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SHORT REPORT

A detailed look at the European Medicines Agency's recommendations for use of Janus kinase inhibitors in patients with atopic dermatitis

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Abstract

Background: Oral Janus kinase inhibitors (JAKi) have been approved for the treatment of several chronic inflammatory conditions, including rheumatoid arthritis (RA) and atopic dermatitis (AD). Prompted by new evidence, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently reassessed the benefit–risk balance of oral JAKi. The PRAC recommended that oral JAKi should be used only if no suitable alternatives are available in patients ≥65 years of age, or who have a history of atherosclerotic cardiovascular (CV) disease, other CV risk factors (e.g. history of long-term smoking) or have malignancy risk factors, and used with caution in patients at risk of pulmonary embolism or deep vein thrombosis. The European Commission's final decision was issued in March 2023.

Objectives: Our goal was to highlight the PRAC recommendations, especially in the context of oral JAKi use in AD.

Methods: Authors summarized the PRAC recommendations, the new clinical evidence on oral JAKi safety and key differences between patients with RA and AD.

Results: Risk of developing adverse events of special interest (e.g. cardiovascular events, malignancy) is higher in patients with RA than in patients with AD, because of the higher prevalence of the underlying risk factors.

Conclusions: The benefit–risk profile of JAKi approved for AD remains favourable, including use as first-line systemic therapy for patients with AD <65 years of age and without CV or malignancy risk factors.

INTRODUCTION

Janus kinase inhibitors (JAKi) act as immunomodulators and can be given orally and topically. Oral JAKi have been approved for the treatment of several chronic inflammatory rheumatological, gastroenterological and skin disorders: rheumatoid arthritis (RA), psoriatic or juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, alopecia areata and atopic dermatitis (AD).

In February 2022, under the Article 20 of Regulation (EC) No. 726/2004, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) initiated a reassessment (EMA/PRAC/68283/2022) of the benefit–risk balance of oral JAKi currently approved for the treatment of chronic inflammatory disorders, based on new pharmacovigilance data.[1,2] The final recommendations of the PRAC, released on 28 October 2022, were endorsed by the EMA's Committee for Medicinal Products for Human Use (CMHP) on 11 November 2022 (EMA/860610/2022).[3] The European Commission's (EC) final decision was issued in March 2023.

This short communication highlights the key recommendations from the PRAC, emphasising their relevance to the use of oral JAKi in AD.

INITIATION OF THE ARTICLE 20 REFERRAL PROCEDURE

The procedure was in part triggered by the final results of the ORAL Surveillance study, a randomized (1:1:1), open-label, long-term, post-authorisation safety trial conducted in patients ($N = 4362$) with active, moderate-to-severe RA despite methotrexate treatment, who were aged ≥50 years and had ≥1 additional cardiovascular (CV) risk factor.[1] The goal was to assess whether the combined dosages of tofacitinib (5 or 10 mg twice daily) were noninferior to tumour necrosis factor α inhibitors (TNFi), both on background of methotrexate, in terms of the risk of adjudicated major CV events (MACE) or malignancies, excluding nonmelanoma skin cancer (NMSC). The study did not demonstrate tofacitinib's noninferiority; it showed an increased risk of MACE and malignancies with tofacitinib versus TNFi in patients with RA, which did not vary by dosage. Post hoc analyses of this trial suggest that the excess risk of MACE, malignancies (excluding NMSC), and VTE in tofacitinib-treated patients was mainly driven by age ≥ 65 years and long-time smoking, and for MACE specifically, history of atherosclerotic CV disease.[4–6]

The PRAC also considered the recently published B023 study, which compared the risk of VTE, MACE or serious infections in patients ($N = 15,212$) with RA treated with baricitinib (mean follow-up: 9 months) or TNFi (mean follow-up: 10 months), using data from 14 disease registries and claims databases from the United States, Europe and Japan.[2] In this study, in which 46% of participants from the three largest US or European databases also received methotrexate, risk of adverse events of interest with this JAKi was also greater than with a TNFi, although the incidence rate differences did not reach statistical significance.

In addition, an analysis of US claims data, prompted by the publication of the ORAL Surveillance study,[1] found no difference in the risk of MACE between tofacitinib- and TNFi-treated patients with RA ($N = 102,263$).[7] The risk was nominally higher, without statistical significance, for tofacitinib in a subset of patients selected to meet enrolment criteria from the ORAL Surveillance study.[7]

Given the largely similar mechanism of action among currently approved JAKi, the Article 20 referral procedure was triggered for all oral JAKi approved for chronic inflammatory conditions: tofacitinib, baricitinib, abrocitinib, upadacitinib and filgotinib. Among these, abrocitinib, upadacitinib and baricitinib are approved in the European Union for treatment of AD.

OUTCOMES OF THE ARTICLE 20 REFERRAL PROCEDURE

With the EC's final decision, PRAC's final recommendations have become legally binding. The indications of JAKi approved for AD remain unchanged: those agents are approved 'for the treatment of moderate-to-severe AD in adults who are candidates for systemic therapy', and are not restricted to those who previously failed other systemic therapies (i.e. no switch to second-line indication). However, the label now includes clarifications about exercising additional caution when prescribing JAKi in certain at-risk subpopulations. Specifically, JAKi should only be used if no suitable treatment alternatives are available in patients ≥65 years of age, or who have a history of atherosclerotic CV disease, other CV risk factors (such as long-term current or long-term past smoker status) or have malignancy risk factors (e.g. current malignancy or personal history of malignancy), and should be used with caution in patients at risk of VTE (pulmonary embolism or deep vein thrombosis).

IMPACT OF AGE

According to the subgroup analyses of the ORAL Surveillance data, the incidence rates of MACE were higher in patients with RA aged ≥65 years (IR [95%CI]: tofacitinib, combined dosages, 1.63 [1.20–2.18] vs. TNFi, 0.91 [0.50–1.52]) than in those aged <65 years (0.72 [0.54–0.94] vs. 0.66 [0.42–0.99], respectively).[1] A similar relationship between age and the incidence rate of malignancies was observed in tofacitinib-treated patients.[1]

The increased risk of MACE, VTE and malignancies for patients ≥65 years of age was also observed in patients with AD. For example, Figure 1 summarizes the incidence of those events by age in patients from the nationwide Danish AD cohort who were not receiving JAKi treatment, and in the safety data pool from the abrocitinib clinical development program (Pfizer data on file).

IMPACT OF SMOKING

In the ORAL Surveillance study, about half of the participants were current or past smokers.[1] Data from the Danish AD Cohort, with participants who did not receive JAKi, do not suggest an increased prevalence of smoking in patients with AD, compared with general population.[8] Based on the smoking duration data from ORAL Surveillance study, according to which >90% of participants who were past smokers and >90% of participants who were current smokers had >10 years of smoking history (Pfizer data on file), a PRAC warning was formulated to address past long-term or current long-term smokers.

EXTRAPOLATION OF RISK FROM RA TO AD

Data from the Phase 3b-4 ORAL Surveillance trial and an analysis of 14 real-world data sources, evaluated by PRAC, support an increased risk of MACE, VTE and malignancies with JAKi versus TNFi in patients with RA with elevated

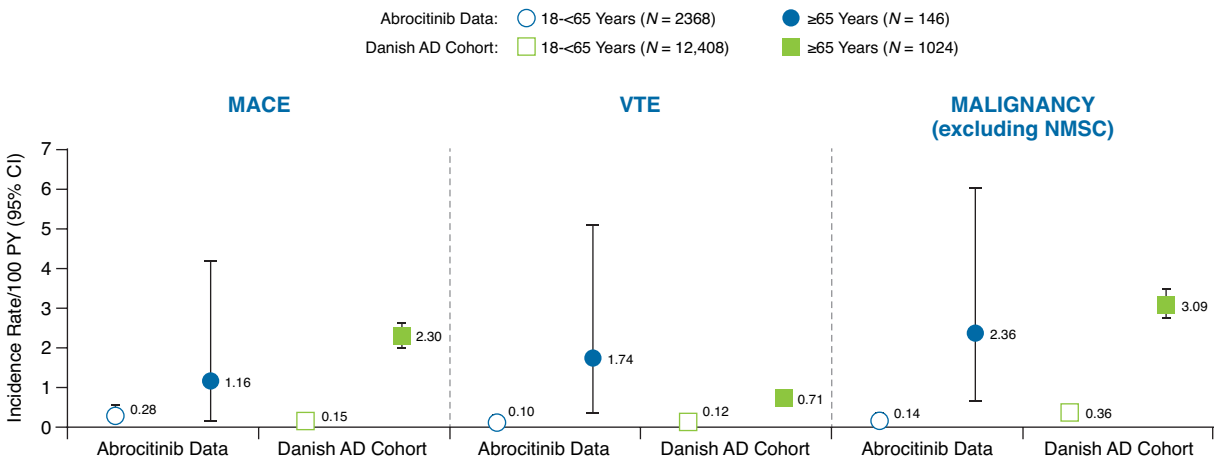

FIGURE 1 Incidence of MACE, VTE and malignancies in patients with AD, by age. The Danish AD cohort comprised patients with AD who did not receive JAKi treatment. Long-term abrocitinib safety data are from the JADE EXTEND study (NCT03422822; planned interim analysis, cutoff date 25 September 2021). Values presented here may change because the JADE EXTEND study is ongoing. Abbreviations: AD, atopic dermatitis; CI, confidence interval; JAKi, Janus kinase inhibitor; MACE, major cardiovascular event; NMSC, nonmelanoma skin cancer; PY, patient-year; VTE, venous thromboembolism.

CV risk.[1,2] In addition, an analysis of the World Health Organization's pharmacovigilance data found an increased risk of malignancies (in particular skin neoplasms), but not of CV events, in patients treated with JAKi compared with the overall population.[9] However, 64% of patients in that sample were treated with tofacininib, which suggests a sample not representative of patients with moderate-to-severe AD.[9]

Because we do not know the potential mechanism by which JAKi would influence the development of these events, a JAKi-associated risk increase in patients with AD cannot be excluded. However, ORAL Surveillance data support the view that an increase in incidence of the adverse events of special interest in patients treated with tofacitinib was driven by the prevalence of baseline CV risk factors, including age.[4–6] Epidemiological data show markedly different prevalence of CV and malignancy risk factors between patients with RA and AD. On average, patients with AD are much younger and, as a result, have a lower background CV and cancer risk, compared to the patients with RA in the ORAL Surveillance study, who in turn had a greater prevalence of CV risk factors than the general population of individuals with RA (Table 1). It should be noted that the interaction of age, inflammatory processes and risk of CVD and cancer is a complex phenomenon,[10] which exceeds the scope of this short communication. In addition, age may interact with other risk factors, and thereby create a cumulative effect.

TNFi AS COMPARATORS IN RA DATA SETS

Observational studies suggest that TNFi are protective for MACE.[11] Since, for ethical reasons, neither the ORAL Surveillance nor the B023 study included a placebo or no-treatment control,[1,2] it is not clear what the absolute increase in risk of MACE attributable to JAKi treatment would be. According to a meta-analysis of short-term clinical trial data, there was no increased risk of MACE or VTE with JAKi versus placebo,[12] and, as mentioned above, study of the World Health Organization's pharmacovigilance data compared patients treated with JAKi with the entire database sample who likely received other treatments.[9] However, to the best of our knowledge, no long-term comparison of pharmacovigilance JAKi treatment data versus no treatment has been performed to date.

ABSOLUTE RISK OF MACE, VTE AND MALIGNANCIES IN ABROCITINIB-TREATED PATIENTS WITH AD

In patients with AD who received abrocitinib long-term, the incidence rates (events per 100 patient-years) of MACE, VTE and malignancies were 0.26, 0.18 and 0.21, respectively (Figure 2). The lower incidence rates of these adverse events of special interest in patients with AD compared with those in the ORAL Surveillance study were likely due to younger age and the lower prevalence of CV risk factors in patients with AD.[13,14]

If these incidence rates, observed in patients with AD, were adjusted based on the hazard ratios observed for tofacitinib versus TNFi in the ORAL Surveillance study (see footnote of Table 2), the resulting values would be 3.2/1000 PY (MACE), 3.0/1000 PY (VTE) and 3.1/1000 PY (malignancies, excluding NMSC). This is approximately equivalent to about three events each in 1000 patients treated for 1 year (Table 2). These estimates were obtained without taking into consideration the substantially lower prevalence of CV risk factors in patients with AD, which suggests that the actual incidence rates would be even smaller.

TABLE 1 Comparison of patient populations with RA and AD (clinical trials and real-world data).

	ORAL Surveillance study, all tofacitinib (RA), *N* = 2911	Abrocitinib program, all abrocitinib (AD), *N* = 3004	Fold difference, ORAL Surveillance study vs. abrocitinib program[a]
Age, years, mean	61.1	33.4	1.8
Age ≥ 65 years, %	30.6	4.9	6.2
History of hypertension, %	65.6	11.9	5.5
History of diabetes mellitus, %	17.3	2.4	7.2
History of coronary artery disease, %	11.4	0.9	12.7
Age ≥ 50 years with at least 1 risk factor, %	100% (inclusion criterion)	10.3	9.7

	Danish national registries[b]		
	Patients with RA, *N* = 48,055	Patients with AD, from the Danish AD cohort, *N* = 13,342	Fold difference, RA vs. AD[c]
Age, years, mean	60.3	37.8	1.6
Age ≥ 65 years, %	42.0	7.6	5.5
History of coronary artery disease, %	8.9	2.6	3.4
History of stroke, %	2.1	0.8	2.6
History of deep vein thrombosis, %	2.3	0.9	2.6
History of pulmonary embolism, %	0.9	0.4	2.2
History of malignancies, excluding NMSC, %	6.9	3.0	2.3

Abbreviations: AD, atopic dermatitis; JAKi, Janus kinase inhibitor; NMSC, nonmelanoma skin cancer; RA, rheumatoid arthritis.
[a]Fold difference calculated as follows: $\left(\frac{\text{ORAL value}}{\text{Abrocitinib Program value}}\right)$.
[b]Patients from Danish national registries did not receive JAKi treatment.
[c]Fold difference calculated as follows: $\left(\frac{\text{RA Cohort}}{\text{AD Cohort}}\right)$.

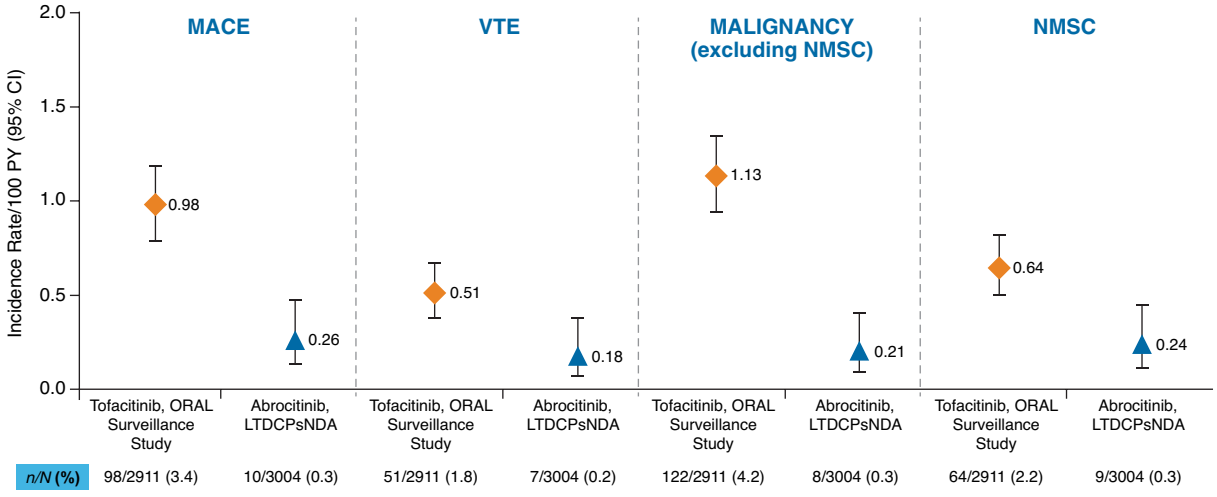

FIGURE 2 Incidence of MACE, VTE and malignancies in the ORAL Surveillance study and in the long-term safety pool[a] of the abrocitinib AD program. [a]Data from the long-term extension study JADE EXTEND (NCT03422822; planned interim analysis, cutoff date 25 September 2021). Values presented here may change because the JADE EXTEND study is ongoing. Abbreviations: AD, atopic dermatitis; LTDCP, long-term dose-controlled pool of abrocitinib in AD; MACE, major cardiovascular event; NMSC, nonmelanoma skin cancer; sNDA, supplemental new drug application; PRAC, Pharmacovigilance Risk Assessment Committee; PY, patient-years; VTE, venous thromboembolism.

Based on these adjusted incidence rates for MACE, VTE and malignancies (excluding NMSC) and the observed incidence rates in the abrocitinib AD long-term safety pool, the absolute increase in risk would be approximately equivalent to 1 event per 1000 patients with AD treated with a JAKi for 1 year (Table 2).

TABLE 2 Incidence of MACE, VTE and malignancies in patients with AD not treated with JAKi, and estimated additional risk of MACE, VTE and malignancies associated with JAKi use, events per 1000 PY.

MACE				VTE				Malignancies, excluding NMSC			
Not treated with JAKi		Treated with JAKi		Not treated with JAKi		Treated with JAKi		Not treated with JAKi		Treated with JAKi	
Danish AD cohort[a]	KPNC cohort[b]	Adjusted abrocitinib data[c]	Absolute additional risk with JAKi[d]	Danish AD cohort[a]	KPNC cohort[b]	Adjusted abrocitinib data[c]	Absolute additional risk with JAKi[d]	Danish AD cohort[a]		Adjusted abrocitinib data[c]	Absolute additional risk with JAKi[d]
3.3	2.6	3.2[d]	≈1	1.8	2.0	3.0[d]	≈1	5.9		3.1[d]	≤1

Abbreviations: AD, atopic dermatitis; ICD, International Classification of Diseases; JAKi, Janus kinase inhibitor; KPNC, Kaiser Permanente Northern California; MACE, major cardiovascular event; NMSC, nonmelanoma skin cancer; PY, patient-years; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

[a]The Danish AD cohort comprised adult patients with AD, all levels of disease severity, who did not receive JAKi treatment. Diagnosis of MACE, malignancies and VTE were based on ICD-10 codes and have been validated using data from patients' medical records (Pfizer data on file).

[b]KPNC comprised patients with moderate-to-severe AD, aged ≥12 years, and enrolled in the Kaiser Permanente Northern California healthcare system. In this study, MACE and VTE were identified using the ICD codes.[15]

[c]Hypothetical scenario, calculated by multiplying the incidence rates of MACE, VTE or malignancies (excluding NMSC) observed in the abrocitinib long-term safety data pool (Pfizer data on file) by the respective hazard ratios (abrocitinib vs. TNFi) reported in the ORAL Surveillance study.[1] Long-term safety data are from the JADE EXTEND study (NCT03422822; planned interim analysis, cutoff date 25 September 2021). Values presented here may change because the JADE EXTEND study is ongoing.

[d]Absolute increase in risk was obtained after adjustment of abrocitinib long-term safety data with the respective hazard ratios reported in the ORAL Surveillance study.[1] Long-term safety data are from the JADE EXTEND study (NCT03422822; planned interim analysis, cutoff date 25 September 2021). Values presented here may change because the JADE EXTEND study is ongoing.

In conclusion, the benefit–risk profile of JAKi approved for AD (i.e. the rates of significant improvement in skin lesions, eczema itch and dermatology-related quality of life vs. the rates of emergent adverse events) remains favourable, including the use as first-line therapy in patients with AD <65 years of age and those without CV or malignancy risk factors.[3,16] For individual patients with risk factors, the benefit–risk profiles of available therapies should be compared. Treatment options should be selected[17] based on shared decision-making between the prescriber and the patient, while keeping in mind that the absolute risk of additional MACE, VTE or cancer events with JAKi, extrapolated from comparison with TNFi in patients with RA, appears to be low.

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CONFLICT OF INTEREST STATEMENT

A. Wollenberg has been an advisor, speaker or investigator for Pfizer Inc., AbbVie, Alcimed, Almirall, Beiersdorf, Bioderma, Chugai, Galapagos, Galderma, Glenmark, GSK, Hans Karrer, LEO Pharma, Eli Lilly and Company, L'Oreal, Maruho, MedImmune, MSD, Novartis, Pierre Fabre, Regeneron, Santen, Sanofi Genzyme and USB. J. P. Thyssen is an advisor for Pfizer Inc., AbbVie, Almirall, Arena Pharmaceuticals, Aslan Pharmaceuticals, Coloplast, Eli Lilly & Co, LEO Pharma, OM Pharma, Regeneron, Sanofi Genzyme, RAPT Therapeutics, and Union Therapeutics; a speaker for Pfizer Inc., AbbVie, Almirall, Eli Lilly and Company, LEO Pharma, Regeneron and Sanofi Genzyme, and received research grants from Pfizer Inc., Regeneron, and Sanofi Genzyme. T. Bieber has been a speaker and/or consultant and/or investigator for Pfizer Inc., AbbVie, Affibody, Almirall, AnaptysBio, Asana Biosciences, ASLAN Pharma, Bayer Health, BioVerSys, Boehringer-Ingelheim, Bristol Myers Squibb, Connect Pharma, Dermavant, DIECE Therapeutics, Domain Therapeutics, EQRx, Galderma, Glenmark, GSK, Incyte, Innovaderm, IQVIA, Janssen, Kirin, Kymab, LEO Pharma, LG Chem, Lilly, L'Oréal, MSD, Novartis, Numab, OM-Pharma, Pierre Fabre, Q32bio, RAPT Therapeutics, Sanofi/Regeneron, and UCB. He is founder and chairman of the board of the non-profit biotech, Davos Biosciences. G. Chan and U. Kerkmann are employees of Pfizer and may own company stock.

DATA AVAILABILITY STATEMENT

On request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to

certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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