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MINIREVIEW

Recommendations for risk minimization when using Janus kinase inhibitors for the treatment of chronic inflammatory skin diseases

Johannes Wohlrab[1,2] | **Thomas Kegel**[3] | **Regina Große**[4] | **Adina Eichner**[1,2]

[1]Department of Dermatology and Venereology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

[2]Institute for Applied Dermatopharmaceutics, Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany

[3]Department of Internal Medicine IV (Hematology and Oncology), Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany

[4]Deparment of Gynecology, Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany

Correspondence
Dr. rer. nat. Adina Eichner, Universitätsklinik für Dermatologie und Venerologie, Martin Luther University Halle-Wittenberg, Ernst-Grube-Straße 40, 06120 Halle (Saale).
Email: adina.eichner@medizin.uni-halle.de

Summary
In accordance with article 20 of Regulation (EC) No 726/2004, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has re-evaluated the safety of Janus kinase inhibitors for the treatment of inflammatory diseases and formulated safety information deviating from the previous indications in the respective summary of product characteristics of the products concerned. These refer to the consideration of a possibly increased risk of venous thromboembolic or severe cardiovascular events, an increased infection rate and an increase in the prevalence of skin cancer across drugs and indications. Therefore, in patients with independent risk factors (age 65 years and older, smokers or former smokers, patients with oral contraception or hormone replacement therapy and other risk factors), it is recommended to use Janus kinase inhibitors therapeutically only if there are no suitable treatment alternatives. To facilitate a pragmatic and thorough detection of high-risk patients in everyday clinical practice, an interdisciplinary checklist was developed that is suitable as a working tool from the perspective of the dermatologist.

KEYWORDS
benefit-risk-ratio, carcinogenic risk, cardiovascular risk, infection risk, Janus kinase inhibitors, safety, side effects, thromboembolic risk

INTRODUCTION

After an assessment of study and safety data, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has stated that tofacitinib for rheumatoid arthritis carries an increased risk of cancer and severe infection, and that baricitinib additionally carries an increased risk of severe cardiovascular events and venous thromboembolism.[1,2] Despite the varying pharmacological properties of Janus kinase inhibitors (JAKi), the different spectra and risk levels for undesired side effects, the varying risks in chronic-inflammatory indications, and variable individual risk factors in patients, the resulting recommendation offers no differentiation of the various compounds but considers Janus kinase inhibitors collectively as a group. The PRAC has thus issued a sweeping assessment for the whole class of medications that has been adopted by the Committee for Medicinal Products for Human Use (CHMP) at the EMA. This has led to a legally binding decision by the European Commission. As a result, the safety of JAKi has been re-assessed in all EU member states, leading to changes in the Summary of Product Characteristics (SmPC) for all JAKi approved in the indications rheumatoid arthritis, psoriasis arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, atopic dermatitis, and alopecia areata.[3]

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RECOMMENDATIONS OF THE EUROPEAN MEDICINES AGENCY (EMA)

The precise wording of the recommendations can be found in the original documents.[2] Based on these, the risks listed in the introduction are considered a class effect and are thus understood to apply to all JAKi approved in inflammatory indications.[2,3] Thus, for patients who are 65 years of age or older, who smoke or are former long-term smokers, and/or who display other risk factors for cardiovascular and/or malignant disease, treatment with JAKi is only recommended if no appropriate alternative treatment options are available.

Patients with other risk factors for venous thromboembolism (VTE) including previous venous thromboembolic events, major surgery, immobilization, use of combined oral contraceptives (COC) or hormone replacement therapy (HRT), or genetic coagulation disorders should receive JAKi only with caution. The harmonized safety assessment has resulted in more or less identically worded safety warnings in the SmPC, which in turn allows us to work out comprehensive management and information recommendations for all dermatologically relevant JAKi medications.

AUTHORS' MOTIVATION

The authors of this publication have been motivated to comment on the present situation because the new legal situation necessitates new recommendations for our day-to-day clinical practice in dermatology. Since the PRAC recommendations are generally of a broad and sweeping nature, the authors aim to explain the backgrounds as far as they are known, and offer well-founded recommendations for patient management. This is particularly important because patients who are already receiving JAKi must be informed about the new safety assessment of their medication in a transparent, scientifically correct, and appropriate manner. It is also our medical responsibility to assess the individual patient's risk factors apart from the clinical data used in the safety assessments, to analyze the risk with individual compounds and their dosage, and to counsel patients objectively about other therapeutic options.

BASIC PHARMACOLOGY

Janus kinases (JAK) are cytoplasmatic tyrosine kinases bound to membrane cytokine receptors that have no intrinsic enzymatic activity.[4,5] There are four subgroups of this enzyme family (JAK1–3 and TYK2). JAK1–2 and TYK2 are expressed ubiquitously while JAK3 is only expressed in cells of the hematopoietic system.[6] Janus kinases form part of the JAK-STAT signal pathway (STAT; signal transducers and activators of transcription); they activate STAT via phosphorylation, and STAT then control the transcription of regulatory proteins.[7] Janus kinases act via binding to cytoplasmatic motives of the transmembrane, hetero- or homodimeric cytokine receptors, thus they are paired and activate each other. In most cases, at least two JAK isoforms are involved in signal transduction.[6] Not all possible combinations of JAK dimers seem to occur. Homodimers have only been found for JAK2, and heterodimers have been reported for JAK1/2, JAK 1/3, JAK1/TYK, JAK2/TYK.[6] There are also seven different STAT which also act as either homodimers or heterodimers; the result is a large molecular variability of the signal cascade with broad regulatory functionality.[8]

Janus kinase inhibitors constitute a chemically heterogeneous group of molecules with different structure-activity relationships. They usually work via reversible, competitive inhibition of JAK activity by binding to the enzymatic center.[4] Binding of the individual JAKi to the binding pockets of various JAK isoforms is electrochemically mediated and – with rare exceptions – concentration dependent. This means that the binding spectrum (selectivity) of the individual compounds depends on the bioavailability of the individual JAKi in the intracellular binding pocket of the JAK.[4] Bioavailability in the target cell results from the applied dose, the distribution and elimination profile of the individual JAKi, and the pharmacological presence of the target cell. Uptake of a JAKi into the cell occurs through a solute carrier (SLC) and its efflux through an ATP-binding cassette (ABC). The proteins involved in this process vary depending on the individual JAKi and influence transport capacity and speed. Pharmacokinetics also depend on the duration of JAKi binding to the binding pocket of the individual JAK (residence time).[4] This depiction explains why the pharmacological effect of JAKi depends on various factors and why selectivity of the clinical effect is limited in defined indications. From a practical perspective, this means that the occurrence of undesired side effects, based on the molecular connections of the JAK/STAT signal pathways explained above, likely depends on the pharmacology of the individual JAKi, the indication, and individual patient factors such as comorbidity, age, concomitant medication, and other influences (pleiotropic effect).[4] JAKi mainly display anti-inflammatory, immunomodulatory, and antiproliferative effects and thus influence the immune response to infection, as well as tumor immunology or rather cytokine-dependent metabolic regulation networks.

RISK OF VENOUS THROMBOEMBOLIC EVENTS

An increased risk of thromboembolic events has been suggested based on study data from individual JAKi.[1,9,10] The actual, individual risk of thromboembolic events during JAKi treatment in dermatological indications is still very low.[11,12] The new safety assessment mainly concerns an increase in the general risk by coincident, independent

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risk factors for venous thromboembolism.[3] A relative contraindication for the use of JAKi would therefore apply primarily in cases of hereditary thrombophilia (such as APC resistance in Factor V Leiden mutation, hyperhomocysteinemia with polymorphism, prothrombin mutation, increased Factor VIII activity, and more rarely protein C deficiency, protein S deficiency, or antithrombin deficiency) as well as acquired thrombophilia (such as primary or secondary antiphospholipid syndrome, or severe liver dysfunction). We also know that a large number of other factors constitute an independent risk for thromboembolism. These include certain medications such as hormones (combined oral contraceptives, hormone replacement therapy) or anti-diuretics, but also nicotine abuse (active smokers, former long-term smokers), inactivity (bed rest, long periods of sitting such as in a wheelchair, major surgery, severe injury, pregnancy/delivery, or obesity) as well as cardiovascular disease (previous myocardial infarction less than three months ago, previous venous thromboembolism, arterial hypertension, severe heart failure, diabetes mellitus).[13–17]

On the other hand, we know that the probability of mutations increases with age, also for the gene segments that encode Janus kinases. This gives rise to cells that may exhibit clonal aberration and in certain microenvironments will cause excessive expression of pro-inflammatory cytokines. If mutated cells achieve clonal dominance, this may, for example, lead to myeloproliferative diseases with expansion of diverse myelocytic cell lines. Systemic mastocytosis (SM), for example, is characterized by massive proliferation of mast cells, while polycythemia vera (PV) shows proliferation of erythrocytes and essential thrombocytosis (ET) shows proliferation of thrombocytes. The mutations responsible for these conditions frequently lead to activation of tyrosine kinases. The *JAK2V617F* mutation, which may occur as a heterozygous or homozygous acquired somatic mutation, leads to an increased activity of JAK2 and is frequently found in polycythemia vera (90 %) and essential thrombocytosis (50 %).[18] Inhibition of JAK2 via appropriate JAKi can effectively treat these diseases and decrease the risk of complications including thromboembolic events.

RISK OF CARDIOVASCULAR EVENTS

The risk of cardiovascular disease is closely related to the thromboembolic risk and correlates with age. Independent of gender, the cardiovascular risk is considered increased from age 65 onwards.[19,20] The pathogenetic foundation of cardiovascular changes is caused by atherosclerosis and assumed to be affected by chronic inflammatory activity in the vessel wall as well as cytokine-mediated endothelial dysfunction based on insulin resistance.[21–23] These lead to remodeling processes in the vessel wall and result in calcification of the arteries – the obvious causes of clinical events such as myocardial infarction and stroke. Nicotine abuse as well as manifest arterial hypertension are the most important risk factors for these events.[19–21] In addition, the presence of metabolic syndrome with manifest, medically untreated LDL hypercholesterinemia, obesity, and type 2 diabetes is also considered highly relevant.[20,24–26] It is assumed that the use of JAKi is associated with an increased risk of major adverse cardiovascular events (MACE).[2] In patients who display one or more of the independent risk factors for MACE described above, the use of JAKi therefore carries a particular risk.

RISK OF SEVERE INFECTION

Activation or re-activation of latent infection is a known event in patients with immunosuppressive treatment including JAKi.[27] This mainly applies to herpes infections (herpes zoster, eczema herpeticum).[28] Since data on other chronic infections such as virus hepatitis, HIV/AIDS, or active/latent tuberculosis are sparse, there is currently no way to overcome the safety concerns regarding the use of JAKi. There is currently no evidence of an increased prevalence of clinical HPV manifestation or bacterial infection. Possibly relevant severe chronic infection should therefore be excluded via infection serology or cell-based procedures (IGRA testing).[4]

CANCER RISK

'The safety warnings also mention a suspected increase of non-melanoma skin cancer (NMSC) prevalence in connection with JAKi use.[2] It is common knowledge that the incidence of NMSC increases with age and depends on genetic disposition (skin type according to Fitzpatrick), UV exposure, and individual use of sun protection.[29] To counter this risk, we should offer our patients advice on the general preventative measures of UV protection (responsible handling of UV exposure, topical sunscreens, and textile sun protection) and strongly recommend the established oncological screening examinations (skin cancer screening).[30]

RECOMMENDATIONS

Since the safety warnings in the SmPC have been changed, it is legally necessary to amend the information we give our patients – both those who are currently on JAKi medication and those who are about to commence treatment with this type of drugs. In both cases, all potential risk factors must be taken into account so we can arrive at an individually appropriate risk-benefit assessment. The authors have developed a check list which is intended as a working aid for the dermatologist's day-to-day practice (Figure 1).

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Checklist for therapeutic use of Janus kinase inhibitors in dermatologic indications

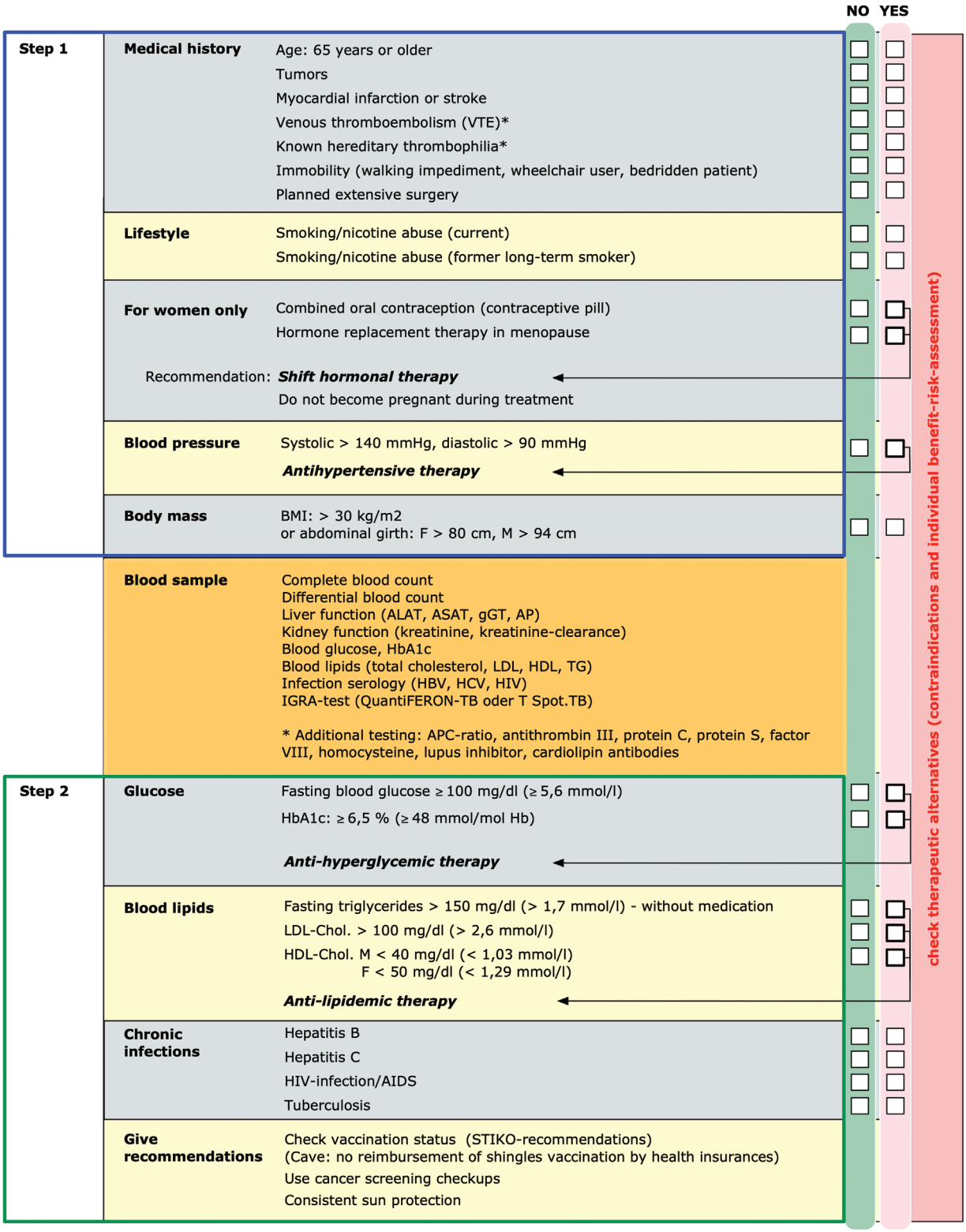

FIGURE 1 Checklist for registration of individual risk factors before and during therapy with Janus kinase inhibitors for the treatment of chronical inflammatory skin diseases.

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There are also recommendations on how to manage common risk situations so a person's individual risk may be reduced. In women taking hormonal contraceptives, the gynecologist should counsel the patient to either switch to progestin-only pills, minipills, or the hormonal coil, or use non-hormonal contraception.[31] In patients on HRT, non-hormonal alternatives such as antidepressants, anticonvulsants, antihypertensives, or plant-based medications should be preferred.[32,33]

Both active and passive smoking increases cardiovascular risk and causes a higher prevalence of coronary heart disease and stroke.[20,34,35] This can be detected early from one pack year (py) onwards and shows a relevant increase depending on the number of pack years.[20] Thus, former smokers (above one py) also have an increased risk. Patients with $\geq$ 1 py should only receive JAKi if there are no therapeutic alternatives and nontreatment is riskier than the planned treatment. The WHO risk calculation tool may be utilized for individual risk assessment (ten-year risk for a severe or lethal cardiovascular event); this is also available online or as an app.[36,37] The same applies to patients with a previous myocardial infarction, stroke, or venous thromboembolic event.[38–40] In individual, exceptional cases, concomitant medical treatment to prevent thrombosis may be tried in order to decrease the individual patient's risk.[41] Established anticoagulation or pharmaceutical platelet aggregation inhibition should be taken into account.

In case of pathological laboratory parameters that may indicate diabetic metabolism or hyperlipidemia, as well as in cases of suspected hypertension, the patient should be referred to the general practitioner for medical treatment.[42]

Patients with active or latent chronic infection should only receive JAKi if there are no therapeutic alternatives and nontreatment is riskier than the planned treatment. Depending on the type of infection, the option of chemopreventative treatment should be considered.[43] Vaccination status according to the STIKO recommendations should be checked, and especially in patients > 50 years, the herpes zoster vaccine is recommended.[44–46]

In patients with a history of cancer, clinical relevance must be taken into account and the individual profile regarding the oncogenic potential of JAKi treatment must be considered. Due to the potentially increased risk of nonmelanocytic skin cancer (NMSC), exposure to natural or artificial UV radiation (including UV combination therapy) should be avoided, and a sun protection strategy must be strictly implemented (behavioral rules as well as physical, textile, and chemical UV protection).[47–50] The usual oncological screenings (including skin cancer screening) should be performed regularly at the recommended intervals.[51]

Pharmacological considerations on the dose-response relationship indicate that dose reduction may be useful to reduce relevant risks during JAKi treatment. However, clear scientific evidence to prove clinical relevance in this regard is lacking.

Please note that although the comments and recommendations presented here have been formulated by the authors to the best of their knowledge based on comprehensive experience with JAKi treatment, patient information before or during treatment must still be offered on an individual basis by the managing physician.

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CONFLICTS OF INTEREST

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