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Review

Implementation of regulatory guidance for JAK inhibitors use in patients with immune-mediated inflammatory diseases: An international appropriateness study

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ABSTRACT

Background and Aims: The Pharmacovigilance Risk Assessment Committee (PRAC) proposed measures to address severe side effects linked to Janus kinase inhibitors (JAKi) in immune-mediated inflammatory diseases (IMID).

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Use of these medications in individuals aged 65 and older, those at high cardiovascular risk, active or former long-term smokers, and those with increased cancer risk should be considered only if no alternatives exist. Caution is advised when administering JAKi to patients at risk of venous thromboembolism. We aim to implement recommendations from regulatory guidelines based on areas of uncertainty identified.

Methods: A two-round modified Research and Development/University of California Los Angeles appropriateness methodology study was conducted. A panel of 21 gastroenterologists, dermatologists and rheumatologists used a 9-point Likert scale to rate the appropriateness of administering a JAKi for each proposed clinical scenario. Scores for appropriateness were categorized as appropriate, uncertain, or inappropriate. Two rounds were performed, each with online surveys and a virtual meeting to enable discussion and rating of each best practice.

Results: Round 1 involved participants rating JAKi appropriateness and suggesting descriptors to reduce uncertainty. Survey results were discussed in a virtual meeting, identifying areas of disagreement. In round 2, participants rated their agreement with descriptors from round 1, and the level of uncertainty and disagreement reduced. Age flexibility is recommended in the absence of other risk factors. Active counseling on modifiable risks (e.g., overweight, mild hyperlipidemia and hypertension) and smoking cessation is advised. Uncertainty persists regarding cancer risk due to various factors.

Conclusions: We outlined regulatory guidance without a personalized evaluation of the patient's risk profile might lead to uncertainty and become an arid technicality. Therefore, we identified gaps and implemented PRAC recommendations to help health professionals in clinical practice.

1. Introduction

The ORAL Surveillance (NCT02092467) was a phase IIIb/IV randomized, open-label, non-inferiority study focusing on safety endpoints [1]. The trial aimed to establish the non-inferiority of tofacitinib in comparison to TNF inhibitors (TNFi) in patients with rheumatoid arthritis (≥50 years older with at least 1 cardiovascular risk factor) for the co-primary outcomes of adjudicated major adverse cardiovascular events (MACE) and adjudicated malignancies (excluding non-melanoma skin cancer). Over a median follow-up period of 4.0 years, the occurrences of MACE and cancer were more frequent with tofacitinib (3.4% [98 patients] and 4.2% [122 patients], respectively) compared to a TNF inhibitor (2.5% [37 patients] and 2.9% [42 patients]). The hazard ratios were 1.33 (95% confidence interval [CI], 0.91 to 1.94) for MACE and 1.48 (95% CI, 1.04 to 2.09) for cancers, ultimately demonstrating that the noninferiority of tofacitinib was not established.

Based on the above findings of the ORAL surveillance trial and those of the B023 study for baricitinib [2], the Pharmacovigilance Risk Assessment Committee (PRAC) proposed measures to mitigate the severe side effects linked to Janus kinase inhibitors (JAKi) used for treating chronic inflammatory diseases [3]. These effects encompass cardiovascular problems, venous thromboembolism (VTE), cancer, and serious infections. For individuals aged 65 and above, those with an increased risk of significant cardiovascular complications, active or former long-term smokers, and those with an elevated cancer risk, these medications should only be considered *if no suitable alternatives are available*. Caution should be exercised when administering JAKi to patients with factors that increase the risk of VTE, beyond the categories mentioned earlier [4–6]. Furthermore, reducing the dosage is recommended for patient groups at risk of VTE, cancer, or major cardiovascular problems, whenever possible. The European Medicines Agency (EMA) has concluded that these safety findings apply to all approved uses of JAKi in immune-mediated inflammatory diseases (IMID) such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis, and alopecia areata.

Due to potential variations in the interpretation of regulations by different physicians, coupled with specific clinical recommendations for patient selection for JAKi use in each IMID, the implementation of regulatory guidance is of utmost importance [7–11].

Therefore, we conducted a modified Research and Development/University of California, Los Angeles (RAND/UCLA) appropriateness methodology (RAM) study with a panel of international gastroenterologists, dermatologists, and rheumatologists with expertise in IMID management.

The study aimed to: (1) determine the most suitable indications and clinical scenarios for administering JAKi in clinical practice; and (2) implement recommendations from regulatory guidelines based on identified areas of uncertainty.

2. Materials and methods

The RAM process is an evidence-based approach that employs a modified multiple-round Delphi panel to determine the appropriateness and face validity of a list of generated items [12]. We used a modified RAM systematic approach to ensure a thorough and collaborative evaluation of the appropriateness of JAKi administration, incorporating expert opinions and refining assessments through iterative rounds of evaluation and discussion.

A global panel comprising 21 gastroenterologists, dermatologists, and rheumatologists from 11 different countries received invitations to engage in the adapted RAM process. Panelists were chosen for their proficiency in managing IMID.

2.1. Vignettes generation

Regarding the generation of vignettes, the modified RAM employed an online survey, drawing insights from previous regulatory directives by EMA, as well as expert opinions. Senior experts AC, LEK, LPB and SD collaborated to devise the original survey (Supplementary Material). They accomplished this by formulating a range of cases relevant to prevalent clinical scenarios with varying cardiovascular risk.

2.2. First survey and analysis results

A web-based survey comprising 27 clinical vignettes (Supplementary Appendix), encompassing various indications for JAKi such as ulcerative colitis, atopic dermatitis, alopecia areata, psoriatic arthritis, axial spondylarthritis, and rheumatoid arthritis was administered to experts. Experts were asked to individually assess the JAKi administration in each scenario, categorizing it as appropriate, inappropriate, or uncertain and to evaluate cases related only to their areas of expertise. Prior to evaluation, panelists were encouraged to consult regulatory guidance from EMA and express their judgment using a 9-point Likert scale (1 for highly inappropriate, 5 for uncertain, and 9 for highly appropriate).

In the subsequent score analysis, the overall appropriateness of JAKi in each clinical vignette was determined as inappropriate, uncertain, or appropriate based on two criteria: (1) the median panel rating and (2) the presence of any disagreement. Disagreement was defined as a voting span equal to or exceeding 4.

Inappropriate statements were defined by median ratings of 1 to 3.5 without disagreement; uncertain statements were defined by median

ratings of >3.5 to 6.5 with or without disagreement or any median rating with disagreement; appropriate statements were defined by median ratings of >6.5 to 9 without disagreement.

Results of the initial survey were distributed to the panelists and discussed in a moderated videoconference per specialty. Areas of disagreement and uncertainty regarding JAKi administration's appropriateness were identified and panelists were asked to explain the rationale behind their responses.

Notably, the modified RAM process did not force a consensus but aims to evaluate the appropriateness of the use of JAKi in each clinical vignette. This involves integrating expert perspectives and fine-tuning evaluations through analysis and discussion.

2.3. Second survey

A revised survey including the same vignettes with comments from discussion was recirculated for a second round of voting. The panelists were invited to vote considering their previous voting and the feedbacks emerged from the discussion.

3. Results

The overall duration of the modified-RAM process was approximately 6 months from vignettes development to the end of the second videoconference, with 60 min allotted for each videoconference. All 21 panelists completed both surveys.

3.1. Round 1

The round 1 data was collected within 14 days of distributing the online questionnaire.

The clinical scenarios for each specialty, the results of the first surveys and the specific comments of the experts for each clinical case are reported in Tables 1, 2, and 3 for gastroenterology, dermatology, and rheumatology, respectively.

Five out of nine clinical vignettes about gastroenterology were rated uncertain, whereas all dermatologic clinical vignettes were rated as uncertain since all of them obtained a voting span equal to or superior to 4. Eight out of nine rheumatologic clinical vignettes were rated uncertain, and one as appropriate.

Some common points emerged during the discussions of all three specialty groups (Table 4).

Addressing modifiable cardiac risk factors, such as slightly increased body mass index (BMI), smoking with a willingness to quit, hypertension, and dyslipidemia were recognized as opportunities for active counseling and cardiovascular risk reduction, evident in various clinical scenarios across gastroenterology (clinical scenario 2, 4, 7), dermatology (clinical scenario 2, 9), and rheumatology (clinical scenario 2, 5).

However, uncertainties were noted, including the ambiguity surrounding the cut-off for prior history of cancer (> 10 years) (gastroenterology clinical scenario 3), the type of cancer (virus-associated vs. non-associated) and staging in certain dermatology (clinical scenario 4) and rheumatology scenarios (clinical scenario 6). Additionally, there was uncertainty on how to manage VTE during JAKi maintenance treatment leading to clinical remission (gastroenterology clinical scenario 5). Moreover, if a clear external causative factor for VTE could be identified (e.g., prolonged immobilization following a motor-vehicle accident), experts tended to agree this should not be considered as a potential risk factor (gastroenterology clinical scenario 5, dermatology clinical scenarios 3). Uncertainty leaning to inappropriate use was highlighted for individuals with distinct, readily identifiable risk factors such as age 65 years or older and long-time smoking (current or past) (gastroenterology clinical scenario 6, dermatology clinical scenario 5), while appropriateness was emphasized in cases where past smoking history had been discussed and recommendations made (gastroenterology clinical scenario 8) or hypertension was controlled under medication (gastroenterology clinical scenario 9, dermatology clinical scenarios 9).

In the specialty-specific discussions, gastroenterology patients' vignettes prompted specific comments on elements deemed appropriate before the administration of JAKi. Experts highlighted the need for flexibility around the age cut-off, particularly in gastroenterology clinical scenario 1. Additionally, appropriateness was emphasized in challenging cases involving difficult-to-treat patients with multiple failures, along with extra-intestinal manifestations (EIM). Physicians acknowledged the value of rapid improvement in symptoms and emphasized the importance of patient-reported outcome measures (PROMs), such as enhanced quality of life, as indicators of appropriateness (gastroenterology clinical scenario 4).

Within the dermatology panel discussions, considerations regarding a proper therapeutic choice, comprising discussion on alternative treatments for atopic dermatitis and alopecia areata surfaced. The presence of atopic comorbidities, such as allergic asthma or specific features such as prurigo nodularis, was noted to favor alternative treatments like anti-IL (dermatology clinical scenario 1 and 6) over the introduction of JAKi. Conversely, JAKi were deemed appropriate in young patients without comorbidities (dermatology clinical scenario 7 and 8). In certain cases, while JAKi were not considered entirely inappropriate, other available treatments appeared to be more suitable as a first line of intervention (dermatology clinical scenarios 1, 2, 5). Notably, uncertainty surrounded the decision of who and when to administer the herpes zoster conjugated vaccine in dermatology clinical scenario 2.

In the context of rheumatology, discussions focused on axial spondylarthritis, rheumatoid arthritis, and psoriatic arthritis patients' vignettes, and physicians identified specific elements deemed appropriate prior to the administration of JAKi. Noteworthy inquiries revolved around the consideration of switching the mode of action versus cycling within the same mode of action after treatment failure (clinical scenario 3, 6, 9), whether occurring early or late, highlighting existing data gaps. Additionally, discussions brought attention to the lack of evidence regarding the relative risk-benefit comparison between TNFi and JAKi. This concern stemmed from the ORAL Surveillance study, which specifically targeted patients with active rheumatoid arthritis despite methotrexate medication and with at least one cardiovascular risk factor, leaving a void in understanding the comparative efficacy and safety profiles between the two treatment approaches. In some cases, rheumatologists considered that JAKi could be appropriate as the patient did not have a high-risk profile; nevertheless the appropriateness of JAKi in such a case ended up being down-graded, due to the existence of several alternatives. In fact, the experts favored other treatments due the larger experience in clinical practice and the stronger evidences on safety particularly in patients with multimorbidity. Cost of treatment was also a factor that influenced the therapeutic choices.

3.2. Round 2

A revised survey including the same vignettes with comments from discussion was recirculated for a second round of voting. The panelists were invited to vote considering their previous voting and the feedback emerged from the discussions.

The data for round 2 were collected within 14 days of distributing the online questionnaire.

For the gastroenterology clinical vignettes, voting span either reduced or remained stable in each clinical vignette. Of 5 uncertain responses in the first round, 1 was changed to appropriate (clinical scenario 5 from 5.3 to 7, disagreement from 5 to 3), whereas the remaining 4 clinical vignettes were uncertain with reduced voting span and level of disagreement decreased after proper discussion (clinical scenarios 2,3,6 and 7). In these cases, JAKi are not absolute contraindications, but other treatments such as ustekinumab or TNFi are considered more suitable initially (Table 1).

For the dermatologic clinical vignettes, there were 5 changes in the

Table 1
Gastroenterology clinical vignettes.

	Clinical vignette	Risk factors	Round 1				Round 2			
			Result (1–9, median)	Voting span	Level of appropriateness	Comments	Result (median)	Voting span	Level of appropriateness	Comments
1	- E2 UC, M, 66 y/o - Non-smoker - 5-ASA and biologic failure (vedolizumab and infliximab) -MCS = 9, MES = 3 -CRP 8 mg/L -Active lifestyle	Age	7.2	3	Appropriate	Not completely in accordance with regulatory guidance	6.7	1	Appropriate	Flexibility around age: the cut-off of 65 years to define elderly should be personalized. The patient has no significant comorbidities
2	-E3 UC, M, 53 y/o -BMI = 27 -5-ASA and adalimumab failure -MCS = 8, MES = 3 -CRP 7 mg/L -PsA, uveitis and inactive lifestyle	-risk of major CV (overweigh, inactivity) -EIM (uveitis and PsA)	6.3	5	Uncertain	JAKi should be considered only after UST theoretically but BMI = 27 is the only risk factors that can be addressed easily JAKi would work on PsA as well, contrary to vedolizumab	6.4	1	Uncertain	JAKi are not absolutely contraindicated, but other treatments are more indicated first. Mild modifiable cardiac risks are opportunity to improve overall health - needs active counseling re: cardiac risk reduction
3	-E2 UC, F, 45 y/o Prior history of cervical cancer 10 years ago, in oncological remission -Failure of conventional therapy (5-ASA and thiopurine) and vedolizumab -MCS = 9, MES = 2 -CRP 9 mg/L, FCAL 200 μg/g -Struggles to make time for hospital appointments -Bleeding and urgency deeply affecting QoL	Likely increased risk of cancer (history of cervical cancer)	5.8	5	Uncertain	Need for definition of oncological remission by the referring oncologist	6.2	4	Uncertain	JAKi are not absolutely contraindicated, but other treatments should be discussed with the patient taking into account his/her willingness
4	-E3 UC, M, 41 y/o -current smoker but willing to quit -Infliximab and vedolizumab failure -MCS = 8, MES = 2 -CRP 6.5 mg/L, FCAL 250 μg/g -Atopic dermatitis, anxiety -Asking for rapid improvement in symptoms	Smoker	7.2	3	Appropriate	Patient's willingness to quit smoking and therapy goal (rapid improvement in symptoms). Not completely in accordance with regulatory guidance	7.1	3	Appropriate	Appropriate with patient education about risk factors. Patient is willing to quit smoking and JAKi would work on atopic dermatitis Rapid improvement in symptoms as priority
5	-E2 UC, F, 29 y/o -Prolonged period of immobility due	VTE	5.2	5	Uncertain	Referral to coagulation expert is key, before resuming JAKi therapy	7	3	Appropriate	JAKi are not absolutely contraindicated, since patient is in

(*continued on next page*)

Table 1 (*continued*)

	Clinical vignette	Risk factors	Round 1				Round 2			
			Result (1–9, median)	Voting span	Level of appropriateness	Comments	Result (median)	Voting span	Level of appropriateness	Comments
	to an accident -Infliximab and vedolizumab failure -Long-term treatment with tofacitinib (>1 year). Currently prescribed 5 mg BID tofacitinib with CS-free clinical remission -MCS = 1 -CRP <5 mg/L									clinical remission and VTE is associated with immobility after accident. Always need for referral to coagulation expert and discussion with the patient
6	-E1 UC, M, 49 y/o -Smoker that switched to e-cigarettes 6 months ago -Family history for CV disease -Failure to Vedolizumab -MCS = 8, MES = 2 -Diabetes on metformin	Increased risk of major CV problems (family history, diabetes) -smoker (recently switched to e-cigarettes)	4.1	6	Uncertain	Diabetes and positive family history for CV events should be taken into account	4.4	5	Uncertain	Favor other available treatments (e.g. UST)
7	-E2 UC, F, 51 y/o, -Hypertension, high-density lipoprotein <40 mg/dL -5-ASA and biologic failure (vedolizumab) -MCS = 1 11, MES = 3 -CRP 5.5 mg/L -Motivated to resume active lifestyle and improve QoL	Increased risk of CV problems (hypertension, dyslipidemia)	5.3	4	Uncertain	Available alternative options	4.8	4	Uncertain	JAKi are not absolutely contraindicated, but other treatments (e.g. UST, TNFi) are more indicated first
8	-E2 UC, 42 y/o -Smoker for 4 years, >10 years ago -5-ASA and biologic failure (infliximab) -MCS = 10, MES = 3 -CRP 18 mg/L -Active lifestyle	None (Prior smoker >10 years ago)	7.9	2	Appropriate	Discuss past smoking history and recommendations. If patient is agreeable, then JAKi probably best for deep remission	7.8	2	Appropriate	Ideal patients for JAKi: young, no comorbidities
9	-E3 UC, 51 y/o —Non- smoker -Hypertension controlled under medication -5-ASA and biologic failure (infliximab and vedolizumab) -Steroid-refractory -MCS = 1, MES = 3 -CRP 15 mg/L -Active lifestyle	None (hypertension controlled under medication)	7.6	3	Appropriate	Hypertension is under control	7.4	3	Appropriate	Appropriate with patient education about risk factors

ASA, 5-aminosalicylic acid; BMI, Body Mass Index; CRP, C-reactive protein; CS, corticosteroids; CV, Cardiovascular; E1, disease limited to the rectum; E2, left-sided disease (distal to splenic flexure); E3, extensive colitis (disease extends proximal to splenic flexure); EIM, Extra-intestinal Manifestation; FCAL, Fecal Calprotectin; JAKi, JAK inhibitors; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Subscore; PsA, Psoriatic arthritis; QoL, Quality of Life; UC, Ulcerative Colitis; UST, ustekinumab.

rating. Of 9 uncertain responses in the first round, 4 were changed to appropriate (clinical scenario 3, 7, 8 and 9), whereas one changed to inappropriate (clinical scenario 4). Of the 4 clinical vignettes that remained uncertain, only 1 had a voting span of 4, suggesting that the level of disagreement decreased after proper discussion. The uncertainty of these 4 clinical vignettes was due mainly to the preference of alternative treatment and not to an absolute inappropriateness of JAKi (Table 2). The gray areas that remained object of disagreement were mainly related to borderline cases in which the presence of risk factors would make low dose JAKi an alternative to other available treatments.

For the rheumatologic clinical scenarios, vignettes 3,6,8 and 9 changed from uncertain to inappropriate due to a decrease in voting span after proper discussion (Table 3). Furthermore, these vignettes illustrated scenarios in which the patient presented non-modifiable, strong contraindications for the use of JAKi's, such as prior ST-elevation myocardial infarction (STEMI), unstable angina pectoris or previous/ongoing history of cancer. Gray areas that still led to disagreement after the second round, evolved around cases with modifiable risk factors and cases with moderate to no risk factors where multiple treatment options beside JAKi were viable.

4. Discussion

JAKi represent an emerging and resourceful class of drugs to treat many IMID [13,14]. The EMA PRAC decision was emanated, mainly based on the results of the ORAL surveillance study to raise caution regarding the use of JAKi in specific categories of patients that were considered at high risk. However, there is still uncertainty regarding how to translate this warning into clinical practice and without considering these individual nuances, regulatory guidance might offer a generic approach that does not fully address the complexities of real-world clinical scenarios.

Optimal treatment choice is a complex process. The accurate assessment of JAKi appropriateness is paramount as part of a treat-to-target strategy in the field of IMID – and in particular when potential risk factor(s) are present. Therefore, we used a modified RAM process to develop guidance on the management of various and common scenarios in clinical practice. The use of clinical vignettes allows comparisons of the indications in clinical practice, in concordance with published EMA and Food and Drug Administration (FDA) guidance. Clinical vignettes have been used in multiple settings to evaluate medical decision making and have been validated against chart abstraction and standardized patients to evaluate quality of care [15–18].

Our results suggest that physician concordance with published EMA and FDA recommendations for clinical vignettes is generally not uniform across a broad spectrum of JAKi indications across multiple IMID. Instead of strictly adhering to a "one-size-fits-all" approach where certain drugs were completely ruled out, experts seemed to prefer assessing and managing risks on a case-by-case basis rather than outright restricting the use of a particular drug. Notably, there was uncertainty and disagreement on the panel regarding several clinical scenarios. After the second round of survey a higher level of agreement was achieved, but some gray areas still remain.

Therefore, in our commitment to enhancing regulatory guidance, we have recognized the necessity of personalized evaluations when assessing patient risk profiles (Fig. 1). Taking a cue from the PRAC recommendations, our implementation strategy aims to apply flexibility into age considerations, especially when devoid of other substantial risk factors. We advocate for active counseling by health professionals, addressing modifiable risk factors (e.g., overweight, dyslipidemia, hypertension without other relevant risk factors) and emphasizing optimization of treatments based on individual needs (e.g., lifestyle, and PROM including quality of life). Additionally, our approach includes dedicated counseling on smoking cessation, extending flexibility to light smokers (meaning 1–5 cigarettes) willing to quit in the absence of other risk factors. Uncertainty remains around e-cigarettes smokers, given the potential long-term effects of e-cigarette consumption have been scarcely studied [19]. Uncertainty was mainly related to cancer history and borderline cases in which the presence of risk factors would favor other available treatments. About prior cancer history and risk, we acknowledged the complexity surrounding factors such as cancer type, stage, length of history, and treatment options, advocating for a personalized evaluation process.

Moreover, when assessing safety profile, different parameters need to be taken into consideration. Firstly, the underlying disease can expose the patient to specific risk, secondly the safety profiles differ among different JAKi.

In a recent safety analysis including data from clinical trials of upadacitinib and 6991 patients (rheumatoid arthritis, $n = 3209$; psoriatic arthritis, $n = 907$; ankylosing spondylitis, $n = 182$; atopic dermatitis, $n = 2693$) different risk profiles were evidenced for this drug based on the treated disease. Serious treatment emergent adverse events were numerically higher in patients with rheumatoid arthritis and psoriatic arthritis, while the rates of MACE, VTE, and malignancies were typically at their lowest in radiographic axial spondyloarthritis (also known as ankylosing spondylitis) and atopic dermatitis [20,21]. Interestingly, as a confirmation that the baseline altered immune and inflammatory profile of each disease can influence the safety profile, increased rates of acne were observed in patients with atopic dermatitis only [20].

There is increasing evidence that tofacitinib is safe and effective in patients with IBD, including those with difficult-to-treat disease [22–24]. The REMIT-UC study provided a comprehensive real-world evaluation of tofacitinib safety with 375 patient-years of follow-up. Key observations include a significantly lower incidence of herpes zoster compared to clinical trial data, potentially linked to vaccination. Regarding thrombosis and cardiovascular risk, VTE rates were low with occurrences in patients with preexisting risk factors (prior thrombosis, active malignancy, and post-surgery), and MACE were not observed [23]. The evidence from real-world study enriches the understanding gained from clinical trials integrated analysis (NCT00787202, OCTAVE Induction 1 and 2, OCTAVE Sustain, OCTAVE Open, and the RIVETING) suggesting that tofacitinib has a favorable safety profile over the studied period [25]. More selective JAKi such as upadacitinib and filgotinib introduces an interesting perspective, due to the increased selectivity that might lead to a more favorable benefit–risk profile. So far, data comes from clinical trials that are underpowered to capture rare adverse events. However, evaluation of safety outcomes coming from systematic reviews and metanalyses including upadacitinib and filgotinib trials in IBD are generally reassuring [26,27].

Regarding dermatological indications, recent real-world data seems to confirm a favorable safety profile of JAKi [28,29]. The most common side effects in real-world data studies on upadacitinib for atopic dermatitis consist mainly in acne and laboratory test abnormalities, including alterations of the lipid profile. Two serious adverse events have been reported [28,29]: a case of thrombophlebitis in a patient with other concomitant risk factors and one case of metastatic pancreatic carcinoma that was diagnosed after 4 weeks of treatment with upadacitinib [26]. When evaluating the efficacy and safety of the three available JAKi approved for atopic dermatitis (abrocitinib, upadacitinib and baricitinib) in a meta-analysis, upadacitinib 30 mg seemed to be superior in efficacy to the other JAKi, but was also associated with a higher frequency of side effects [30].

Overall, the results from the rheumatology vignettes for the appropriateness of the use JAKi generally reflect the most recent

Table 2
Dermatology clinical vignettes. Dermatologic clinical vignettes that were object of the survey.

	Clinical vignette	Risk factors	Round 1				Round 2			
			Result (1–9, median)	Voting span	Level of appropriateness	Comments	Result (median)	Voting span	Level of appropriateness	Comments
1	- AD, M, 19 y/o - Light smoker - Allergic asthma - No previous biologics	Smoker	6.0	4	Uncertain	Asthma as a comorbidity: favor dupilumab as a first choice	5.00	4	Uncertain	JAKi are not absolutely contraindicated, but other treatments are more indicated first
2	- AD, F, 32 y/o - BMI 28 - Previous use of dupilumab - Eczema herpeticum in the past - OCP for PCOS	BMI 28	5.5	4	Uncertain	Favor another anti-IL because of eczema herpeticum. Advise patient to vaccine against H. zoster	5.00	3	Uncertain	JAKi are not absolutely contraindicated, but other treatments are more indicated first
3	- AD, M, 52 y/o - VTE 2 years before following a MV accident - Family history of MI - HTN and hyperlipidemia under control with medications - Previous failure of tralokinumab and dupilumab	VTE, HTN and hyperlipidemia. family history of MI	6.0	5	Uncertain	This is a severe case with many risk factors. Each risk factor needs to be carefully evaluated: VTE was due to an external cause (MV accident), HTN and hyperlipidemia are under control, FH of MI is the only strong risk factor in this case. Due to the failure of other available treatments, low dose JAKi is indicated	7.5	2	Appropriate	Due to other treatment failures, low dose JAKi is indicated
4	- AD, M 58 y/o - Ex smoker - Severe pruritus NRS 9/10 - Prostate cancer 6 years before, under remission	Previous history of cancer. Ex smoker	5.0	6	Uncertain	There is no clear cut-off regarding cancer: it is important not only to consider time since cancer remission, but also to evaluate the type of cancer and the stage. Favor other available treatments (e.g. dupilumab)	3.0	3	Inappropriate	Favor other available treatments (e.g. dupilumab)
5	- AD, M, 67 y/o - Stable angina and HTN under medication - Sub-erythrodermic - Previous failure of dupilumab	Age above 65. Stable angina and HTN	7.0	6	Uncertain	In the presence of CV risk factors, it is safer to try other biologics	4.0	2	Uncertain	Other biologics or low dose JAKi are indicated
6	- AD, F, 64 y/o - Family history of CV disease, HTN and diabetes - HTN, diabetes on metformin, anxiety - Prurigo-nodularis associated features, NRS pruritus 9/10	Diabetes, HTN, Family history of CV diseases	4.5	4	Uncertain	Clinical presentation as prurigo nodularis: favor dupilumab	3.5	2	Uncertain	Clinical presentation as prurigo nodularis: favor dupilumab

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Table 2 (*continued*)

	Clinical vignette	Risk factors	Round 1				Round 2			
			Result (1–9, median)	Voting span	Level of appropriateness	Comments	Result (median)	Voting span	Level of appropriateness	Comments
	- No previous biologic therapies									
7	- AD, F, 20 y/o - No previous biologic therapies	None	9.0	7	Uncertain	Some experts believe this is the ideal patient for JAKi, others would favor other treatments	9.0	1	Appropriate	Ideal patients for JAKi: young, no comorbidities
8	- AA, M, 20 y/o - Mild AD since infancy	None	9.0	6	Uncertain	Ideal patients for JAKi: young, no comorbidities	9.0	1	Appropriate	Ideal patients for JAKi: young, no comorbidities
9	- AA, F, 42 y/o - Smoked - HTN controlled with life-style modification - FH of diabetes	Smoker, HTN, FH of diabetes	6.5	7	Uncertain	Counsel patient regarding the profile risks and how to minimize risk factors: smoke is modifiable, HTN can be controlled. AA patients need to be fully aware of the risks to make an informed decision	8.0	1	Appropriate	Appropriate with patient education about risk factors

All atopic dermatitis cases and alopecia areata cases are severe (EASI>24 and SALT>90 respectively) and eligible for systemic therapies with JAKi. AA, alopecia areata; AD, atopic dermatitis; CV, cardiovascular; FH, family history; HTN, hypertension; IL, interleukins; MI, myocardial infarction; MV, motor vehicle; NRS, numeric rating scale; OCP, oral contraceptive pill; PCOS, Polycistic ovary syndrome; VTE, venous thromboembolism.

recommendations for the use of JAKi's in psoriatic arthritis, axial spondylarthritis, and rheumatoid arthritis provided by European Alliance of Associations for Rheumatology (EULAR), only prompting for a JAKi use in low risk scenarios and when other more suitable modes of actions had already failed [31–33]. To note, a post hoc analysis of the ORAL Surveillance trial effectively identifies two distinct subpopulations within tofacitinib rheumatoid arthritis users, characterized by different relative risk profiles compared to TNFi. The 'high-risk' group is notably linked to specific risk factors such as age 65 years or older, current or former smokers, and history of atherosclerotic cardiovascular disease [34]. These distinguishing risk factors were responsible for the elevated risk noted in tofacitinib treated [10]. For patients considered 'low-risk'—those under the age of 65 who had never smoked but exhibited other prevalent cardiovascular risk factors—no discernible increase in risk (HRs ≈ 1) was observed when compared to TNFi over a follow-up period of up to 6 years. The absolute risk remained minimal and was consistently supported across tofacitinib programs spanning up to 10 years of observations [35]. The results of this ORAL surveillance trial post hoc analysis highlight the relevance of personalized risk assessments, providing insights into the safety profile of JAKi across different subgroups, and encouraging a thoughtful reflection on potential implications for clinical practice and treatment guidelines. The same conclusion were reached in other retrospective studies showing no major safety signals in patients with rheumatoid arthritis treated with JAKi [36,37].

Our study has some important strengths. We employed a validated modified RAM process and assembled a panel of experts in IMID to assess clinical scenarios. The paramount importance of adhering to current regulatory guidance on this topic is a focal point of our approach. Notably, our study refrains from forcing consensus, and its strength lies in the inclusion of internationally recognized IMID experts, all experienced in advanced therapy use and regulatory guidance. In assessing appropriateness, the recognition of specialists' responsibilities indirectly highlights cost differences. In fact, by understanding that specialists consider cost considerations in their decision-making process, the study acknowledges the complex interplay between medical appropriateness and economic factors. This comprehensive strategy seeks to transcend mere technicalities, addressing uncertainties and providing health professionals with a robust framework for clinical practice.

While acknowledging these strengths, we also recognize certain limitations. Firstly, the vignettes are based on the opinions of panelists rather than empirical evidence. Their purpose is to encompass the empirical variety of clinical scenarios encountered in daily practice. The study could not adopt a more rigorous methodology to minimize bias due to the intrinsic subjectivity of clinical decision-making, particularly in challenging clinical scenarios. Despite efforts to standardize and make the cases comparable across different medical specialties, some cases ended up having more cardiovascular risk factors or history. This variability may have influenced the decision-making process, particularly in rheumatology, leading to more conservative approaches. This transparency about limitations adds integrity to our study by acknowledging the inherent complexities and potential biases in our chosen methodology.

PRAC recommendations, informed by a more personalized understanding of risks and benefits, provide health professionals with nuanced insights. This helps them make informed decisions tailored to the unique characteristics of each patient, reducing uncertainty, and ensuring a more effective and patient-centered approach to healthcare.

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Authors' contributions

All authors have made substantial contributions and reviewed and approved the final manuscript.

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Analysis/interpretation and manuscript editing for important intellectual content: all authors.

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Table 3
Rheumatology clinical vignettes.

	Clinical vignette	Risk factors	Round 1				Round 2			
			Result (1–9, median)	Voting span	Level of appropriateness	Comments	Result (median)	Voting span	Level of appropriateness	Comments
1	- axSpA, M, 32 y/o - Purely axial disease. After adalimumab failure ASDAS score increase from 1.5 to 2.4. CRP 6 mg/L. MRI showing SI-joint active inflammation with enthesitis and new bone formation - Failed adalimumab - Lately increase in disease activity	None	8	5	Uncertain	An IL-17i is preferred at this stage	8	5	Uncertain	According to PRAC, JAKi can be given since he has no risk factors. But in clinical practice one would try IL-17i first (more known safety profile).
2	-axSpA, F, 70 y/o - Diet and exercise-controlled hypertension - Purely axial disease. After infliximab failure ASDAS score increase from 1.7 to 2.3. CRP 7 mg/L. - Osteoporosis - Ulcerative colitis - Failed adalimumab and infliximab	- Age 70 - Diet and exercise-controlled hypertension	5	6	Uncertain	Failure of 2 monoclonal antibodies against TNF and ulcerative colitis. TNFi are not a suitable option, IL-17i less desirable, JAKi also less desirable because of CV risk and age. Information needed on the activity of the ulcerative colitis. Shared decision making is important. Use of JAKi at reduced dose in absence of alternative. Possibly appropriate as hypertension is controlled	5	4	Uncertain	More risk factors, but also higher indication for JAKi (failure to TNFi and IL-17i less desirable if UC active), JAKi are still appropriate, provided there is a shared decision making and patient is properly informed of the benefits and harms. Consider the use of other TNFi such as certolizumab or golimumab instead of a JAKi in that situation. NSAID should be tapered as soon as targeted therapy is initiated.
3	-axSpA, M, 68 y/o - Purely axial disease. After secukinumab failure ASDAS score increase from 2.1 to 2.9. CRP 9 mg/L. MRI showing active SI-joint inflammation with enthesitis. - Hypertension - Hyperlipidemia - Current smoker 36 pack-years - Prior AMI - Failed: adalimumab, certolizumab pegol and secukinumab	-68 y/o - Hypertension -Hyperlipidemia -Current smoker, 36 pack-years - Prior AMI	1	5	Uncertain	Difficult to treat patient, with failure to 3 bDMARDs from 2 mechanisms of action. But given the risk factors, JAKi should only be given as a last option. Shared decision making is very important. Consider going back to adalimumab. Try ixekizumab before a JAKi.	1	1	Inappropriate	High risk factor profile. JAKi only as last option. Despite the fact that there are few options available, it is preferable to still try all before going to JAKi. JAKi only in the absence of another alternative. Too many risk factors, prior AMI is considered a strong contra-indication.
4	-RA, F, 39 y/o - Poor effect from MTX and leflunomide. Early joint damage, residual pain, high levels of RF, ACPA and CRP.	None	8	3	Appropriate	JAKi are appropriate, but given less knowledge about long-term side events, start with a TNFi (costs also play a role in the decision).	8	2	Appropriate	Low-risk factor profile; JAKi are appropriate. But given the larger experience, accumulated knowledge, and costs, TNFi would have priority.

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Table 3 (*continued*)

	Clinical vignette	Risk factors	Round 1				Round 2			
			Result (1–9, median)	Voting span	Level of appropriateness	Comments	Result (median)	Voting span	Level of appropriateness	Comments
						Perfect place for a JAKi or IL-6i. JAKi is an adequate option at the same level as bDMARD.				If monotherapy preferred: JAKi or IL-6 inhibitors. Revisit lower dosage of MTX, potentially SC administration, in combination with TNFi.
5	-RA, M, 54 y/o - Hyperlipidemia well treated with statins - Increased disease activity during last 3 months (increase in ACPA, joint pain and swelling. Normal CRP). Has been on adalimumab treatment for 7 months. - Failed MTX, leflunomide and adalimumab	Hyperlipidemia well treated with statins	6	6	Uncertain	Given the risk factor together with failure of one TNFi only, the first choice would not be a JAKi. Try another bDMARD (another MOA than TNFi). Could be appropriate since CV risk factors are under control.	5	4	Uncertain	Medium-risk profile. Failure to only one TNFi, so medium indication (there are other alternatives). In practice try other MOA first (more accumulated knowledge), but not inappropriate to consider JAKi. Shared decision with the patient is crucial
6	-RA, F, 74 y/o - Smoker, not willing to quit - History of cervical cancer - Failed MTX, leflunomide, adalimumab and certolizumab pegol - Disease control for 12 years, but increase in disease activity for the last 3 months (increase in ACPA, RF, CRP and joint pain)	Age 74 Smoker not willing to quit History of cervical cancer	2	7	Uncertain	Given the risk factors, age + smoking + previous cancer, JAKi is not appropriate. Consider IL-6i	2	1	Inappropriate	High-risk factor profile, medium indication (failure to TNFi, there are other options). Leave JAKi for last option, given the high-risk factor profile. More information about hysterectomy / oncological follow-up.
7	-PsA, F, 29 y/o -After secukinumab start, total clinical remission in PsO, but increase in swollen/tender joint count, enthesitis and MDA (2 out of 7) - PsO - Failed MTX-mono therapy (leukopenia), adalimumab, secukinumab	None	8	4	Uncertain	Consider IL-23i No risk factors present, but JAKi is not the best for skin control. JAKi is appropriate but there are other suitable options such as IL-23i or other bDMARDs.	8	7	Uncertain	Low risk factor profile. JAKi are appropriate. Indication is medium-high (failure to TNFi and IL-17i). So only IL-23i or JAKi. IL-23i are better for skin control, but JAKi are a very suitable alternative option.
8	-PsA, M, 44 y/o -Prior STEMI -Lately increase in disease activity, increase in PsO (more plaques). DAPSA score now 39 from 25 since certolizumab start. -PsO -Failed MTX, adalimumab and certolizumab pegol	Prior STEMI	2	7	Uncertain	JAKi less desirable than IL-17i, considering cardiovascular risk. IL-23i also an option. Prior STEMI is considered a strong contra-indication.	2	3	Inappropriate	JAKi in absence of alternatives only. High-risk factor profile JAKi less desirable, first IL-17i or IL-23i. Other drugs can be more appropriate for the coexistence of PsA and poorly controlled PsO.

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Table 3 (*continued*)

	Clinical vignette	Risk factors	Round 1				Round 2			
			Result (1–9, median)	Voting span	Level of appropriateness	Comments	Result (median)	Voting span	Level of appropriateness	Comments
9	-PsA, M, 59 y/o - Smoker, 15 pack-years - Unstable angina pectoris - Lately increase in disease activity, primarily joints, skin well controlled with topicals. - PsO - Prostate cancer - Failed MTX, adalimumab, certolizumab pegol, ixekizumab	Smoker Unstable angina pectoris Prostate cancer	2	5	Uncertain	High risk (UAP + smoking + cancer), but failure to 2 TNFi and one IL-17i. Therefore, JAKi would be, in shared decision making and taking the patient's goal into account, an option (also IL-23i, likely first).	1	1	Inappropriate	Consider IL-23i Preferably bimekizumab or secukinumab. JAKi not appropriate considering risk factors.

axSpa, Axial Spondyloarthritis; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive Protein; SI, Sacro Iliac; Il-17i, Interleukin 17 Inhibitor; NSAID, Non-Steroid Anti-Inflammatory Drug; CV, Cardiovascular; AMI, Acute Myocardial Infarct; RA, Rheumatoid Arthritis; MTX, Methotrexate; RF, Rheuma-Factor; ACPA, Anti-Citrullinated Protein Antibodies; IL6i, Interleukin 6 Inhibitor; bDMARD, Biologic Disease Modifying Anti-Rheumatic Drug; SC, Sub-Cutaneous; MOA, Mode Of Action; PsA, Psoriatic Arthritis; PsO, Psoriasis; IL23i, Interleukin 23 Inhibitor; STEMI, ST-Segment Elevation Myocardial Infarction; UAP, Unstable Angina Pectoris.

Table 4
Common points emerged during the discussions of all three specialty groups following 1st round.

Common points emerged during the discussions of all three specialty groups 1st round	Clinical scenario
Modifiable cardiac risks factors such BMI, smoking but willingness to quit, hypertension, and dyslipidemia as an opportunities to improve overall health	Gastroenterology clinical scenario 2, 4, 7 Dermatology clinical scenario 2 and 9 Rheumatology clinical scenario 2 and 5
Uncertainty around the cut off regarding prior history of cancer (> 10 years), but also regarding type of cancer (i.e. viral associated vs non-associated) and staging	Gastroenterology clinical scenario 3 Dermatology clinical scenario 4 Rheumatology scenario 6
Uncertainty around how to deal with VTE during JAKi maintenance treatment leading to clinical remission, and when a clear external causative factor for VTE can be identified (e.g., prolonged immobilization following a motor-vehicle accident)	Gastroenterology clinical scenario 5 Dermatology clinical scenarios 3
Uncertainty leaning to inappropriateness in those with distinct, readily identifiable risk factors such as age 65 years or older and long-time smoking (current or past)	Gastroenterology clinical scenario 6 Dermatology clinical scenario 5
Appropriateness after discussing past smoking history and recommendation and hypertension controlled under medication	Gastroenterology clinical scenario 8, 9 Dermatology clinical scenarios 9

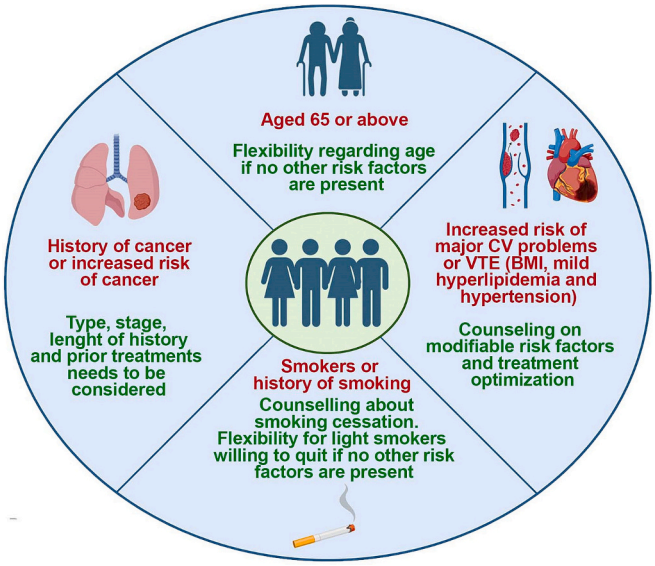

Fig. 1. Implementation of JAKi regulatory guidance based on patient's risk profile.

Declaration of Competing Interest

Virginia Solitano and Magnus Petersen declare no conflict of interest.

Paola Facheris has served as consultant for Eli Lilly.

Ferdinando D'Amico has served as a speaker for Sandoz, Janssen, Galapagos, and Omega Pharma. He has also served as advisory board member for Abbvie, Ferring, Galapagos, and Nestlè.

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Integral text of first round of vignettes.Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2023.103504.

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