepancies noted here in contrast to RA may be a reflection of how the pathophysiology of different diseases intersects with JAK inhibition and unexplained mechanisms behind cardiovascular disease and malignancy.

3.6 The Role of JAK Specificity

Although the safety of other JAKi has not yet been subject to post-marketing studies, the FDA has applied a blanket warning for the two other JAKi registered for use in autoimmune diseases (baricitinib and upadacitinib) given their similar mechanisms of action [49]. It remains unknown whether JAK specificity contributes to safety profile; while tofacitinib inhibits both JAK1 and JAK3, the other JAKi of interest in RA include baricitinib, which inhibits JAK1 and JAK2, and JAK1-selective upadacitinib and filgotinib [2]. In theory, this selectivity may facilitate more targeted blockade of the JAK cascade and its downstream immunomodulatory effects on particular inflammatory responses, but how this translates clinically to efficacy and safety remains to be seen, especially given the inherent redundancies between the signaling pathways with different JAKs [50, 51].

3.7 Safety of Other JAKi

Real-world data and integrated analyses for baricitinib and upadacitinib in RA have largely demonstrated a consistent safety profile without increased rates of MACE or malignancy over time. An integrated database consisting of nine phase 1b/2/3 trials and one long-term extension study of patients with RA taking either 2 mg or 4 mg of baricitinib investigated the long-term safety of baricitinib through 9.3 years of treatment, amounting to 14,744 patient-years [52]. The IR for MACE in all baricitinib doses was 0.5 (0.40–0.64); rates were similar in the 2 mg (0.42, 0.21–0.74) and 4 mg (0.54, 0.41–0.69) subsets. In a risk-enriched population aged 50 years or older with at least one cardiovascular risk factor, there was a higher incidence of MACE (0.77, 0.56–1.04), though this figure approximated more closely to the TNFi rates (0.73, 0.52–1.01) in ORAL Surveillance than tofacitinib (0.98, 0.79–1.19) [10]. Regarding malignancy (excluding NMSC), the IR stabilized at 0.9 (0.77–1.09) after 48 weeks, with respiratory and mediastinal ($n = 26$), breast ($n = 23$), and gastrointestinal ($n = 19$) cancers being most frequently reported. Compared with the general US population using SEER, a cancer dataset derived from population-based registries, an age-adjusted standardized IR of 1.07 (0.90–1.26) suggested a similar incidence of malignancy as the general population. The IRs for NMSC and lymphoma were 0.3 (0.25–0.44) and 0.06 (0.03–0.11), respectively.

A large US study of registry and insurance data propensity score-matched 7606 baricitinib-treated patients with RA with patients who received TNFi, amounting to 5879 and 6512 person-years of exposure, respectively [53]. A numerically higher but non-statistically significant IRR was observed for baricitinib for MACE (1.54, 0.93–2.54), with a difference in incidence rates of 0.22 (0.07–0.52) per 100 person-years, translating to an additional two MACE per year for every 1000 patients treated with baricitinib rather than TNFi. In a 12-week phase 2b RCT with a 52-week extension period in a Japanese cohort, 145 patients with active RA despite methotrexate therapy were randomized initially to placebo or 1 mg, 2 mg, 4 mg, or 8 mg of baricitinib during the first 12 weeks, then re-randomized to 4 mg or 8 mg during the extension period for those on other doses [54]. While MACE were not specifically described, hyperlipidemia and hypercholesterolemia were commonly reported. Malignancy occurred in one patient in each arm of the extension period, a case of rectal cancer and chondrosarcoma. Also in Japan, a post-marketing surveillance study examined the safety of baricitinib for RA over 24 weeks [55]. Out of 4731 patients over 1863 patient-years, MACE occurred in seven patients (0.15%) and malignancy in 17 (0.36%). A British observational study that included 69 patients treated with baricitinib, 54 with tofacitinib, and 8 with both found one case of malignancy in the tofacitinib arm but no MACE or malignancy events with baricitinib [56].

In relation to upadacitinib, an international RCT spanning across China, Brazil, and South Korea that randomized 338 patients with RA on stable conventional synthetic DMARDs (csDMARDs) to upadacitinib 15 mg daily or placebo reported no MACE or NMSC in either group after 12 weeks (although one patient in the upadacitinib arm was diagnosed with breast cancer on the day of randomization) [57].

Integrated analyses of existing phase 3 trials of upadacitinib have also been encouraging. Data from five randomized trials of upadacitinib 15 mg or 30 mg compared with methotrexate or adalimumab with 4020 patient-years of exposure revealed similar rates of MACE and malignancy across treatment groups [58]. There was a trend to higher IRs with 30 mg compared with 15 mg for both MACE (1.0, 0.5–1.6 versus 0.6, 0.4–1.0), malignancies (excluding NMSC) (1.4, 0.8–2.2 versus 0.9, CI 0.5–1.3), and NMSC (1.1, 0.6–1.8 versus 0.3, 0.1–0.6), suggesting a dose-dependent effect. In PsA, an analysis of one RCT evaluating upadacitinib 15 mg and 30 mg and another that included adalimumab as well pooled 2257 upadacitinib-treated patients for 2505 patient-years of exposure found similar safety profiles with regard to MACE and cancer [59]. Differing from the aforementioned RA analysis, numerically higher IRs were observed for the 15 mg dose in comparison with 30 mg for NMSC (0.8, 0.4–1.5 versus 0.7, 0.3–1.4) and MACE (0.3, 0.1–0.8 versus 0.2, 0.0–0.7), while the opposite was true for malignancies (excluding NMSC) (0.7, 0.3–1.4 versus 0.9, 0.4–1.6).

The long-term safety for upadacitinib is also a matter of interest in atopic dermatitis and UC, where it is sometimes given in higher doses than RA. A 2-year interim analysis of a phase 3 RCT ($n = 272$) of upadacitinib 15 mg versus 30 mg versus placebo in moderate-to-severe atopic dermatitis with 1:1 re-randomization of placebo patients to either upadacitinib dose at week 16 described one case of rectal cancer and one of cerebellar hemorrhage in the upadacitinib 15 mg group, representing an IR of 0.3 for both malignancy and MACE [60]. A clinical program consisting of two phase 3 multicenter RCTs of induction therapy in patients with moderately to severely active UC with upadacitinib 45 mg versus placebo for 8 weeks ($n = 989$), followed by one maintenance RCT with re-randomization to upadacitinib 15 mg versus 30 mg versus placebo for 52 weeks ($n = 451$) [61]. In the induction studies, no events of cancer or MACE were reported. In the maintenance trial, one case of malignancy (excluding NMSC) was reported in both the placebo (breast cancer) and upadacitinib 15 mg (breast cancer) groups and two in the upadacitinib 30 mg group (colon and prostate cancer); two cases of NMSC in

the upadacitinib 30 mg group; and one MACE (myocardial infarction) in the placebo group.

Filgotinib, another JAK1-selective JAKi, is not marketed in the USA after the FDA rejected the initial filing in 2020 in light of concerns about male reproductive safety, but data from Europe and Japan regarding MACE and malignancy have been consistent with other JAKi. An integrated analysis of safety data from seven trials of filgotinib 100 mg or 200 mg in moderately to severely active RA included 3691 patients with 6081 patient-years and a median of 1.6 years and maximum 5.6 years of exposure [62]. Exposure-adjusted IRs for MACE for filgotinib 100 mg versus 200 mg were 0.6 (0.4–1.1) versus 0.4 (0.2–0.7); for malignancies (excluding NMSC), 0.5 (0.3–1.0) versus 0.6 (0.4–0.9); and for NMSC, 0.1 (0.0–0.5) versus 0.2 (0.1–0.4), respectively. In UC, preliminary findings from an ongoing long-term extension study of a phase 2b/3 trial of filgotinib 200 mg with 971 patient-years of exposure included exposure-adjusted IRs of 0.3 (0.1–0.9) for MACE and 0.8 (0.4–1.6) for malignancies (excluding NMSC) [63].

In summary, registration trial extension studies and real-world evidence examining non-cardiovascular risk-enriched patient populations have repetitively failed to demonstrate any clear increase in cardiovascular and cancer risk with any JAKi over what might be expected with TNFi. In contrast, patients with RA with existing cardiovascular risk seem to incur increased rates of both incident cardiovascular events and cancer with tofacitinib when compared with TNFi in the context of both RCT and real-world evidence, although fewer comparable data for other JAKi or for other indications exist.

4 Risk and Its Plausibility

While these data for other JAKi appear to dispel major fears about cardiovascular and cancer safety, is there any biological plausibility of JAKi giving rise to these adverse events in the first instance? Broadly speaking, side effects observed with DMARD therapy can often be mechanistically explained by the drug's pharmacodynamics. For instance, type I interferons are key antiviral cytokines, and JAK inhibition has been linked to a heightened risk of herpes zoster through an effect on downstream signaling from type I interferons via TYK2 and JAK1 [64]. Similarly, JAKi have been labeled with a special concern for small bowel perforation [8, 65], which could be explained by the effect of JAK inhibition on IL-6 receptor signaling through JAK1, JAK2, and TYK2 [64].

In contrast, the mechanisms behind the potential risk for VTE, MACE, and cancer are still unclear.

4.1 VTE

While not the focus of this review, VTE was the first clinically important adverse event subject to substantial regulatory warnings for JAKi. As a consequence, it has been investigated for a longer period of time, and an exploration of whether this phenomenon can be mechanistically explained is worthwhile in trying to understand whether the processes that may underpin MACE and malignancy may be explainable from a mechanistic point of view.

Inflammatory disease activity in RA is associated with increased risk of VTE [66], whereby inflammation causes immunothrombosis, characterized by alterations in the endothelium surface [67]. Numerous cells, cytokines, chemokines, and adhesion molecules work together to generate a specific environment that leads to thrombus formation [68]. The effects on thrombus development have been elucidated for many cytokines [69]. Therefore, blocking the JAK-signal transducer and activator of transcription (STAT) pathway that supports the action of a particular cytokine may result in either a decrease or increase in the risk of VTE depending on the specific function of that cytokine [70].

From a hematopoiesis perspective, blocking JAK2 should suppress platelet production by the inhibition of thrombopoietin (TPO) signaling [71]. The direct effect of changes in JAK–STAT signaling and risk of VTE can also be informed by the phenotype of patients who have JAK2 genetic variants, which through gain of function may lead to thrombocytosis and VTE [72, 73]. In line with this, inhibition of JAK2 by ruxolitinib has been associated with significantly lower rates of thrombosis in patients with polycythemia vera, suggesting that JAK2 inhibition can decrease thrombosis risk in a myeloproliferative milieu [74].

However, clinical trials with JAKi in patients with inflammatory arthritis have shown increases in platelet counts. One study observed transient increases in platelet counts after initiation of JAKi therapy without association with VTE [75]. Another suggested that a higher risk of VTE with JAKi was associated with an elevation in platelet counts, but this elevation returned to baseline with long-term follow-up [76]. This underpins the complexity of the JAK–STAT signaling pathway that involves a wide range of activating ligands and downstream signaling effects.

Few studies have directly explored the association between JAK inhibition and risk components of VTE. A sub-analysis of the ORAL Surveillance study analyzed 291 protein biomarkers and three genetic markers such as C-reactive protein, D-dimer, TPO, factor VIII, thrombin–antithrombin complex, tissue factor pathway inhibitor, plasminogen activator inhibitor-1, protein C, antithrombin, apolipoprotein C-III, and leptin, along with

276 markers from a high-throughput proteomic assay. D-Dimer levels were weakly linked to a higher risk of developing VTE in this RA population, but the authors concluded that more data are necessary to inform the proper clinical application of this test. The study did not find associations between any of the other analytes and higher rates of VTE with tofacitinib compared with TNF inhibition [77]. Preliminary investigations have explored the putative convergence of genomic VTE risk factors on JAK–STAT signaling, including STAT target genes [78]. An overlap between differentially expressed genes and STAT target genes includes cyclins, an interesting observation given that VTE with cyclin-dependent kinase (CDK) 4/6 inhibitors used in oncology occurs in up to 5% of clinical trials and 10% in real-world settings [79, 80]. Cyclin D and CDK4/6 are downstream STAT target genes that regulate cell progression in early gap 1 phase in the cell cycle [81]. This suggests that factors separate to blockade of cytokine signaling and dampening of inflammation may also be involved in increasing VTE risk with JAK inhibition.

4.2 MACE

While it is recognized that inflammatory disease activity in RA is associated with increased risk of MACE [82], the consequence of dysregulated JAK–STAT signaling has not been as clearly elucidated. STAT signaling has been generally associated with harmful effects on the heart; in contrast, a cardioprotective effect with STAT3 has been observed [83–86]. Only a few studies have directly explored the mechanistic associations between JAK inhibition and risk of MACE. JAKi in the treatment of RA induce a significant increase in high-density and low-density lipoprotein levels [87], and dyslipidaemia has been reported for both non-selective JAKi [88–92] and JAK1-selective inhibition [93]. Inhibition of the JAK–STAT pathway by tofacitinib contributes to lipid release via enhanced expression of cellular liver X receptor alpha and ABCA1 synthesis [94]. How an increase in lipid levels with JAKi use translates to clinical outcomes, however, is not fully understood.

Conventionally, hyperlipidemia is a risk factor for MACE, but this is not necessarily the case for patients with RA, whereby an elevated risk of MACE may exist despite relatively low cholesterol levels. This is the so-called "lipid paradox," with changes in lipid levels representing a response to attenuation of inflammation [95]. Data are conflicting about the effect that tofacitinib treatment exerts on some parameters associated with lowered MACE risk; decreased carotid intima-media thickness (IMT) [96] and attenuated vascular inflammation as determined by fluorodeoxyglucose-positron emission tomography/computed tomography (CT) [97] have been described with tofacitinib, although another study found that carotid IMT increased despite treatment [98].

4.3 Malignancy

The ramifications of inflammatory disease activity in RA also extend to an increased risk of cancer [99]. Given the established role of JAKi in the treatment paradigm of hematopoietic malignancies [100], the potential for JAK inhibition in managing solid tumors has been of interest. Collectively, data from preclinical cancer models of solid tumors demonstrate that JAK inhibition can prevent tumor proliferation and growth [101]. However, most solid tumors that exhibit increased JAK–STAT signaling lack somatic JAK mutations, thus differing from myeloproliferative diseases.

A preclinical study demonstrated that JAK inhibition negatively affects the phenotype and function of natural killer (NK) cells [102]. In support of these findings, NK cells with acquired STAT5 deficiency have reduced antitumor cytotoxicity in melanoma mice models [103]. Furthermore, tofacitinib decreases NK cell activation and lymphoma cell-killing efficacy by decreasing their capacity for degranulation and cytokine secretion [104]. Interestingly, CD8 T cells have also been shown to be affected by JAKi [105, 106].

In summary, whilst a likely mechanism exists to explain herpes zoster reactivation from JAKi, and plausible pathways may link VTE to JAKi, explanatory pathophysiology for both cardiovascular and cancer risk from JAKi remains speculative.

5 Individual-Level Factors Influencing Cardiovascular and Cancer Risk in Patients with Autoimmune Disease

At a molecular level, the risk that JAKi contribute to MACE and malignancy is clearly an intricate affair. The same can be said of an individual patient's degree of risk when considering how their underlying disease and other treatments contribute to this risk.

In addition to traditional cardiovascular risk factors, it is understood that chronic inflammatory diseases inherently pose an increased risk of cardiovascular disease [107–110]. This notion has been particularly well established in RA, in which it is recognized that inflammatory processes are pivotal to atherosclerotic processes through endothelial dysfunction and maladaptive vessel wall remodeling [111], and that the disease may confer an additional 50% risk over and above other risk factors [109, 112, 113]. There is less supportive evidence in patients with PsA [114, 115], but an increased cardiovascular risk is also suspected. The magnitude of risk conferred by a wide range of autoimmune diseases was recently assessed in a

large epidemiological study using data from 22 million people in the UK [116]. Among patients with rheumatic diseases, namely RA, SLE, systemic sclerosis (SSc), polymyalgia rheumatica, axial spondyloarthritis, and Sjögren's syndrome, there was an overall 68% higher risk for cardiovascular disease, with the greatest associations observed in SSc (HR 3.59, 2.81–4.59) and SLE (HR 2.82, 2.38–3.33). Beyond rheumatic autoimmune diseases, the association between non-rheumatic autoimmune conditions and cardiovascular risk has also been acknowledged. In a meta-analysis of ten cohort studies, Feng et al. observed that patients with inflammatory bowel disease had an increased risk of ischemic heart disease (RR 1.24, 1.14–1.36) [117]. Meanwhile, no increased risk of cardiovascular disease has been shown among patients with alopecia areata [118, 119].

Furthermore, disease activity in RA correlates with the cardiovascular risk in this patient population, adding another layer of complexity. To this end, a study by Solomon et al. examined the relationship between RA disease activity measured longitudinally and the risk of cardiovascular events [82]. Among a large cohort followed for a median of 2.7 years, they found a 21% reduction in cardiovascular risk for each 10-point lowering of the clinical disease activity index, while achieving remission from a state of high disease activity saw a 53% reduction. These data suggest that controlling disease activity in RA might be important, not only to lower pain and improve joint health, but also to attenuate the risk of adverse cardiovascular outcomes. Future research may look to expound on the role of gut dysbiosis, a recognized hallmark of RA [120], in the development of inflammation, and in turn, cardiovascular risk; this has already been hypothesized to play a potential role in IBD [121, 122].

In terms of cancer outcomes, RA is associated with an increased risk of some malignancies, as demonstrated in a meta-analysis that indicated highest risk for lymphoma and lung cancer [123]. This association is explained in part by certain shared risk factors, such as smoking, as well as underlying inflammation. The best data supporting the role of chronic inflammation in the pathogenesis of lymphoma in RA is derived from a seminal case-control study of Swedish patients with RA in whom the risk of lymphoma substantially increased in a subset with very severe disease, leading to the conclusion that high inflammatory activity is a major risk determinant for lymphoma [124].

The association between other immune-mediated diseases and malignancy risk is more controversial. Skin cancer, particularly NMSC, is among the most commonly reported cancers in PsA [125, 126]. In ankylosing spondylitis, evidence remains inconclusive, with possible increased risk of hematological, skin, and other solid cancers reported in a number of studies [127–130]. IBD has been associated with an increased risk of colorectal cancer, small bowel cancer, intestinal lymphoma, and cholangiocarcinoma [131].

Further complicating matters is the modulatory effect that various therapies may have on cardiovascular risk. TNF is a pro-inflammatory cytokine involved in inflammation and lipid metabolism, and higher levels have been associated with cardiovascular disease in epidemiological studies [132]. Inhibition of TNF has accordingly been shown to improve markers for atherosclerosis such as carotid IMT and pulse wave velocity [133], and decreases the incidence of cardiovascular events in RA and PsA [134]. This is important to consider when interpreting ORAL Surveillance: were both JAKi and TNFi actually cardioprotective but TNFi more so? Both csDMARDs and non-TNFi biologics have also been shown to reduce cardiovascular risk in RA and PsA, while glucocorticoids, even at prednisone-equivalent doses of less than 5 mg daily, and non-steroidal anti-inflammatory drugs (NSAIDs) likely confer an increased risk in these patients [107, 134, 135].

Regarding cancer risk, TNF plays a key role in apoptosis and cell survival and has been demonstrated to exert an anti-tumor effect [136, 137]. As such, safety concerns about the risk of cancer have been raised with TNFi, although there is an overall preponderance of evidence that is reassuring that this class of medications does not increase the risk of most solid tumors, except for NMSC [138–143]. Malignancy risk is less well established with other therapies, although methotrexate may cause a small increased risk of lymphoproliferative disorders [144, 145].

6 Guidance on JAKi Use from Regulation and Guidelines

Although falling short of explicitly calling cardiovascular and malignancy risks a class effect, the FDA has placed labels on all JAKi, warning about safety signals. For example, while tofacitinib gets its own specific warning about observed risks, the label for upadacitinib references increased rates of MACE, lymphoma, and lung cancer with "another JAK inhibitor" [146]. Despite avoiding terminology that would unambiguously describe this as a class effect, the presence of a black box warning describing increased MACE and malignancies serves as a clear warning of risk for prescribers of all JAKi. At the same time, the FDA revised the indication for all JAKi for inflammatory arthritis, such that they are approved only for use after inadequate response to or intolerance of at least one TNFi. Beyond this, the FDA has not given specific guidance about use in special populations, leaving a void to be filled by professional body guidelines [17].

In contrast, the EMA's Pharmacovigilance Risk Assessment Committee, prompted by a multi-database observational cohort study on baricitinib [53], has produced specific guidance designed to "minimise the risk of serious side effects associated with Janus kinase (JAK) inhibitors," which include "cardiovascular conditions, blood clots, cancer and serious infections" [147]. Although yet to reach a final decision by the European Commission, the wording makes it clear that the EMA considers these to be class effects and that safety findings relating to tofacitinib "apply to all approved uses of JAK inhibitors in chronic inflammatory disorders" [147]. In the same vein, the Medicines and Healthcare products Regulatory Agency in the United Kingdom released a drug safety update highlighting the same risks and explicitly referring to these as "class effects across JAK inhibitors used for chronic inflammatory disorders" [148].

Although no JAK inhibitors have been removed from the market for any indication, the EMA has produced a series of recommendations designed to curtail their use in populations considered at higher risk. In particular, the EMA has recommended that, where alternative treatment options exist, JAKi should be avoided in patients with an extensive smoking history, baseline increased risk of cancer, increased cardiovascular risk, or age greater than 65. Further guidance has been given for healthcare professionals to conduct regular skin checks in patients prescribed a JAKi.

In response to these regulatory updates, several learned organizations have published statements and guideline updates. The 2022 European Alliance of Associations for Rheumatology guidelines for the management of RA provide the most comprehensive response and broadly reflect the EMA guidance, with caution recommended in the same risk groups as the EMA [149]. However, after extensive deliberation, the authors elected to keep JAKi on the same line of therapy as bDMARDs, thus deviating from the FDA-revised indication that necessitates trial of a TNFi. Published guidelines for RA management from other professional associations including ACR and the National Institute for Health and Care Excellence in England have yet to be updated to reflect these safety signals [150, 151]. Going forward, threading the needle between rigid rules and clinician discretion will be the great balancing act, particularly when many patients might derive great therapeutic value from being prescribed a JAKi.

The future landscape of JAKi is uncertain and will likely be shaped by the ongoing discussions surrounding their safety profile. While some guidelines have been established, further studies are necessary to give clinicians clear, evidence-based guidance. The delicate balance between patient empowerment and responsible prescription will remain a challenge for healthcare professionals. To mitigate risks, clear and evidence-based guidance on safe use will be crucial. As more data become available, it will be important for regulatory agencies and professional organizations to stay vigilant and continue to revise their recommendations accordingly. Ultimately, the goal must be to provide patients with the most effective treatments that are safe and well-tolerated, and this will require continued collaboration and communication between the medical community, regulatory agencies, and pharmaceutical companies.

7 Practical Approach for Clinicians

The cardiovascular and cancer risks attributable to JAKi, as demonstrated incrementally comparing tofacitinib versus TNFi in patients with RA with baseline cardiovascular risk in a rigorous phase 4 RCT, have proven challenging for many to interpret and act upon. This is largely because of the complexity of the context in which it sits. Data informing this risk have evolved substantially over the course of 10 years of registered use, but understanding relevant clinical implications requires an appreciation of the magnitude of risk in different diseases, against different comparators, with multiple other factors frequently contributing to that risk. In addition, there is an inherent stochasticity, not only in the development of cancer and cardiovascular adverse events following JAKi use, but also in the capacity of JAKi to achieve a clinical response, a clinical state which itself mitigates cancer and cardiovascular risk in many diseases, and there are few known predictive factors for either. It is unsurprising that the broader implications of this signal have been hard to interpret.

Clinicians have the advantage of considering single patients at a time but must ensure that rigor trumps exception in decision-making, and we propose a number of mitigating strategies useful in clinical practice (Box 1). This is necessary but challenging, as clinical scenarios quickly become complicated, even when considering the at-risk population with baseline cardiovascular risk. Patients with RA, the prototypic disease in which JAKi risk has mainly been studied, have multiple options at a similar stage of the disease algorithm, all with varying contraindications but equivalent efficacy. Among them, TNFi have a far greater depth of collective experience over 25 years, with a comparatively well-understood risk profile, and remain a hard standard to surpass. Perhaps, if JAKi for RA were considered in isolation without the context of a plethora of choice of effective RA therapies, the magnitude of risk would much less frequently outweigh potential efficacy gains, but for this indication JAKi are now held to the standard set by TNFi.

Box 1: List of mitigation strategies for clinicians

- Where equally efficacious therapeutic options exist
  - For new initiators, use as a later line of therapy behind safer but equally efficacious therapies
  - For ongoing users who have had ongoing therapeutic success, open and informed discussion about therapeutic risk/benefit, which might change with change risk or benefit considerations
- Where no equally efficacious therapeutic options exist: consideration of whether the difference in efficacy from other therapies (or no therapies) outweighs any difference in safety, noting tha t many alternative therapies also confer other risks
- Awareness of other risks from such therapy, knowing that risk factors for cardiovascular and cancer in JAKi patients may also confer other increased risks such as infection
- Ensuring age-appropriate screening is undertaken, noting practical challenges in ad hoc screening
- Optimization of risk mitigation strategies: using the opportunity for increased awareness and discussion, improve action on modifiable risk factors
- Counseling of patients, appreciating some inherent uncertainty exists
- Decision-making considering the complex needs of individual patients, dynamically responding to changes in risk-benefit analysis

Nevertheless, as for all bDMARDs, predicting TNFi clinical response in individual patients remains challenging. Among many choices, some patients may only clinically respond to a single therapeutic agent. Even once a response is achieved, it may dissipate over time despite optimal use, often due to the development of anti-drug immunogenicity. As a consequence, prescribers are wary of switching away from effective therapies on the basis of an incremental risk, particularly when such a switch might lead to a loss of response and a consequent increased cancer and cardiovascular risk. Additionally, a return to therapies previously effective in an individual patient may not confer the same clinical response as it did initially. It may therefore be inevitable that, despite known risk, some patients with RA will need a JAKi on a risk–benefit balance, and for some, exploring other therapeutic options after a JAKi response may be considered too risky in terms of losing clinical response. For other patients with known risk, if these caveats do not apply, JAKi use as a first-line therapy should be unpalatable on the basis of the patient's known risks. Categorizing patients appropriately remains a substantial challenge in clinical practice.

JAKi beyond RA may be less frequently employed, but often will have fewer therapeutic alternatives, and fewer data inform both benefit and risk in these situations. For some indications such as PsA, higher baseline risks and safer alternative options make such extrapolation across indications straightforward. For other indications, particularly for off-label use within orphan diseases, the few alternative therapeutic agents may be substantially less appealing than TNFi and may confer greater cancer or cardiovascular risks themselves. For this reason, it is critical that regulation does not confer undue practical impairment of access to such therapies among attempts to inform prescribers and patients of attendant risks.

Furthermore, the unknown capacity to extrapolate this risk within class creates greater uncertainty. This risk has only clearly been demonstrated for tofacitinib, and it remains plausible that some component of this risk is agent specific. Future data may help to inform this, particularly from post-marketing requirement studies for baricitinib currently underway, but such questions will likely remain incompletely answered with respect to other JAKi such as upadacitinib and filgotinib. In the absence of clear alternative explanations or meaningful points of differentiation within class beyond the theoretical benefits of JAK selectivity [51], it has to be considered that these agents cannot be completely exonerated and that some possibility of risk exists.

In fact, we may have to accept that we may never have data sufficient to inform every situation, and that RCTs may not be the most effective and informative tool in this respect. To some extent, we will need to accept some uncertainty, and that, at least within RA, calls for more data being required should carry limited weight. Uncertainty will not only need to be communicated with patients, but clinicians will also need to learn how to navigate uncertainty. To this end, guidance is useful, and if regulatory warnings are adopted with appropriate caveats and do not stymie personalized care for patients, then they can also play an important role in communicating risk to patients and prescribers.

This signal and the attendant changes it has already brought should rightfully have impacted clinician decision-making [152]. Regulation should drive awareness and lead concern among clinicians, but given competing clinical needs in practice, also rightfully does not appear to have substantially inhibited funding of JAKi in major jurisdictions, either when governed by health technology assessment

(HTA) bodies or private insurance. It is therefore incumbent on clinicians to not become complacent about either the risk that JAKi might confer on relevant patients, or the impact of the natural history of disease and the capacity of therapeutic agents to modify this. Other clinical factors may also already be relevant in therapeutic agent selection, including the expense of JAKi in contrast to price reductions in TNFi driven by patent expiry and biosimilar uptake in many jurisdictions. Therapeutic algorithms in the context of some HTA-based systems have already practically pushed JAKi to later lines of therapy. Other safety risks may also affect JAKi use in similar patient populations, including increased risk of general infection, herpes zoster, and VTE, and further therapeutic selection has likely occurred from this as well. Nevertheless, to help navigate this uncertainty, further practical guidance will be useful, particularly in high-risk groups such as those with a past history of cancer or cardiovascular disease. Learned bodies addressing practice in such areas will need to provide frameworks to help clinicians make responsible decisions as much as they possibly can. Constructive scrutiny of clinical prescribing practice in a collaboratively supportive manner, through peer or self-review, may also guard against aberrant practice and add to a milieu where clinicians can be confident of making better decisions.

Regulatory attention to cancer and cardiovascular risk from JAKi in such patients may be leading clinicians to be more conscious of managing and preventing these risks more broadly. A focus on safety should drive increased diligence for dedicated counseling and age-appropriate screening, and in some high-risk subpopulations there may be a role for engagement with dedicated programs or screening techniques such as CT coronary angiogram. Many other factors such as smoking and obesity may realistically confer higher magnitudes of risk, and risk factor modification remains of great importance, particularly given advances in their non-pharmacological and pharmacological management. This could, and should, signal a broader holistic approach to medicines' safety amongst sub-specialty prescribers, who may otherwise be tempted to neglect the broader health needs of their patients. Better strategic health service interventions are also likely to be needed to improve screening and implement appropriate preventative medicine in patients [153].

Practically, navigating this process for individual patients necessitates some element of joint decision-making, and in this, patient preferences matter. Many different individual patient factors will be important. Not all will be of equal weight: even when an oral mode of action might influence patient choices, its importance is likely to be contextual to other risks and benefits for most patients. Key contributors to patient impression include the primary diagnosis and its functional impact, previous cancer and cardiovascular disease experience (both personal and sociocultural), and previous JAKi experience. Some patients will be able to contextualize their own risk, but others will need assistance, and a lack of unbiased patient-facing information remains an unmet need. Ultimately, however, most patients will seek substantive guidance from their treating clinicians, and it behooves clinicians who might prescribe JAKi to become more skilled at such counseling.

Thankfully, such conversations are not without precedent, albeit in different contexts [154]. Rheumatology prescribers frequently counsel regarding NSAIDs and cardiovascular disease and concerns previously held about TNFi and cancer risk, although these therapeutic scenarios are largely more straightforward in terms of efficacy in context. Furthermore, expectations for therapeutic outcomes have changed across autoimmune diseases, particularly regarding quality of life and disease-related disability, and there is a greater appetite for therapeutic action in a treat-to-target manner across many relevant diseases than previously. It is also plausible that changes in understanding, therapeutic agent cost, or baseline risk may change the considered risk–benefit balance as it stands. A variety of different responses might be appropriate, but if JAK inhibitors are to be prescribed at all, and certainly if they are to be prescribed contrary to regulatory guidance, all clinicians considering JAKi will need to make, communicate, and document decisions on the basis of the complex needs of individual patients, dynamically responding to changes in risk–benefit analysis.

At present, this essential compound risk calculation will require the clinician to consider many factors in tandem [152]. Baseline risk and baseline benefit from JAKi differ between patients. Given disease-related factors already are hard to categorize and quantify, and clinical scenarios are often complex, this calculation will often rely solely on rough mental calculus. Having said this, a diversity of clinical scenarios and a need to consider individual patient scenarios should not be a veil for ignoring risk. It is undoubtedly true that there are other therapies and disease states that have greater cancer or cardiovascular risk quotients but have unsolved risk calculation, although this is arguably true of some metabolic syndrome risk factors as well. Nevertheless, the knowledge that long-term therapeutic choices might lead to unnecessary iatrogenic changes in risk should mean that improving decision-making remains a priority. This remains a gray area in which the development of new technologies may lead to better risk–benefit calculation to inform both clinicians and patients as one possibility, and while this process of shared-decision making is complex, machine-learning-driven recommendations and dynamic decision support for optimal therapeutic agent selection in the future could improve both safety and efficacy [155, 156]. Until then, patients will rely on clinicians to consider many factors relevant to their individual situation, communicate those

factors clearly to them, mitigate risk wherever possible, and make the best shared decisions they can.

8 Conclusion

Many questions remain around the safety of JAKi and how they fit in the landscape of RA treatment as well as other inflammatory diseases. From a mechanistic perspective, further research is required to explain the cardiovascular and cancer risks observed, and clinically, comparisons among the different JAKi will help to determine if a class effect is indeed at play. We clinicians are no strangers to uncertainty, and it is prudent that we continue to share the decision-making process with our patients at this time.

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Declarations

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