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Recommendation

Expert consensus statement on the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: 2024 update

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ABSTRACT

In light of the introduction of new Janus kinase inhibitors (JAKi), new indications for JAKi and recent safety considerations that have arisen since the preceding consensus statement on JAKi therapy, a multidisciplinary taskforce was assembled, encompassing patients, health care professionals, and clinicians with expertise in JAKi therapy across specialties. This taskforce, informed by two comprehensive systematic literature reviews, undertook the objective to update the previous expert consensus for using JAKi developed in 2019. The taskforce deliberated on overarching principles, indications, dosage and comedication strategies, warnings and contraindications, screening protocols, monitoring recommendations, and adverse effect profiles. The methodology was based on the European Alliance of Associations for Rheumatology standard operating procedures, with voting on these important elements. Furthermore, an updated research agenda was proposed. The task force did not address when a JAKi should be prescribed but rather considerations once this decision has been made. This update aimed to equip clinicians with the necessary knowledge and guidance for the efficient and safe administration of this expanding and significant class of drugs.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) comprise a variety of diseases, including not only rheumatoid arthritis (RA), psoriatic arthritis (PsA); axial spondyloarthritis (AxSpA)/ankylosing spondylitis; connective tissue diseases, also called systemic autoimmune rheumatic diseases, such as systemic lupus erythematosus (SLE) and systemic sclerosis, but also inflammatory skin diseases such as psoriasis (PsO); atopic dermatitis (AD) and autoimmune alopecia; inflammatory bowel diseases (IBDs) namely Crohn disease (CD) and ulcerative colitis (UC); and others, including multiple sclerosis. Each of these represents a distinct, organ-specific or systemic clinical entity with a genetic predisposition mostly linked to the presence of certain immune response genes, which under specific environmental conditions allows immunologic tolerance to be broken [1,2]. For some, we may have a clue on this breaking point [3], and for others, there are indications for viral involvement [4,5]. All of the listed conditions share the pathogenesis of an immune-mediated inflammatory response involving a variety of common and disparate cytokines, among them those related to the polarisation of T cells, various lymphokines, as well as proinflammatory cytokines [6,7].

Cytokines, after binding to their cell membrane–associated cognate receptors, activate a variety of intracellular signal transduction mechanisms. Important proinflammatory cytokines use mitogen-activated protein kinases (MAPK) and/or nuclear factor kappa B (NFκB) for this purpose [8], whereas the majority of cytokines involved in immune cell activation and various proinflammatory messenger molecules act via the Janus kinase (JAK) pathway [9]. Interestingly, neither inhibitors of MAPK nor NFκB have been successfully translated as therapeutics in people with IMIDs [10,11] In contrast, Janus kinase inhibitors (JAKi) have been approved for a variety of IMIDs over the last decade and continue to be studied in others.

In order to account for the complexity of using JAKi in various diseases, a large taskforce has developed an expert consensus statement on the use of JAKi in IMIDs a few years ago [12]. However, since its publication, JAKi have been approved for a variety of new indications and, even more importantly, safety issues when compared with tumour necrosis factor (TNF) inhibitors (TNFi) have arisen [13] and warnings and precautions for the use of JAKi have been updated. Therefore, it was deemed important to revisit the efficacy and safety of JAKi and develop an update of the consensus statement. It should be clarified that diseases other than IMIDs in which JAKi may also be indicated, such as haematologic malignancies or COVID-19, will not be addressed in this study. The result of the taskforce's deliberations and decisions are presented in this article.

METHODS

The expert consensus statement was developed in line with the general methodology provided by the European Alliance of Associations for Rheumatology (EULAR) in its standard operating procedures (SOPs) for the development of recommendations [14]. First a steering committee (PN, AK, VK, DA, TD, RF, IM, JP, NS, YT, MT, KW, MdW, JSS) was formed to address all necessary aspects for a systematic literature research (SLR) in a face-to-face meeting on April 16, 2023; the SLR, which included all articles published between March 1, 2019 (the data cut of the 2019 SLR), and October 14, 2023, focused on the efficacy and safety of all JAKi across indications. The results of the SLR were presented to the steering group on November 10, 2023, in another face-to-face meeting. The steering group then prepared proposals for changes of the consensus statement that were to be presented to the full taskforce. Levels of evidence (LoE) were assessed according to the Oxford Centre for Evidence-Based Medicine [15]. On January 10, 2024, the taskforce met at 2 different times to discuss the SLR results, review the steering group's proposals, and update the previous statement. The morning session (Central European time) was designated to accommodate mainly participants from Asia, while the afternoon session was set to enable experts from the Americas to contribute. Patients and nonphysician health care professionals were also present.

The overarching principles (OAPs) and individual recommendations address issues related to JAKi treatment of patients diagnosed with IMIDs. Of note, the taskforce did not discuss when to initiate JAKi therapy, as this should be covered by the respective disease-specific management recommendations. The taskforce focused on assessing if the items previously established were still valid based on the information accrued over the past 4 years and, consequently, on changes from the prior publication if deemed pertinent. The voting rules adhered to the EULAR SOPs, which stipulate to accept a proposal if a 75% majority is reached; if a 75% majority is not reached, the discussion continues and an amendment is presented which is again voted for, with a >66% majority of participants necessary for acceptance; again, if this next proposal is not approved, another round of discussions takes place, after which the new proposal has to be voted on by >50% of the members present in the room. The deliberations and changes were noted and recorded to allow their presentation in this report. After the meeting, all taskforce members received the ultimately approved version of the recommendations together with information on the LoE for each item to allow for a final vote on the level of agreement (LoA) for each of the items. Of note, an individual item which includes more than one aspect may have more than one LoE assigned, as will be seen in the individual items.

The last results of the LoA voting were received in February 2024. For the OAPs, only the voting results and LoA are presented, since they are general, explanatory statements mostly related to good clinical practice that do not require specific assessment of evidence.

RESULTS

In the prior consensus statement, published in 2019 [12], the process leading to the OAPs and recommendations outlined below was explained in detail [12] and in an abbreviated form in the methods' section above. As before, the recommendations were divided into a number of elements judged to be important in clinical practice and for the use of these points of guidance (Table 1).

These elements include: 4 OAPs (4 in 2019), 2 points on indications (2 in 2019), 4 items on treatment dose and comedications in different IMIDs (4 in 2019), 6 entries related to contraindications (5 in 2019), 7 items on prescreening and risks (7 in 2019), 3 entries regarding laboratory and clinical monitoring (3 in 2019) and 5 points on adverse effects (5 in 2019). While the number of bullet points has remained the same for most elements, many of these underwent changes based on recent insights. Further, each recommendation is accompanied by its associated LoEs, strength of recommendation (SoR), vote (% final approval), and the taskforce's LoA with the final wording. Please note that for some recommendations, the LoEs, and thus SoRs, are low despite a strong vote and agreement by the task force members. Such results generally reflect the absence of a study or studies performed to specifically investigate the point(s) raised, even if secondary indications are present. Therein, we rely on expert opinion, although often supported by some underlying data.

For readers who are familiar with the previous version of this expert consensus statement, we have indicated which changes have been made and why. Nevertheless, Table 1 with all recommendations is a stand-alone new version without any reference to the previous publication.

Overarching principles

Of the 4 OAPs, 3 were unchanged, and for 1, a slight wording change was applied to maintain uniformity with other principles. Key points of the discussions, taskforce voting results and LoAs are addressed further.

Item A: Initiation of JAKi therapy and the treatment target to be achieved should be based on a shared decision between the patient and the clinician, fully informing the patient on the potential benefit and risks of this therapy (vote, 100%; LoA, 9.94)

The term medical specialist in the previous version was altered to clinician to keep uniformity with the term used in OAP 3 and 4. It acknowledges that a variety of specialties and health professionals are involved in the management of patients taking JAKi. The importance of shared decision making between clinician and patient was again emphasised as was the necessity to provide the patient with full and adequate information on the risk and benefit of JAKi therapy. However, there was a slight amendment from the previous 'which requires full information of the patient' to the new 'fully informing the patient' to streamline the wording. The SLRs provided the latest evidence on efficacy and safety, building upon the 2019 SLR [16], to guide the taskforce. Clinicians interested in the details are referred to the separate publications [17,18]. Long-term safety data with a number of JAKi now extends to over a decade particularly in rheumatologic and dermatologic diseases [19–23].

Item B: Therapeutic approaches to treating patients with chronic inflammatory conditions should be in line with international/national recommendations (algorithms) for the management of the respective disease (vote, 100%; LoA, 9.72)

The taskforce continues to recommend general management principles for individual diseases in line with international and national guidelines. The minor change made was to eliminate 'and' between 'international' and 'national' to simply read 'international/national', since these are not always fully aligned. Thus, when international or national recommendations differ, the

Table 1
Overarching principles and individual recommendations by different categories

Item	Recommendation	LoE/SoR	Final vote (%)	LoA
Overarching principles				
A	Initiation of JAKi therapy and the treatment target to be achieved should be based on a shared decision between the patient and the clinician, fully informing the patient on the potential benefit and risks of this therapy.	NA	100	9.9 ± 0.4
B	Therapeutic approaches to treating patients with chronic inflammatory conditions should be in line with international/national recommendations (algorithms) for the management of the respective disease.	NA	100	9.7 ± 0.6
C	The points-to-consider when initiating JAKi therapy do not provide information on when JAKi should be used in the treatment algorithm, but rather attempt to assist the clinician once the decision to prescribe a JAKi has been made.	NA	100	9.7 ± 0.5
D	These points-to-consider address specific (but not all) aspects related to the application of JAKi therapy and the clinician should additionally refer to the disease-specific product information.	NA	100	9.8 ± 0.5
I. Indications				
1.	Patients with immune-mediated inflammatory diseases (IMIDs); as of 2024, depending on the specific drug, these include rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, ulcerative colitis, Crohn disease, psoriasis, atopic dermatitis, vitiligo, and alopecia areata.	1a/A	100	9.9 ± 0.3
2.	Currently, there is no direct evidence from head-to-head comparisons to show efficacy or safety superiority of one JAKi over another.	5/D	94	9.9 ± 0.3
II. Treatment dose and comedication				
1.	Use the dose recommended for the specific disease.	1a/A	100	9.8 ± 0.5
2.	Consider dose adjustments in patients with higher age,* significant renal or hepatic impairment,* other comorbidities and/or at risk of drug interactions.	2b/C, *5/D	100	9.6 ± 1.0
3.	Regarding comedication, follow specific recommendations for the respective disease.	1a/B	100	9.8 ± 0.5
4.	Consider dose reduction of the JAKi in patients in sustained remission according to established assessment instruments (regarding use of such instruments, see recommendation V/3).	1b/B	94	9.1 ± 1.3
III. Warnings or contraindications				
1.	Severe active (or recurrent)* infections, including tuberculosis and opportunistic infections.	2b/B, *4/D	94	9.7 ± 0.6
2.	Current (or history of) malignancies.	5/D	94	9.2 ± 0.9
3.	Severe organ dysfunction such as advanced chronic liver disease and severe renal disease (creatinine clearance of <30 mL/min).	5/D	100	9.7 ± 0.6
4.	Pregnancy and lactation.	5/D	100	9.8 ± 0.6
5.	History of arterial and venous thromboembolic events.	2b/B	100	9.5 ± 0.8
6.	Vaccination with live vaccines.	5/D	100	9.6 ± 1.0
IV. Pretreatment screening and risks				
1.	Patient history and physical examination, with a focus on warnings and contraindications.	5/D	100	9.9 ± 0.4
2.	Consider risk factors for venous thromboembolic events, especially a history of thromboembolism; cardiovascular risk such as a history of cardiovascular event; risk for malignancy, such as smoking history*.	2b/B, *5/D	100	9.9 ± 0.3
3.	Routine laboratory testing (full and differential blood counts, liver blood tests, renal function); and lipid levels as a baseline.	5/D	100	9.7 ± 0.6
4.	Hepatitis B virus (HBV) testing (HBV surface antigen, HBV surface antibody, HBV core antibody, and with/without HBV DNA testing) and hepatitis C virus (HCV) testing (HCV antibody, with HCV RNA testing if antibody positive).	2b/B	100	9.9 ± 0.3
5.	HIV testing in high-risk populations.	2b/B	100	9.6 ± 1.0
6.	Tuberculosis screening as per national recommendations.	2b/B	100	9.9 ± 0.3
7.	Assess and update vaccination status in accordance with national recommendations; consider vaccination against herpes zoster.	5/D	100	9.7 ± 0.5
V. Laboratory and clinical monitoring				
1.	Periodic minimal laboratory monitoring: full and differential blood counts, liver and renal function tests, lipid levels.	2b/B, *5/D	100	9.8 ± 0.5
2.	Regular skin examination (for detection of skin cancer), as per national recommendations.	5/D	94	8.9 ± 1.5
3.	Evaluate response using validated, disease-specific measures of disease activity; for evaluation and definition of response, be aware that C-reactive protein and erythrocyte sedimentation rate may be reduced by JAKi independently of reduction of disease activity and possibly even in infections*.	2b/B, *5/D	100	9.9 ± 0.7
VI. Adverse effects				
1.	Serious infections (similar to biological disease-modifying antirheumatic drugs), opportunistic infections including TB, herpes zoster (increased rates compared with biological disease-modifying antirheumatic drugs) may occur; the risk of infectious events can be lowered with reduction or elimination of concomitant glucocorticoid use.	2b/B	100	9.7 ± 0.7
2.	Rates of malignancy may be higher with JAK inhibition compared with TNF inhibitors; the risk of non–melanoma skin cancer is elevated.	2b/B	94	9.5 ± 0.7
3.	Lymphopenia, thrombocytopenia, neutropenia, and anaemia may occur; anaemia especially occurring with JAKi that inhibit JAK2.	1b/B	100	9.5 ± 1.1
4.	There is a dose-dependent risk of venous thromboembolic events, especially pulmonary embolism with JAK inhibition, particularly in patients with risk factors for venous thromboembolic events.	2b/B	100	9.7 ± 0.6
5.	Elevations of creatine phosphokinase are noted with JAKi but have usually not been associated with clinical events; elevations of creatinine have been noted with JAKi but have not been associated with renal failure or hypertension.	2b/B	100	9.6 ± 0.7

JAK, Janus kinase; JAKi, Janus kinase inhibitor; LoA, level of agreement; LoE, level of evidence; SoR, strength of recommendation; TNF, tumour necrosis factor.

clinician should choose the most appropriate recommendations considering individual country and access limitations.

Item C: The points-to-consider when initiating JAKi therapy do not provide information on when JAKi should be used in the treatment algorithm but attempt to assist the clinician once the decision to prescribe a JAKi has been made (vote, 100%; LoA, 9.72)

The usage of the terminology 'consensus statement' or 'recommendations' or 'points-to-consider' and not 'guidelines' throughout was regarded as an important distinction when opinion and low LoE are used and for medicolegal implications, since a decision to use a given drug in a specific patient is always one that relates to that individual in a patient-clinician relationship and does not require strict guidelines but rather general considerations related to safety and efficacy in each specific circumstance. No guideline can address all circumstances that may be pertinent in a particular patient with a particular diagnosis, unique comorbidities, a personal disease history as well as treatment history, and concomitant medications or similar aspects (see also item D).

Item A: These points-to-consider address specific (but not all) aspects related to the application of JAKi therapy and the clinician should additionally refer to the disease-specific product information (vote, 100%; LoA, 9.81)

The importance of disease-specific product information should be carefully considered. As new data emerge, updates to recommendations are necessary over time. A large number of clinical trials investigating JAKi are currently being conducted, with 487 trials involving JAKi therapy registered on clinicaltrials.gov at the time of writing.

I. Indications

Item 1: Patients with IMIDs; as of 2024, depending on the specific drug, these include those with RA, juvenile idiopathic arthritis, PsA, AxSpA, UC, CD, PsO, AD, vitiligo, and alopecia areata (LoE, 1A; SoR, A; vote, 100%; LoA, 9.91)

Since 2019, different JAKi have been approved for several additional IMIDs. The taskforce noted that treatment dose and comedications are important considerations in different IMIDs, and the status quo (2024) is mentioned. This list may soon be expanded. For example, while clinical trial evidence of efficacy of JAKi for patients with hidradenitis suppurativa exists, this is not an approved indication as yet [24]. Deucravacitinib has been approved for PsO, might be approved for PsA once phase 3 trials are successfuly finalized and has been investigated in a phase 2 trial of SLE and demonstrated significant efficacy at 3 mg twice daily [25]. Moreover, positive phase 2 randomised controlled trial (RCT) data have been presented for upadacitinib in SLE at 30 mg daily dose [26]. Further, JAKi are under active investigation in other IMIDs including interferonopathies, dermatomyositis, vasculitis, polymyalgia rheumatic, and giant cell arteritis among many others. Of note, AxSpA includes both radiographic and nonradiographic spondyloarthritis. Further, baricitinib has received regulatory approval in combination with remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 infection in hospitalised adult and paediatric patients requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. However, similar to other non-IMID indications such as haematologic malignancies, COVID-19 is not considered an IMID nor was it included in the SLR, which is the reason why it has been excluded from the present indication list [27]. The different JAKi and their approved indications are listed in Table 2, while the different IMIDs for which JAKi are approved and the respective JAKi are shown in Table 3.

Item 2: Currently, there is no direct evidence from head-to-head comparisons to show efficacy or safety superiority of one JAKi over another (LoE, 5; SoR, D; vote, 94%; 1 abstention; LoA, 9.91)

The taskforce debated whether this recommendation should be a note in the text but agreed that it should be included to assuage attempts to claim superior efficacy between JAKi, as there is no evidence at the present time from multinational, multicenter RCTs that one JAKi is more efficacious clinically, structurally, or functionally than any other JAKi. There remain no clinical trials of JAKi after intolerance or lack of efficacy of another JAKi. This item has been minimally adjusted compared with the previous statement to make clear that any potential

Table 2
JAK inhibitors approved primarily by EMA and/or FDA at the time of writing

Drug	Main target	Indications	Metabolism and dose
Abrocitinib	JAK1, JAK2	AD	100-200 mg daily
Baricitinib	JAK1, JAK2	RA, AD, AA, JIA, COVID-19[a]	>66% renal excretion; 2-4 mg daily
Delgocitinib	Pan-JAK	AD[b]	Topical
Deucravacitinib	TYK2	PsO	CyP1A2 13% renal excretion, active metabolite BMT-153261; 6 mg daily
Fedratinib	JAK1-FLT3	Myelofibrosis	400 mg daily
Filgotinib	JAK1	RA	CES2, active metabolite (1:10 potency); 100-200 mg daily
Gusacitinib	JAK/Syk	AD	2-4 mg daily
Momelotinib	JAK1, JAK2/ACRV1	Myelofibrosis	200 mg daily
Oclacitinib	JAK1, JAK2, JAK3	Canine AD	0.4-0.6 mg/kg chewable tablet
Paricitinib	JAK2/Flt3	Myelofibrosis	200 mg twice daily
Peficitinib	Pan-JAK	RA[b]	NNMT, SULT2A1, 16% renal excretion; 150 mg daily
Ritlecitinib	JAK3, TEC	AA	50 mg daily
Ruxolitinib	JAK1, JAK2	Myelofibrosis, Polycythemia vera, GvHD, vitiligo (topical)	CyP3A4; 5-10 mg twice daily
Tofacitinib	JAK1, JAK3, JAK2	RA, PsA, AxSpA, ulcerative colitis, JIA	CyP3A4, 30% renal excretion; 5 mg twice daily
Upadacitinib	JAK1, JAK2	RA, PsA, AD, JIA UC, CD, AxSpA (including nr AxSpA)	CyP3A4 20% renal excretion; 15-30 mg daily

AA, alopecia areaty; ACRV1, activin A receptor, type 1; AD, atopic dermatisis; AxSpA, axial spondyloarthritis; CD, Crohn disease; CES, carboxyesteraseisoform; CyP cytochrome P; EMA, European Medicines Agency; ER, extended release; FDA, Food and Drug Administration; FLT-3, fms like tyrosine kinase 3; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; NNMT, nicotinamide N-metbyltransferase; nr, nonradiographic; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SULT, sulfotransferase; Syk, spleen typrosine kinase; TYK2, tyrosine kinase 2; TEC, tyrosine kinase expressed in hepatocellular carcinoma; UC, ulcerative colitis.

[a] Approved by FDA in combination with remdesivir.

[b] Approved in Japan.

Table 3
Approved JAK inhibitors for specific IMID indications (at the time of writing)

Indication	Approved JAKi
Rheumatologic diseases	
Rheumatoid arthritis	Baricitinib (JAK1, JAK2), filgotinib (JAK1), peficitinib (pan-JAK), tofacitinib (JAK 1, JAK3, JAK2), upadacitinib (JAK1, JAK2)
Psoriatic arthritis	Tofacitinib (JAK1, JAK3, JAK2), upadacitinib (JAK1, JAK2)
Axial spondyloarthritis	Tofacitinib (JAK1, JAK3, JAK2), upadacitinib (JAK1, JAK2)
Juvenile idiopathic arthritis	Tofacitinib (JAK1, JAK3, JAK2), baricitinib (JAK1, JAK2)
Dermatologic diseases	
Psoriasis	Deucravacitinib (TYK2)
Atopic dermatitis	Abrocitinib (JAK1, JAK2), baricitinib (JAK1, JAK2), gusacitinib (JAK/Syk), upadacitinib (JAK1, JAK2)
Alopecia areata	Baricitinib (JAK1, JAK2), ritlecitinib (JAK3, TEC)
Vitiligo	Ruxolitinib (JAK1, JAK2) – topical
Inflammatory bowel disease	
Crohn disease	Upadacitinib (JAK1, JAK2)
Ulcerative colitis	Tofacitinib (JAK1, JAK3, JAK2), upadacitinib (JAK1, JAK2)

IMID, immune-mediated inflammatory disease; JAK, Janus kinase; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

difference would have to be shown in trials directly comparing 2 or more drugs ('from head-to-head comparisons to show efficacy or safety superiority' now replaces 'of superiority regarding efficacy or safety') (Table 1).

II. Treatment dose and comedications in different diseases

Item 1: Use the dose recommended for the specific disease (LoE, 1a; SoR, A; vote, 100%; LoA, 9.84)

This recommendation (unchanged) highlights dose adjustments per disease indication; for example, in the treatment of IBD differing induction and maintenance dosing are clearly defined.

Item 2: Consider dose adjustments in patients with higher age, significant renal or hepatic impairment, other comorbidities, and/or at risk of drug interactions (LoE, 2b/5; SoR C/D; vote, 100%; LoA, 9.61)

JAKi metabolism is summarised in Table 2. As previously described in the 2019 consensus paper, JAKi that are metabolised by the hepatic cytochrome P (CYP) 450 pathway lead to drug interactions with other inhibitors of this pathway, such as ketoconazole, and promoters, such as rifampicin, necessitating dosage adjustments. Baricitinib is 70% renally excreted, so dosage should be reduced in patients with kidney disease and reduced glomerular filtration rate. Filgotinib is metabolised by hepatic carboxylesterases, and its less potent major metabolite GS-829845 (by a factor of 10) is a pharmacologically active, selective inhibitor of JAK1. Upadacitinib undergoes hepatic oxidation with minor CYP metabolism, and peficitinib undergoes hepatic conjugation. Organic anion transporter 3 inhibitors, such as probenecid, interact with baricitinib requiring a dose reduction to 2 mg/d. Rifampicin, when used in latent tuberculosis (TB) prophylaxis or therapy for active TB, increases hepatic metabolism of tofacitinib and upadacitinib, so that a dose increase needs to be considered. Ketoconazole has the opposite effect, inhibiting tofacitinib and upadacitinib metabolism, so a dose reduction is suggested.

The general meaning of this item remains unchanged, but some details have been amended. Higher age is no longer specified as '>70 years' as age-related health status is relative to comorbidities, frailty, and re-definition of meaningful age groups [28]. The taskforce debated the designation 'impaired hepatic function' as this was considered to be not meaningfully measurable; for example, transaminase monitoring does not adequately measure hepatic function. Aadvanced chronic liver disease' would be the preferred term [29], but it is less well recognised [10,11], and therefore, it was agreed to keep the previous terminology. Comorbidities include those relevant to JAKi therapy, such as cardiovascular disease, malignancy, or high thrombosis risk (eg, past thromboembolic events, obesity, use of contraceptives, or recent surgery). Reduced renal function may necessitate dose reduction. It is also noted that some haematologic abnormalities that may affect the JAKi dose, such as neutropenia and lymphopenia, may be drug induced rather than a comorbidity.

Item 3: Regarding comedication, follow specific recommendations for the respective disease (LoE, 1a; SoR, B; vote, 100%; LoA, 9.79)

This bullet that included only a statement about RA in 2019 was shortened so as to not single out a specific disease, since comedication will depend on the specific disease, and this was felt to be sufficiently covered in the new formulation of this item. Of note, for many indications, combination with methotrexate (MTX) shows superior efficacy to JAKi monotherapy; examples include RA [13,14,30–32] and CD [33]. Immunogenicity, which is an important issue for combining biological agents with MTX [34], is not an issue with oral small molecules. Since data on the added efficacy of comedication are not available for all diseases for which JAKi are approved, the LoE(SoR is mixed.

Item 4: Consider dose reduction of the JAKi in patients in sustained remission according to established assessment instruments (regarding use of such instruments, see recommendation V/item 3; LoE, 1b; SoR, B; vote 94%; 1 abstention; LoA, 9.12)

This bullet point previously focused on RA, but, since this is relevant in other diseases too, such as UC, this part of the respective item I/4 in the previous recommendations was deleted and text about pertinent assessment instruments added to be more general. In a large randomised phase 3 trial in RA patients, after reaching low disease activity/remission (LDA/REM) for several months, maintenance of LDA/REM was greater with continued baricitinib 4 mg daily compared with tapering to 2 mg. Nevertheless, a large proportion of patients receiving the reduced dosing could maintain LDA/REM and among those who flared, the majority recaptured these treatment targets after reinitiating the 4-mg dosage [35]. Patients with UC who are treated with tofacitinib-induced stable remission could de-escalate the dose and maintain remission, especially in those in deep endoscopic remission and those without previous TNFi failure [36].

III. Warnings and contraindications

The heading was altered to 'warnings and contraindications' as 'contraindications' are not always absolute and depend upon the patient journey and comorbidities,

Item 1: Severe active (or recurrent) infections, including TB and opportunistic infections (LoE, 2b/5; SoR, B/D; vote, 94%; 1 abstention; LoA, 9.73)

JAKi therapy may still be appropriate, taking safety issues into consideration. 'Chronic' infection was changed to 'recurrent' infection as a warning that also active infections may recur without being chronic (ie, chronic infections are always also 'active'). The risk of infections is similar among the currently approved JAKi, with filgotinib having a lower risk of herpes zoster on systematic review of RA trials [37], which was, however, not confirmed by sensitivity analyses [38,39]. Asian patient populations are more prone to develop herpes zoster than non-Asian patients [40,41]. TB and opportunistic infections were observed during JAKi therapy, with higher rates at increased doses and in older patients [20,41,42].

Item 2: Current (or history of) malignancies (LoE, 5; SoR, D; vote, 94%; 1 abstention; LoA, 9.15)

Differing from the 2019 version (describing 'current malignancies') and given the ORAL Surveillance results [13] with a numerical imbalance in rates of some malignancies when compared with TNFi, the term 'or history of' malignancies was added to this recommendation. Long-term registry follow-up data are needed to provide more evidence. This is important as patients with previous malignancies (typically within the last 5 years before study inclusion) are usually excluded from clinical trials. Registries including patients with comorbidities and concomitant medications that would exclude them from clinical trials, however, show no signal that JAKi therapy increases lymphoproliferative or solid tissue malignancy apart from an increase in non–melanoma skin cancer (NMSC) when compared with MTX and placebo [43,44]. However, in the ORAL Surveillance trial, a population particularly prone to develop major cardiovascular events was studied and an imbalance in lung cancer (but not breast cancer) incidence seen [13]. Many of these patients had a history of current or past smoking with a small imbalance in baseline smoking rates compared with the group treated with TNFi. Moreover, it is currently unknown whether JAKi could be used to treat checkpoint inhibitor–associated side effects (eg, checkpoint inhibitor–induced arthritis and IBD).

Item 3: Severe organ dysfunction such as decompensated advanced chronic liver disease and severe renal disease (creatinine clearance < 30 mL/min; LoE, 5; SoR, D; vote, 100%; LoA, 9.67)

The term 'severe hepatic disease' was now replaced by 'decompensated advanced chronic liver disease', the designation preferred by hepatologists over the older term 'liver cirrhosis' since this is defined by noninvasive criteria such as liver stiffness [29]. In this respect, JAKi should not be used in patients with a Child score of ≥9 points or a history or presence of hepatic decompensation (eg, ascites, hepatic encephalopathy grade of ≥2, and variceal bleeding); and for those with creatinine clearance of <30 mL/min, dose adjustments should be made. Of note, certain JAKi (baricitinib, filgotinib, and upadacitinib) are contraindicated for patients with creatinine clearance of <15 mL/min.

Item 4: Pregnancy and lactation (LoE, 5; SoR, D; vote, 100%; LoA, 9.76)

No change was made to this point compared with the previous consensus statement. Women of childbearing age should adhere to effective contraception while taking JAKi because of evidence of animal teratogenicity. Further, evidence from animal models on lactational pharmacokinetics showed an excretion of JAKi in breast milk. Sufficient human data on inadvertent pregnancies during JAKi therapy are currently lacking. An insufficient human database on lactation rather than evidence of harm is the reason for recommending to avoid JAKi during breastfeeding. Previous concerns on spermatogenesis based on animal data for filgotinib have been refuted in the filgotinib spermatogenesis studies, MANTA and MANTA-RAy. Filgotinib at 200 mg daily for 13 weeks had no impact on semen variables or sex hormones in men with active IBD or inflammatory rheumatic disease [45]. Paternal fertility appears unaffected by other JAKi in animal studies, but again, there are only limited human data available. 'The EULAR points-to-consider for the use of antirheumatic therapy in reproduction, pregnancy and lactation' [46] have been updated recently; this update will be available soon and can provide further guidance.

Item 5: History of arterial and venous thromboembolic events (LoE, 2b; SoR, B; vote, 100%; LoA, 9.45)

This recommendation was changed from 'recurrent VTE' to 'history of' arterial 'or' venous thromboembolic events to emphasise that arterial as well as venous thromboembolism (VTE) are increased in a dose-dependent manner with JAKi compared with using TNFi [47]. While it is notable that active inflammation is thrombogenic [48], the data on increased thromboembolic risk stem from placebo-controlled and active controlled trials [49], although this has not been studied as a primary outcome. Thus, careful risk/benefit assessment is needed in this clinical situation.

Item 6: Vaccination with live vaccines (LoE, 5; SoR, D; vote, 100%; LoA, 9.55)

This recommendation was added given increased use of recombinant and live vaccination in particular as far as herpes zoster is concerned.

IV. Pretreatment screening and risks

Item 1: Patient history and physical examination, with a focus on warnings and contraindications (LoE, 5; SoR, D; vote, 100%; LoA, 9.91)

The second half of the recommendation was added for consistency. Risk factors for adverse events of interest such as major adverse cardiac events (MACEs), VTE, TB, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, complicated diverticulitis, and herpes zoster history should be considered. Basic skin checks for NMSC should be performed for those at risk.

Item 2: Consider risk factors for venous thromboembolic events, especially a history of thromboembolism and whether this was provoked or unprovoked, as well as cardiovascular risk factors such as a history of cardiovascular event and the risk for malignancy, including smoking history (LoE, 2b/5; SoR, B/D; vote, 100%; LoA, 9.91)

This item was the last in this category in 2019. Based on the importance of thromboembolism considerations, it was moved up and expanded regarding other risk factors, including cardiovascular events and malignancy, especially lung cancer. The taskforce was aware that there is some redundancy with item 1 in this section, but this is deliberate, and the repetition and expansion should prompt higher vigilance, given that subanalyses of the ORAL Surveillance trial showed that those with a

previous cardiovascular event are at particular risk to develop MACEs [50,51]. Of note, registry and cohort data, even when looking at patients at risk, did not show such increased risks [52,53]; however, the LoE of cohort studies compared with that of an RCT is lower, and more data will have to come from further RCTs.

Item 3: Routine laboratory testing (full and differential blood counts, liver blood tests, renal function, and lipid levels as a baseline; LoE, 5; SoR, D; vote, 100%; LoA, 9.73)

This item, like that of other points with a low LoE, is solely based on expert opinion, since no study investigated which laboratory tests are indispensable before starting JAKi therapy. The taskforce felt that, for example, creatine phosphokinase (CPK) testing was not routinely needed, although asymptomatic CPK increases may occur under JAKi treatment [54,55]. Of note in this respect, myalgia without rhabdomyolysis has been occasionally reported, so CPK testing should be done if respective symptoms develop [20]. Regarding liver blood tests (bilirubin, albumin, aspartate transaminase, alanine transaminase, alkaline phosphatase, and γ-glutamyl transferase), most clinicians are using aspartate transaminase/alanine transaminase at baseline and during monitoring.

Item 4: HBV testing (HBV surface antigen, HBV surface antibody, HBV core antibody, and with/without HBV DNA testing) and HCV testing (HCV antibody, with HCV RNA testing if antibody test was positive; LoE, 2b; SoR, B; vote, 100%; LoA, 9.88)

Hepatitis serology is recommended for all patients. While this recommendation has remained the same as in 2019, hepatitis D (δ) virus should also be tested in all patients with HBV infection. Patients with chronic HBV infection should receive JAKi only after consultation with a hepatologist for potential combination with antiviral agents. Similarly, patients with positive-result HCV RNA, should have HCV treated before JAKi therapy with hepatologist involvement.

Item 5: HIV testing in high-risk populations (LoE, 2b; SoR, B; vote, 100%; LoA, 9.58)

No new data exist since 2019, and the readers are referred to the previous deliberations for further details [12].

Item 6: TB screening as per national recommendation (LoE, 2b; SoR, B; vote, 100%; LoA, 9.91)

Risk of reactivation or new infection is similar to TNFi [13,56,57], so that screening according to national guidelines is recommended. Patients with latent TB should have initial concomitant anti-TB therapy; generally, isoniazid for 4 to 8 weeks is recommended and continued as per national guidelines.

Item 7: Assess and update vaccination status in accordance with national recommendations; consider vaccination against herpes zoster (LoE, 5; SoR, D; vote, 100%; LoA, 9.73)

The EULAR vaccination recommendations may assist clinicians treating IMIDs [58]. As mentioned in the 2019 recommendations, virus reactivation has been documented with JAKi therapy particularly herpes zoster (but also simplex and human papilloma viruses), in a dose-dependent manner. Herpes zoster vaccination is recommended, either using the live-attenuated vaccine with 2 to 4 weeks cessation of JAKi therapy or with the recombinant vaccine. Studies suggest that pausing MTX for 1 to 2 weeks at the time of vaccination reduces blunting of vaccine response [59,60].

V. Laboratory and clinical monitoring

This section has been moved from its previous position as number VI to now become element V for reasons of logical flow. The taskforce simply felt that the laboratory portion would fit better immediately after the section on pretreatment screening and before dealing with adverse events (now section VI).

Item 1: Periodic minimal laboratory monitoring: full and differential blood counts, liver and renal tests, and lipid levels (LoE, 2b/5; SoR, B/D; vote, 100%; LoA, 9.76)

In the previous version of the consensus statements, specific time points were recommended, but the taskforce felt that this was too prescriptive, and this debate was resolved by simply stating ‘periodic’, as was previously done after specifying initial detailed time points. With regard to lipid levels, it was suggested to measure these periodically, preferably also at baseline, and if levels are increased to suggest lipid lowering therapy as per national guidelines. With testing of liver and renal function, it was acknowledged that not all instruments (eg, liver enzyme tests) are practically adequate to assess ‘function’.

Item 2: Regular skin examination (for detection of skin cancer), as per national recommendations (LoE, 5; SoR, D; vote, 94%; 1 abstention; LoA, 8.88)

This bullet point was changed from the previous recommendation of ‘annual skin examinations’, since it was felt that this depended on local risks and, therefore, national recommendations should be adhered to.

Item 3: Evaluate response using validated, disease-specific measures of disease activity; for evaluation and definition of response, be aware that C-reactive protein and erythrocyte sedimentation rate may be reduced by JAK inhibitors independently of reduction of disease activity and possibly even for infections. (LoE 2b/5, SoR B/D, Vote 100%, LoA 9.97)

Several instruments used to assess disease activity include C-reactive protein (CRP) as one of the components. Since JAKi inhibits interleukin (IL)-6 signalling and IL-6 is a direct (hepatic) activator of acute phase reactants (APRs), APR/CRP decreases, and even their normalisation can often occur in the absence of significant clinical changes, suggesting the presence of LDA/REM without respective clinical evidence. Therefore, instruments should be used that do not include APRs to preclude such erroneous results [61]. For example, the American College of Rheumatology (ACR) and EULAR have recommended to not use the disease activity score (DAS; original or using 28 joint counts) to determine remission but rather other measures, such as Boolean criteria without CRP or clinical disease activity index (CDAI) definitions of remission [62]. The same caveat may pertain to the use of Axial Spondyloarthritis Disease Activity Score (ASDAS) in AxSpA [63], although it is otherwise a more reliable instrument than other ones used previously, or Minimal Disease Activity (MDA), Psoriatic Arthritis Disease Activity Score (PASDAS), and Disease Actvity Index for Psoriatic Arthritis (DAPSA) (although not clinical DAPSA) in PsA [64]. Indeed, claims that one drug may be better than another one could be (and are) made when using such measures [65], without such superiority being necessarily reflected in other objective assessments of disease activity, such as swollen joint counts in RA; at the least, potential small and clinically irrelevant differences may be highly exaggerated when using instruments comprising APRs. Regarding infections, one should be aware of the possibility that the CRP response may be blunted, but there

are some data suggesting that CRP does increase in the course of infections in patients treated with JAKi [66].

VI. Adverse effects

This element was moved from its previous position as section V to now become group VI of the recommendations (see earlier).

Item 1: Serious infections (similar to biologic disease-modifying antirheumatic drugs), opportunistic infections including TB, and herpes zoster (increased rates compared to biological disease-modifying antirheumatic drugs) may occur; the risk of infectious events can be lowered with reduction or elimination of concomitant glucocorticoid use (LoE, 2b; SoR, B; vote, 100%; LoA, 9.70)

This item remained essentially unchanged, simply reflecting the currently available data regarding infections under JAKis. As mentioned earlier, herpes zoster rates may be lower with filgotinib than those with the other JAKis, but this is an impression, albeit based on the data from placebo and active controlled trials and not deducted from head-to-head comparisons of different JAKi. Dose-dependent risks for serious infections were observed in several trials [13,41,56,67,68] with higher age being an important risk factor [21,57,69,70].

Item 2: Rates of malignancy may be higher with JAK inhibition compared with those with TNF inhibitors; the risk of NMSC is elevated (LoE, 2b; SoR, B; vote, 94%; 1 abstention; LoA, 9.52)

This recommendation was reformulated to reflect data from the ORAL Surveillance trial on patients enriched for cardiovascular risk factors [13,71]. The wording 'may' was used despite the fact that this was an RCT comparing a JAKi, tofacitinib, with TNFi, but a confirmatory RCT is needed to change 'may' to 'is', especially since data from registries, which have primarily been implemented to find rarer adverse events, do not show an increased malignancy risk with JAKi [43,72]. As indicated earlier, the ORAL Surveillance trial included a particular group of patients at risk for developing malignancies due to a high prevalence of current or past smokers.

Item 3: Lymphopenia, thrombocytopenia, neutropenia, and anaemia may occur – anaemia especially occurring with JAKi that inhibit JAK2 (LoE, 1b; SoR, B; vote, 100%; LoA, 9.52)

Since anaemia of chronic disease is improved at the group level with filgotinib [39,73,74], the second half of this recommendation was added to reflect the fact that anaemia occurs primarily upon inhibition of JAK2, since erythropoietin signals via the JAK2 homodimer. Lymphocyte counts of $<0.5 \times 10^9$/L are associated with increased risk of serious and opportunistic infection. Neutropenia 0.5 to 1.0×10^9/L is common with JAKi, but rarely associated with infections [55,75]. Only a few haematologic abnormalities were observed in deucravacitinib-treated patients; however, larger studies are still ongoing [76–78].

Item 4: There is a dose-dependent risk of venous thromboembolic events, especially pulmonary embolism with JAK inhibition, particularly in patients with risk factors for venous thromboembolic events (LoE, 2b; SoR, B; vote, 100%; LoA, 9.67)

This point, which focused on high-dose tofacitinib and on baricitinib in 2019 [47,79,80], was expanded to reflect that the increased VTE risk may pertain to all JAKi, as long as no opposing data from RCTs have become available. It remains unknown whether this is an effect of JAK2 inhibition or a JAK class effect, nor is the exact mechanism for this adverse effect understood [52,53,81]. Risk factors for VTEs have been mentioned earlier.

Table 4
Research agenda

1. What is the efficacy and safety of switching between JAKi in nonresponders or due to lack of tolerability?
2. What are the predictors of response to JAKi when compared with other disease-modifying antirheumatic drugs used for RA?
3. Do JAKi reduce cardiovascular risk by interfering with inflammation, despite the results of the ORAL Surveillance study?
4. Is VTE a class effect or a JAK2 inhibition effect and what is the mechanism of VTE? What is the actual risk of VTE when treating with a JAKi?
5. What is the safety of JAK inhibition in patients with previous or current malignancy or who develop a malignancy while on therapy?
6. Are JAKi effective and safe as therapy for autoimmune diseases induced by checkpoint inhibitors in patients with malignancy?
7. How safe are JAKi in HBV/HCV–infected patients and other viral infections such as human papilloma virus? In case of active infections, especially COVID-19, should JAKi be temporarily discontinued? If so for how long?
8. How safe are JAKi in pregnancy and lactation? What should be recommended if a woman taking a JAKi becomes pregnant?
9. Safety of JAKi in elective surgery – should they be discontinued and if so for how long and when should they be restarted?
10. What is the efficacy of JAKi in extra-articular (EA) RA manifestations including vasculitis, nodulosis, lung involvement, overlap syndromes, and EA manifestations of axial spondyloarthritis and inflammatory bowl diseases?
11. What is the efficacy and safety of combination therapies with JAKi and other targeted therapies, especially biological disease-modifying antirheumatic drugs in patients with severe RA or other diseases?
12. What are the distinct molecular *in vivo* downstream effects of JAK inhibition in the setting of individual diseases?
13. What are the differences between different JAKi (eg, TyK2i) regarding safety?
14. Are JAKi plus methotrexate (MTX) more efficacious than MTX + glucocorticoids (GC) in disease-modifying antirheumatic drug –naive RA (at least in the short term)?
15. What is the mechanism for JAKi-induced acne?
16. Can the dose of all JAKi be tapered or discontinued in remission?
17. Do drug levels of JAKi correlate with adherence to drug?
18. What is the mechanism leading to JAKi-induced creatinine and creatine phosphokinase elevations?
19. Will JAKi be efficacious in pre-RA or in preventing RA?
20. What is the effect of JAKi on pain and fatigue and what are the mechanisms?
21. How long should one interrupt JAKi therapy before and/or after vaccination?
22. Are there clinically meaningful efficacy differences between the different JAKi (including deucravacitinib)?

HBV, hepatitis B virus; HCV, hepatitis C virus; JAK, Janus kinase; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis.

Item 5: Elevations of CPK are noted with JAKi but have usually not been associated with clinical events; elevations of creatinine have been noted with JAKi but have not been associated with renal failure or hypertension (LoE, 2b; SoR, B; vote, 100%; LoA, 9.55)

This last recommendation remained essentially the same as in 2019. The data accrued since the last SLR further strengthen and confirm this conclusion [54,55]. Moreover, acne occurs more frequently on JAKi than that on placebo [82], although this analysis did not include filgotinib, which may have a different profile in this respect. Finally, a research agenda was discussed during and after the meeting, tabulated in Table 4.

DISCUSSION

This update presents an amended version of the consensus statement for using JAKi in IMIDs, developed in 2019. The

update became necessary because despite the short time since the development of the original document, new JAKi have been approved and licensed for several new indications. Most importantly, new safety issues have arisen, especially on cardiovascular and malignancy risks [13].

This statement differs from disease management recommendations in two important ways: first, as already pointed out, it does not deal with how a particular disease should be managed but rather with how JAKi should be used once the respective decision has been made; and second, it does not address a specific disease but rather the range of IMIDs for which JAKi have been approved. To this end, the taskforce included not only experienced clinicians from relevant specialties but also health care professionals and patients across nations and continents who focused on changes since the previous publication. The amendments were based on SLRs over the intervening period, which covered efficacy and safety aspects across IMIDs, being published separately in the future [17,18].

The taskforce discussions and decisions addressed general principles, indications and contraindications, screening, and monitoring, as well as a research agenda for the usage of JAKi therapy in patients with IMIDs. They cover the significant advances in JAKi therapy since 2019 regarding the development of novel agents such as the Tyk2 inhibitors; new approvals for novel indications, such as AxSpA, AD, and IBD; economic aspects given the advent of generics with implications for effective affordable therapy (especially for low income countries); data from trials focusing on safety, long-term extension studies of clinical trials, as well as registry data including patients with comorbidities and concomitant medications that would preclude their enrolment in clinical trials; as well as black box warnings from the Food and Drug Administration and European Medicines Agency adding safety concerns and dictating the place of JAK inhibition in therapy for a number of countries.

Since COVID-19 is not an IMID, it has not been addressed in this update, but it should be pointed out that baricitinib, in combination with remdesivir, has been approved for COVID-19 treatment and that EULAR has published recommendations that include advice for the management using immunomodulatory therapy such as JAKi in the setting of acute COVID-19 infection [83].

Baricitinib, deucravacitinib, filgotinib (in Europe and Japan), peficitinib (in Japan), tofacitinib, and upadacitinib are licensed for one or more autoimmune inflammatory diseases. Integrated safety analyses of tofacitinib up to 9.5 years (22 875 patient-years of exposure) [21,84], baricitinib up to 9.3 years (13 148 patient-years of exposure) [19,85–87], filgotinib to 5.6 years (5493 patient-years of exposure) [39,88], and upadacitinib (4020 patient-years of exposure) [20,56] have been published to complement the SLR safety analysis [89].

JAK selectivity has led to the development of novel molecules. Tyk2 inhibitors target signal transduction by IL-12, IL-23, IL-10, and type 1 interferons. Some of them, like deucravacitinib, bind covalently to the pseudokinase domain rather than reversibly to the adenosine triphosphate (ATP) pocket of the kinase domain [90]. Deucravacitinib has approval for PsO, a comprehensive PsA clinical trial programme [91,92], and is currently under investigation in SLE [25]. Also under development are beprocitinib and SAR-20347, which are inhibitors of Tyk2 and JAK1, while ropsacitinib inhibits Tyk2 and JAK2 and was under investigation in PsO and hidradenitis suppurativa, at the time of writing.

Follow-up data from long-term extensions of clinical trials and registry data has yet to demonstrate that ‘JAK 1 selectivity/preferred’ convincingly shows advantages in efficacy or safety between JAKi – apart from possibly reduced zoster and thromboembolic rates as well as less anaemia for filgotinib [22]. However, whether increased cardiovascular and thrombosis risk, as suggested by a head-to-head safety study (compared with TNF inhibition) [13] is a JAKi class effect or rather a specific JAK2 inhibition effect remains an unsettled question for the research agenda as does the possible mechanism for increased malignancy risk compared with that of TNFi. The safety and contraindication statements outlined in the respective sections of this update have been crafted to manage that risk until more definitive data are available. The task force encouraged the design of new outcome trials in this space to generate high-quality data.

Since drugs should generally be used at the minimum effective dose, the recommendations also address dose reduction once the desired state has been achieved. As far as this has been studied, good outcomes are maintained in most patients upon dose reduction, and in those in whom disease activity then increases, the good disease state is usually recaptured by returning to the previously more effective dose. Moreover, as indicated in the monitoring section, for all JAKi that interfere with IL-6 signal transduction and thus directly with CRP production, instruments that include CRP should presumably not be used in clinical trials and with caution in clinical practice to prevent potentially false trial results and erroneous continuation of an insufficiently efficacious JAKi. This is not an issue for Tyk2-selective inhibition.

Generic JAKi are now available in a number of countries, and the first clinical equivalence study of originator tofacitinib and a generic has been published [93]. Generic small molecules have the potential to provide highly effective therapy at a more affordable price particularly for countries where access is a major limitation due to cost, especially when long-term therapy is required, although cost containment is also an issue in high-income countries. In any case, recommendations remain as for the originator drugs.

The current consensus statement is certainly not a final one. Many other indications and many other JAKi are currently being investigated, and some of these studies are listed in Table 5.

In conclusion, this update acknowledges that a variety of specialists and health professionals are involved in the management of patients taking JAKi and emphasises the need for adequate information to provide informed consent. The update stresses the use of national and international guidelines and recommends dose adjustments in the setting of comorbidities like renal impairment and concomitant medications like rifampicin. Evidence for JAKi tapering while maintaining efficacy and recapture on flare has been updated. Given the ORAL Surveillance trial as well as extensive registry data, when JAKi therapy is considered, safety considerations like thrombosis, MACE, and malignancy must be taken into account, as well as individual risk and benefit, the patients disease journey, comorbidities, and concomitant medications. The research agenda remains important to answer questions of risk, mechanistic issues, safety in pregnancy and lactation, and adequacy of monitoring and more high-quality outcome trials are highly recommended. Once these data or other new information become available, a further update of this consensus statement will be desirable.

Competing interests

PN received grants for research, clinical trials, and for advice and lectures from Pfizer, Novartis, Janssen, UCB, Lilly, AbbVie, Samsung, BMS, Servatus, and Amgen. AK reports speakers bureau and consultancy for AbbVie, Amgen, Galapagos, Janssen, Eli Lilly, MSD, Novartis, Pfizer, and UCB. DA reports consultancy

Table 5
Status of using JAK inhibitors in IMIDs (green: approved, white: in trial; at the time of writing)

	TOFA	BARI	UPA	FILGO	PEFI	DEUC	RITLE	ABRO	RUXO
RA	Ph3	Ph3 Completed FDA 2 mg EMA 4 mg approved	Ph3 Completed FDA,EMA approved	Ph3 Completed EMA approved FDA pending	Ph2 Completedmultinational Ph3 Asia approved in Japan. China/Taiwan/Sth Korea ongoing				
PsA	Ph3 completed FDA,EMA approved		Ph3 Completed FDA,EMA approved	Ph2 completed, Ph3 term early		Ph2 completed, Ph3 ongoing			
rAxSpA	Ph3 completed FDA,EMA approved		Ph3 Completed FDA,EMA approved	Ph2 completed, Ph3 withdrawn					
nrAxSpA			Ph3 Completed FDA,EMA approved						
SLE		Ph3 completed, (SLE-BRAVE)	Ph3 ongoing (SELECT-SLE)			Ph2 completed, Ph3 ongoing			
DLE				Ph2 completed		Ph2 ongoing POETYK-SLE			Ph 2 single arm ongoing
LN				Ph2 completed		Ph2 terminated low recruitment			
SjS	Ph2 ongoing	Ph2 ongoing		Ph2 completed		Ph3 ongoing POETYK-SJS-1			
JIA	Ph3 completed FDA,EMA approved	Ph3 Completed, EMA approved							
UC	Ph3 completed FDA,EMA approved		Ph3 completed FDA,EMA approved	Ph3 completed, EMA approved	Ph2 completed	Ph2 completed	Ph2 completed		
CD	Ph2 completed		Ph3 Completed FDA,EMA approved	Ph2 completed		Ph 2 ongoing			
PsO	Ph3 completed				Ph2 completed	Ph3 completed FDA, EMA approved			

(*continued*)

Table 5
(Continued)

	TOFA	BARI	UPA	FILGO	PEFI	DEUC	RITLE	ABRO	RUXO
AD	Ph2 completed for topical TOFA	Ph3 completed, EMA approved 4 msg	Ph3 Completed FDA,EMA approved					Ph3 completed FDA EMA approved	Ph3 completed TRuE AD1-3
AA	Ph2 pilot study	Ph3 completed FDA 2 mg EMA 4 mg approved	Ph3 ongoing UPA-AA			Ph 2 ongoing	Ph3 completed FDA, EMA approved (>age 12)		Ph2 completed
Vit							Ph2 completed Ph3 ongoing, Tranquillo & Tranquillo 2		Ph3 completed FDA, EMA approved (also >age12)
HS			Ph2 completed, Ph3 ongoing Step-Up-HS)			Single centre Ph2 ongoing			Single arm single centre Ph2 ongoing

AA, alopecia areata; ABRO, abrocitinib; AD, atopic dermatitis; BARI, baricitinib; CD, Crohn disease; DEUCRA, deucravacitinib; DLE, discoid erythematosus; EMA, European Medicines Agency; FDA, Food and Drug Administration; FILGO, filgotinib; HS, hidradenitis supprativa; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; LN, lupus nephritis; nrAxSpA, nonradiographic axial spondylarthropathy; PEFI, peficitinib; Ph, phase; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; rAxSpA, radiographic axial spondylarthropathy; RITLE, ritlecitinib; RUXO, ruxolitinib; SjS, Sjogren syndrome; SLE, systemic lupus erythematosus; TOFA, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; Vit, vitiligo.

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Patient consent for publication

Patient involvement and participation in voting as well as commenting on the manuscript occurred throughout the process.

Ethical approval

Ethics approval was not sought nor needed for this study that involved a literature search, meetings, and voting procedures.

Data availability statement

All data obtained during the process have been disclosed in this article, and there is nothing else to share.

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REFERENCES

[1] Theofilopoulos AN, Kono DH, Baccala R. The multiple pathways to autoimmunity. Nat Immunol 2017;18(7):716–24. doi: 10.1038/ni.3731.
[2] Gutierrez-Arcelus M, Rich SS, Raychaudhuri S. Autoimmune diseases - connecting risk alleles with molecular traits of the immune system. Nat Rev Genet 2016;17(3):160–74. doi: 10.1038/nrg.2015.33.
[3] Petersen J, Ciacchi L, Tran MT, Loh KL, Kooy-Winkelaar Y, Croft NP, et al. T cell receptor cross-reactivity between gliadin and bacterial peptides in celiac disease. Nat Struct Mol Biol 2020;27(1):49–61. doi: 10.1038/s41594-019-0353-4.
[4] Harley JB, Chen X, Pujato M, Miller D, Maddox A, Forney C, et al. Transcription factors operate across disease loci, with EBNA2 implicated in autoimmunity. Nat Genet 2018;50(5):699–707. doi: 10.1038/s41588-018-0102-3.
[5] Zhang L. A common mechanism links Epstein-Barr virus infections and autoimmune diseases. J Med Virol 2023;95(1):e28363. doi: 10.1002/jmv.28363.
[6] Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001. doi: 10.1038/nrdp.2018.1.
[7] McInnes IB, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. Nat Rev Immunol 2021;21(10):680–6. doi: 10.1038/s41577-021-00603-1.
[8] Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003;2(6):473–88. doi: 10.1038/nrd1109.
[9] Bonelli M, Kerschbaumer A, Kastrati K, Ghoreschi K, Gadina M, Heinz LX, et al. Selectivity, efficacy and safety of JAKinibs: new evidence for a still evolving story. Ann Rheum Dis 2024;83(2):139–60. doi: 10.1136/ard-2023-223850.
[10] Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. Signal Transduct Target Ther 2020;5(1):209. doi: 10.1038/s41392-020-00312-6.
[11] Ganguly P, Macleod T, Wong C, Harland M, McGonagle D. Revisiting p38 mitogen-activated protein kinases (MAPK) in inflammatory arthritis: a narrative of the emergence of MAPK-activated protein kinase inhibitors (MK2i). Pharmaceuticals (Basel) 2023;16(9):1286. doi: 10.3390/ph16091286.
[12] Nash P, Kerschbaumer A, Dörner T, Dougados M, Fleischmann RM, Geissler K, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. Ann Rheum Dis 2021;80(1):71–87. doi: 10.1136/annrheum-dis-2020-218398.
[13] Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386(4):316–26. doi: 10.1056/NEJMoa2109927.
[14] The European Alliance of Associations for Rheumatology. EULAR SOPs – standard operating procedures for task forces [Internet]. 2024. Available from: https://wwweularorg/web/static/lib/pdfjs/web/viewerhtml?file=https://wwweularorg/document/download/702/412c1a86-96e4-4089-86a6-c6554204c6f9/679. Accessed January 8, 2024.
[15] OCEBM Levels of Evidence Working Group, Center for Evidence-based Medicine. OCEBM Levels of Evidence. Oxford: University of Oxford; 2011.
[16] Kerschbaumer A, Smolen JS, Nash P, Doerner T, Dougados M, Fleischmann R, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. RMD Open 2020;6(3):e001374. doi: 10.1136/rmdopen-2020-001374.
[17] Konzett VK, Efficacy of Janus kinase inhibitors in immune-mediated inflammatory diseases a systematic literature review informing the 2024 update of an international consensus statement, https://doi.org/10.1016/j.ard.2025.01.023.
[18] Konzett VK, Safety of Janus kinase inhibitors in immune-mediated inflammatory diseases – a systematic literature review informing the 2024 update of

an international expert consensus statement, https://doi.org/10.1016/j.ard.2025.01.024.
[19] Taylor PC, Takeuchi T, Burmester GR, Durez P, Smolen JS, Deberdt W, et al. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. Ann Rheum Dis 2022;81(3):335–43. doi: 10.1136/annrheumdis-2021-221276.
[20] Burmester GR, Cohen SB, Winthrop KL, Nash P, Irvine AD, Deodhar A, et al. Safety profile of upadacitinib over 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. RMD Open 2023;9(1):e002735. doi: 10.1136/rmdopen-2022-002735.
[21] Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open. 2020;6(3):e001395. doi: 10.1136/rmdopen-2020-001395.
[22] Tanaka Y, Genovese MC, Matsushima H. Long-term safety, efficacy, and patient-centered outcomes of filgotinib in the treatment of rheumatoid arthritis: current perspectives. Patient Prefer Adherence 2023;17:2499–516. doi: 10.2147/PPA.S417677.
[23] Corbella-Bagot L, Riquelme-McLoughlin C, Morgado-Carrasco D. Long-term safety profile and off-label use of JAK inhibitors in dermatological disorders. Actas Dermosifiliogr 2023;114(9):T784–801. doi: 10.1016/j.ad.2023.08.002.
[24] Martora F, Scalvenzi M, Ruggiero A, Potestio L, Battista T, Megna M. Hidradenitis suppurativa and JAK inhibitors: a review of the published literature. Medicina (Kaunas) 2023;59(4):801. doi: 10.3390/medicina59040801.
[25] Morand E, Pike M, Merrill JT, van Vollenhoven R, Werth VP, Hobar C, et al. Deucravacitinib, a tyrosine kinase 2 inhibitor, in systemic lupus erythematosus: a phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2023;75(2):242–52. doi: 10.1002/art.42391.
[26] Merrill JT, Tanaka Y, D'Cruz D, Vila-Rivera K, Siri D, Zeng X, et al. Efficacy and safety of upadacitinib or elsubrutinib alone or in combination for patients with systemic lupus erythematosus: a phase 2 randomized controlled trial. Arthritis Rheumatol 2024;76(10):1518–29. doi: 10.1002/art.42926.
[27] Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med 2021;384(9):795–807. doi: 10.1056/NEJMoa2031994.
[28] Geifman N, Cohen R, Rubin E. Redefining meaningful age groups in the context of disease. Age (Dordr) 2013;35(6):2357–66. doi: 10.1007/s11357-013-9510-6.
[29] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Faculty Baveno VII. Baveno VII - renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–74. doi: 10.1016/j.jhep.2021.12.022.
[30] Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41(9):1552–63.
[31] Burmester GR, Mariette X, Montecucco C, Monteagudo-Sáez I, Malaise M, Tzioufas AG, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66(6):732–9.
[32] Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barré E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015;74(1):19–26. doi: 10.1136/annrheumdis-2014-206106.
[33] Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut 2007;56(9):1226–31. doi: 10.1136/gut.2006.099978.
[34] Jani M, Barton A, Warren RB, Griffiths CEM, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford) 2014;53(2):213–22. doi: 10.1093/rheumatology/ket260.
[35] Takeuchi T, Genovese MC, Haraoui B, Li Z, Xie L, Klar R, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. Ann Rheum Dis 2019;78(2):171–8. doi: 10.1136/annrheumdis-2018-213271.
[36] Vermeire S, Su C, Lawendy N, Kobayashi T, Sandborn WJ, Rubin DT, et al. Outcomes of tofacitinib dose reduction in patients with ulcerative colitis in stable remission from the randomised RIVETING trial. J Crohns Colitis 2021;15(7):1130–41. doi: 10.1093/ecco-jcc/jjaa249.
[37] Winthrop K, Isaacs J, Calabrese L, Mittal D, Desai S, Barry J, et al. Opportunistic infections associated with Janus kinase inhibitor treatment for rheumatoid arthritis: a structured literature review. Semin Arthritis Rheum 2023;58:152120. doi: 10.1016/j.semarthrit.2022.152120.
[38] Winthrop K, Buch MH, Curtis J, Burmester GR, Aletaha D, Amano K, et al. POS0092. Herpes zoster in the filgotinib rheumatoid arthritis program. Ann Rheum Dis 2021;80(Suppl 1) 255.1-6. doi: 10.1136/annrheumdis-2021-eular.1408.
[39] Winthrop KL, Tanaka Y, Takeuchi T, Kivitz A, Matzkies F, Genovese MC, et al. Integrated safety analysis of filgotinib in patients with moderately to severely active rheumatoid arthritis receiving treatment over a median of 1.6 years. Ann Rheum Dis 2022;81(2):184–92. doi: 10.1136/annrheumdis-2021-221051.
[40] van Oorschot D, Vroling H, Bunge E, Diaz-Decaro J, Curran D, Yawn B. A systematic literature review of herpes zoster incidence worldwide. Hum Vaccin Immunother 2021;17(6):1714–32. doi: 10.1080/21645515.2020.1847582.
[41] Winthrop KL, Nash P, Yamaoka K, Mysler E, Khan N, Camp HS, et al. Incidence and risk factors for herpes zoster in patients with rheumatoid arthritis receiving upadacitinib: a pooled analysis of six phase III clinical trials. Ann Rheum Dis 2022;81(2):206–13. doi: 10.1136/annrheumdis-2021-220822.
[42] Winthrop KL, Loftus EV, Baumgart DC, Reinisch W, Nduaka CI, Lawendy N, et al. Tofacitinib for the treatment of ulcerative colitis: analysis of infection rates from the ulcerative colitis clinical programme. J Crohns Colitis 2021;15(6):914–29. doi: 10.1093/ecco-jcc/jjaa233.
[43] Huss V, Bower H, Hellgren K, Frisell T, Askling J, Behalf of the ARTIS group. Cancer risks with JAKi and biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis or psoriatic arthritis: a national real-world cohort study. Ann Rheum Dis 2023;82(7):911–9. doi: 10.1136/ard-2022-223636.
[44] Molina-Collada J, Alonso F, Otero L, Bohórquez C, Díaz Torné C, Pérez García C, et al. Cancer risk with biologic and targeted synthetic DMARDs in patients with rheumatic diseases and previous malignancies: results from the BIOBADASER register. Semin Arthritis Rheum 2024;64:152341. doi: 10.1016/j.semarthrit.2023.152341.
[45] Reinisch W, Hellstrom W, Dolhain R, Sikka S, Westhovens R, Mehta R, et al. Effects of filgotinib on semen parameters and sex hormones in male patients with inflammatory diseases: results from the phase 2, randomised, double-blind, placebo-controlled MANTA and MANTA-RAy studies. Ann Rheum Dis 2023;82(8):1049–58. doi: 10.1136/ard-2023-224017.
[46] Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016;75(5):795–810. doi: 10.1136/annrheumdis-2015-208840.
[47] Mease P, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis 2020;79(11):1400–13. doi: 10.1136/annrheumdis-2019-216761.
[48] Molander V, Bower H, Frisell T, Askling J. Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden. Ann Rheum Dis 2021;80(2):169–75. doi: 10.1136/annrheumdis-2020-218419.
[49] Center for Drug Evaluation and Research. Statistical review – clinical studies – olumiant (baricitinib) [Internet]. 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000StatR.pdf
[50] Charles-Schoeman C, Buch MH, Dougados M, Bhatt DL, Giles JT, Ytterberg SR, et al. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance. Ann Rheum Dis 2023;82(1):119–29. doi: 10.1136/ard-2022-222259.
[51] Kristensen LE, Danese S, Yndestad A, Wang C, Nagy E, Modesto I, et al. Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance. Ann Rheum Dis 2023;82(7):901–10. doi: 10.1136/ard-2022-223715.
[52] Hoisnard L, Pina Vegas L, Dray-Spira R, Weill A, Zureik M, Sbidian E. Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study. Ann Rheum Dis 2023;82(2):182–8. doi: 10.1136/ard-2022-222824.
[53] Meissner Y, Schäfer M, Albrecht K, Kekow J, Zinke S, Tony H-P, et al. Risk of major adverse cardiovascular events in patients with rheumatoid arthritis treated with conventional synthetic, biologic and targeted synthetic disease-modifying antirheumatic drugs: observational data from the German RABBIT register. RMD Open 2023;9(4):e003489. doi: 10.1136/rmdopen-2023-003489.
[54] Panaccione R, Isaacs JD, Chen LA, Wang W, Marren A, Kwok K, et al. Characterization of creatine kinase levels in tofacitinib-treated patients with

ulcerative colitis: results from clinical trials. Dig Dis Sci 2021;66(8):2732–43. doi: 10.1007/s10620-020-06560-4.
[55] Charles-Schoeman C, Giles JT, Lane NE, Choy E, Furst DE, Vencovský J, et al. Impact of upadacitinib on laboratory parameters and related adverse events in patients with RA: integrated data up to 6.5 years. Rheumatol Ther 2024;11(1):157–75. doi: 10.1007/s40744-023-00624-3.
[56] Cohen SB, van Vollenhoven RF, Winthrop KL, Zerbini CAF, Tanaka Y, Bessette L, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis 2021;80(3):304–11. doi: 10.1136/annrheumdis-2020-218510.
[57] Winthrop KL, Harigai M, Genovese MC, Lindsey S, Takeuchi T, Fleischmann R, et al. Infections in baricitinib clinical trials for patients with active rheumatoid arthritis. Ann Rheum Dis 2020;79(10):1290–7. doi: 10.1136/annrheumdis-2019-216852.
[58] Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79(1):39–52. doi: 10.1136/annrheumdis-2019-215882.
[59] Araujo CSR, Medeiros-Ribeiro AC, Saad CGS, Bonfiglioli KR, Domiciano DS, Shimabuco AY, et al. Two-week methotrexate discontinuation in patients with rheumatoid arthritis vaccinated with inactivated SARS-CoV-2 vaccine: a randomised clinical trial. Ann Rheum Dis 2022;81(6):889–97. doi: 10.1136/annrheumdis-2021-221916.
[60] Park JK, Lee YJ, Shin K, Kang EH, Ha YJ, Park JW, et al. A multicenter, prospective, randomized, parallel-group trial on the effects of temporary methotrexate discontinuation for one week versus two weeks on seasonal influenza vaccination in patients with rheumatoid arthritis. Arthritis Rheumatol 2023;75(2):171–7. doi: 10.1002/art.42318.
[61] Aletaha D, Smolen JS. Remission in rheumatoid arthritis: missing objectives by using inadequate DAS28 targets. Nat Rev Rheumatol 2019;15(11):633–4. doi: 10.1038/s41584-019-0279-6.
[62] Studenic P, Aletaha D, de Wit M, Stamm TA, Alasti F, Lacaille D, et al. American College of Rheumatology/EULAR remission criteria for rheumatoid arthritis: 2022 revision. Ann Rheum Dis 2023;82(1):74–80. doi: 10.1136/ard-2022-223413.
[63] Sieper J, Porter-Brown B, Thompson L, Harari O, Dougados M. Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. Ann Rheum Dis 2014;73(1):95–100. doi: 10.1136/annrheumdis-2013-203559.
[64] Kerschbaumer A, Smolen JS, Aletaha D. Disease activity assessment in patients with psoriatic arthritis. Best Pract Res Clin Rheumatol 2018;32(3):401–14. doi: 10.1016/j.berh.2018.08.004.
[65] Rubbert-Roth A, Enejosa J, Pangan AL, Haraoui B, Rischmueller M, Khan N, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. N Engl J Med 2020;383(16):1511–21. doi: 10.1056/NEJMoa2008250.
[66] Hendricks OC, Chrysidis S, Gerwien J, Saifan C, de Leonardis F, Lopez-Romero P, et al. CRP changes during bacterial infections in baricitinib-treated patients with RA. Arthritis Rheumatol 2018;70(Suppl 9):1683.
[67] van Vollenhoven R, Takeuchi T, Pangan AL, Friedman A, Mohamed MF, Chen S, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. Arthritis Rheumatol 2020;72(10):1607–20. doi: 10.1002/art.41384.
[68] McInnes IB, Kato K, Magrey M, Merola JF, Kishimoto M, Haaland D, et al. Efficacy and safety of upadacitinib in patients with psoriatic arthritis: 2-year results from the phase 3 SELECT-PsA 1 study. Rheumatol Ther 2023;10(1):275–92. doi: 10.1007/s40744-022-00499-w.
[69] Balanescu AR, Citera G, Pascual-Ramos V, Bhatt DL, Connell CA, Gold D, et al. Infections in patients with rheumatoid arthritis receiving tofacitinib versus tumour necrosis factor inhibitors: results from the open-label, randomised controlled ORAL Surveillance trial. Ann Rheum Dis 2022;81(11):1491–503. doi: 10.1136/ard-2022-222405.
[70] Winthrop KL, Citera G, Gold D, Henrohn D, Connell CA, Shapiro AB, et al. Age-based (<65 vs ≥65 years) incidence of infections and serious infections with tofacitinib versus biological DMARDs in rheumatoid arthritis clinical trials and the US Corrona RA registry. Ann Rheum Dis 2021;80(1):134–6. doi: 10.1136/annrheumdis-2020-218992.
[71] Curtis JR, Yamaoka K, Chen YH, Bhatt DL, Gunay LM, Sugiyama N, et al. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: results from the open-label, randomised controlled ORAL Surveillance trial. Ann Rheum Dis 2023;82(3):331–43. doi: 10.1136/ard-2022-222543.
[72] Khosrow-Khavar F, Desai RJ, Lee H, Lee SB, Kim SC. Tofacitinib and risk of malignancy: results from the safety of tofacitinib in routine care patients with rheumatoid arthritis (STAR-RA) study. Arthritis Rheumatol 2022;74(10):1648–59. doi: 10.1002/art.42250.
[73] Favalli EG, Buch MH, Galloway J, Constantin A, Durez P, Van Hoek P, et al. AB0454: safety of filgotinib in patients with RA: laboratory analysis results from a long-term extension study. Ann Rheum Dis 2023;82(Suppl 1):1417–8. doi: 10.1136/annrheumdis-2023-eular.2129.
[74] Loveikyte R, de Haas A, Oortwijn A, Eskens B, Jamoul C, Muller K, et al. P393 effect of filgotinib on anaemia in patients with ulcerative colitis in SELECTION. J Crohns Colitis 2023;17(Suppl 1):i525–7. doi: 10.1093/ecco-jcc/jjac190.0523.
[75] Kay J, Harigai M, Rancourt J, Dickson C, Melby T, Issa M, et al. Changes in selected haematological parameters associated with JAK1/JAK2 inhibition observed in patients with rheumatoid arthritis treated with baricitinib. RMD Open. 2020;6(3):e001370 doi:10.1136/rmdopen-2020-001370
[76] Morand E, Merola JF, Tanaka Y, Gladman D, Fleischmann R. TYK2: an emerging therapeutic target in rheumatic disease. Nat Rev Rheumatol 2024;20(4):232–40. doi: 10.1038/s41584-024-01093-w.
[77] Fleischmann RM, Thaçi D, Gooderham M, Strober B, Korman NJ, Banerjee S, et al. POS1040: safety of deucravacitinib, an oral, selective tyrosine kinase 2 inhibitor: as assessed by laboratory parameters – results from a phase 2 trial in psoriatic arthritis and 2 phase 3 trials in psoriasis. Ann Rheum Dis 2022;81(Suppl 1):835–6. doi: 10.1136/annrheumdis-2022-eular.1862.
[78] Strober B, Blauvelt A, Warren RB, Papp KA, Armstrong AW, Gordon KB, et al. Deucravacitinib in moderate-to-severe plaque psoriasis: pooled safety and tolerability over 52 weeks from two phase 3 trials (POETYK PSO-1 and PSO-2). J Eur Acad Dermatol Venereol 2024;38(8):1543–54. doi: 10.1111/jdv.19925.
[79] Salinas CA, Louder A, Polinski J, Zhang TC, Bower H, Phillips S, et al. Evaluation of VTE, MACE, and serious infections among patients with RA treated with baricitinib compared to TNFi: a multi-database study of patients in routine care using disease registries and claims databases. Rheumatol Ther 2023;10(1):201–23. doi: 10.1007/s40744-022-00505-1.
[80] Molander V, Bower H, Frisell T, Delcoigne B, Di Giuseppe D, Askling J, et al. Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis. Ann Rheum Dis 2023;82(2):189–97. doi: 10.1136/ard-2022-223050.
[81] Ingrassia JP, Maqsood MH, Gelfand JM, Weber BN, Bangalore S, Lo Sicco KI, et al. Cardiovascular and venous thromboembolic risk with JAK inhibitors in immune-mediated inflammatory skin diseases: a systematic review and meta-analysis. JAMA Dermatol 2024;160(1):28–36. doi: 10.1001/jamadermatol.2023.4090.
[82] Martinez J, Manjaly C, Manjaly P, Ly S, Zhou G, Barbieri J, et al. Janus kinase inhibitors and adverse events of acne: a systematic review and meta-analysis. JAMA Dermatol 2023;159(12):1339–45. doi: 10.1001/jamadermatol.2023.3830.
[83] Alunno A, Najm A, Machado PM, Bertheussen H, Burmester GRR, Carubbi F, et al. 2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19. Ann Rheum Dis 2022;81(1):34–40. doi: 10.1136/annrheumdis-2021-221366.
[84] Burmester GR, Nash P, Sands BE, Papp K, Stockert L, Jones TV, et al. Adverse events of special interest in clinical trials of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and psoriasis with 37 066 patient-years of tofacitinib exposure. RMD Open 2021;7(2):e001595. doi: 10.1136/rmdopen-2021-001595.
[85] Bieber T, Katoh N, Simpson EL, de Bruin-Weller M, Thaçi D, Torrelo A, et al. Safety of baricitinib for the treatment of atopic dermatitis over a median of 1.6 years and up to 3.9 years of treatment: an updated integrated analysis of eight clinical trials. J Dermatolog Treat 2023;34(1):2161812. doi: 10.1080/09546634.2022.2161812.
[86] King B, Mostaghimi A, Shimomura Y, Zlotogorski A, Choi GS, Blume-Peytavi U, et al. Integrated safety analysis of baricitinib in adults with severe alopecia areata from two randomized clinical trials. Br J Dermatol 2023;188(2):218–27. doi: 10.1093/bjd/ljac059.
[87] Guttman-Yassky E, Thyssen JP, Silverberg JI, Papp KA, Paller AS, Weidinger S, et al. Safety of upadacitinib in moderate-to-severe atopic dermatitis: an integrated analysis of phase 3 studies. J Allergy Clin Immunol 2023;151(1):172–81. doi: 10.1016/j.jaci.2022.09.023.
[88] Winthrop K, Aletaha D, Caporali R, Tanaka Y, Takeuchi T, Van Hoek P, et al. POS0844: integrated safety analysis of filgotinib in patients with moderate to severe active rheumatoid arthritis with a maximum exposure of 8.3 years. Ann Rheum Dis 2023;82(Suppl 1):721–2. doi: 10.1136/annrheumdis-2023-eular.1553.
[89] Szekanecz Z, Buch MH, Charles-Schoeman C, Galloway J, Karpouzas GA, Kristensen LE, et al. Efficacy and safety of JAK inhibitors in rheumatoid arthritis: update for the practising clinician. Nat Rev Rheumatol 2024;20(2):101–15. doi: 10.1038/s41584-023-01062-9.
[90] Jensen LT, Attfield KE, Feldmann M, Fugger L. Allosteric TYK2 inhibition: redefining autoimmune disease therapy beyond JAK1-3 inhibitors. EBioMedicine 2023;97:104840. doi: 10.1016/j.ebiom.2023.104840.

[91] Armstrong AW, Gooderham M, Warren RB, Papp KA, Strober B, Thaçi D, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J Am Acad Dermatol 2023;88(1):29–39. doi: 10.1016/j.jaad.2022.07.002.

[92] Strober B, Thaci D, Sofen H, Kircik L, Gordon KB, Foley P, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 program for evaluation of TYK2 inhibitor psoriasis second trial. J Am Acad Dermatol 2023;88(1):40–51. doi: 10.1016/j.jaad.2022.08.061.

[93] Zhao J, Huang H, Wang Y, Deng X, Geng Y, Zhang X, et al. Real-world clinical equivalence of generic and branded tofacitinib: a prospective longitudinal cohort study in patients with rheumatoid arthritis. Mayo Clin Proc 2024;99(1):26–38. doi: 10.1016/j.mayocp.2023.08.029.