PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case-time control study and a nested case-control study based on the French national health insurance (SNDS) cohort.
AUTHORS	BERTHE, Pauline; Scailteux, Lucie-Marie; Lescoat, Alain; STAUMONT, DELPHINE; Coiffier, Guillaume; Guéret, Pierre; Dupuy, Alain; Oger, Emmanuel; Droitcourt, Catherine

VERSION 1 – REVIEW

REVIEWER	Melikhov, Oleg Institute of Clinical Research
REVIEW RETURNED	16-Feb-2022

GENERAL COMMENTS	1. To define research question (currently "objective", p.5). 2. To clarify study objectives (currently "questions", p.5). 3. To formulate study hypothesis or explain why the hypothesis is not formulated. 4. To clarify primary (secondary) variables/ endpoint/ outcomes, to reach the study objective(s (currently "outcomes", p. 10-11).

REVIEWER	Wang, Suli Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Department of Rheumatology
REVIEW RETURNED	19-Feb-2022

GENERAL COMMENTS	This protocol is to investigate the association between JAKis prescribed for AD and VTEs, which will address the following two questions: 1)is the risk of VTEs higher in adults with AD exposed to JAKis than in AD adults not exposed to JAKis, and (2) does the initiation of treatment with a JAKi trigger VTEs? The following are my comments: 1. A study about "Tofacitinib and risk of cardiovascular outcomes" was recently published in the journal of Ann Rheum Dis. In that multidatabase, population- based study including 102263 rheumatoid arthritis patients, tofacitinib was not associated with an increased risk of cardiovascular outcomes when compared with tumour necrosis factor inhibitors. I think the discussion and analysis of this paper may improved and ameliorated according it. 2. In the previous studies, tofacitinib, either as monotherapy or in combination with non- bDMARDs were associated with 15% to 20% increase in low- density lipoprotein cholesterol (LDL- C) and high- density lipoprotein cholesterol (HDL- C levels) when comparing 4 weeks after treatment initiation with baseline. HDL- C and LDL- C: HDL- C levels, as we know, are more reliable

	predictors of CV events. Were these indicators monitored in this study, though the patients of AD were relatively young?

VERSION 1 – AUTHOR RESPONSE

REVIEWER: 1

Dr. Oleg Melikhov, Institute of Clinical Research
Comments to the Author:

1. To define research question (currently "objective", p.5).
2. To clarify study objectives (currently "questions", p.5).

REPLY to comments 1 and 2:
Thank you for your comments.
The objective of our study is to investigate the association between JAK inhibitors prescribed for atopic dermatitis and venous thromboembolic events, using data from the French national health insurance system between 2017 and 2025.
We will address two research questions: (i) is the risk of VTEs higher in adults with AD exposed to JAKis than in AD adults not exposed to JAKis, and (ii) does the initiation of treatment with a JAKi trigger VTEs?

We have clarified this point by positioning the study objective and the research questions in the introduction section as follows: “Our objective is to investigate the association between JAKis prescribed for AD and VTEs, using data from the French national health insurance system between 2017 and 2025. We will address two research questions: (i) is the risk of VTEs higher in adults with AD exposed to JAKis than in AD adults not exposed to JAKis, and (ii) does the initiation of treatment with a JAKi trigger VTEs?” (page 4).

We have also modified the methods and analysis section as follows: “Hence, we have designed: (i) a nested case-control study and (ii) a case-time-control study in a cohort of adults with AD with data from the French national health insurance system (2017-2025)” (page 3).

3. To formulate study hypothesis or explain why the hypothesis is not formulated.

REPLY:
The study null hypotheses are formulated as follows: (i) VTE risk is equal in adults with AD exposed or not exposed to JAKis, (ii) JAKi initiation does not trigger VTE. We have clarified this point in the method and analysis section (page 8).

4. To clarify primary (secondary) variables/ endpoint/ outcomes, to reach the study objective(s (currently "outcomes", p. 10-11).

REPLY:
The primary endpoint is venous thromboembolic event (VTE); it is a composite endpoint encompassing pulmonary embolism, managed mostly in hospital and identified through hospital discharge ICD-10 code (Table 2), and deep-vein thrombosis managed mostly in an outpatient setting and identified through a dedicated and validated algorithm (manuscript under review).
This point has been clarified as follows in the revised manuscript: “The primary endpoint is VTE; it is a composite endpoint encompassing pulmonary embolism, managed mostly in hospital and identified

through hospital discharge ICD-10 code (table 2), and deep-vein thrombosis managed mostly in an outpatient setting and identified through a dedicated and validated algorithm (manuscript under review)" (page 10).

REVIEWER: 2

Dr. Suli Wang, Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital
Comments to the Author:
This protocol is to investigate the association between JAKis prescribed for AD and VTEs, which will address the following two questions: 1)is the risk of VTEs higher in adults with AD exposed to JAKis than in AD adults not exposed to JAKis, and (2) does the initiation of treatment with a JAKi trigger VTEs?
The following are my comments:
1. A study about "Tofacitinib and risk of cardiovascular outcomes" was recently published in the journal of Ann Rheum Dis. In that multidatabase, population- based study including 102263 rheumatoid arthritis patients, tofacitinib was not associated with an increased risk of cardiovascular outcomes when compared with tumour necrosis factor inhibitors. I think the discussion and analysis of this paper may improved and ameliorated according it.

REPLY:
Thank you for your comments.
Thank you for this update. At the time of the submission of our manuscript, this study "Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study. Khosrow-Khavar F, Kim SC, Lee H, Lee SB, Desai RJ. Ann Rheum Dis. 2022" was not yet published.

The study has specifically investigated the risk of MACEs or major adverse cardiovascular events including myocardial infarction and stroke under tofacitinib but not the risk of venous thromboembolic events. The outcomes of our study protocol are venous thromboembolic events.

2. In the previous studies, tofacitinib, either as monotherapy or in combination with non- bDMARDs were associated with 15% to 20% increase in low- density lipoprotein cholesterol (LDL- C) and high-density lipoprotein cholesterol (HDL- C levels) when comparing 4 weeks after treatment initiation with baseline. HDL- C and LDL- C: HDL- C levels, as we know, are more reliable predictors of CV events. Were these indicators monitored in this study, though the patients of AD were relatively young?

REPLY:
Our data source is the French Health insurance administrative database named SNDS (for the Système National des Données de Santé). This database is exhaustive at the national level and contains anonymous and individual data on demographic characteristics (gender, date of birth, date of death); all medical reimbursements including drugs and their date of issue, laboratory tests, medical procedures outpatient medical care and visits, all hospitalizations and their associated diagnostic codes from the International Classification of Diseases, 10th Revision (ICD-10) and all causes of death according the ICD-10.
However, information on the results of laboratory tests is not available in the medicoadministrative database. We will have the information on the laboratory tests and its dates but not the test results. This point has been clarified in the data sources section as follows: "Information on medical procedures or biological results are not available in the SNDS" (page 9).

Furthermore, cholesterol levels are not predictors of venous thromboembolic events. Some studies suggest, however, a beneficial effect of statin use on venous thromboembolism (Kunutsor S et al.

Lancet Haematol. 2017). The use of statins can be assessed from the SNDS and we propose to add in the covariates. This point have been added in the revised manuscript: “The results will be adjusted for several covariates, including the patient’s chronic comorbidities (using Bannay et al.’s algorithm for use of the Charlson Comorbidity Index with an electronic healthcare database) and the use of statins or systemic corticosteroids” (page 13). This covariate has been added in Figures 2 and 3, and Table 2.

VERSION 2 – REVIEW

REVIEWER	Melikhov, Oleg Institute of Clinical Research
REVIEW RETURNED	27-Apr-2022

GENERAL COMMENTS	Thank you for giving me an opportunity to review your manuscript bmjopen-2021- 059979 entitled “Risk of venous thromboembolic events associated with JAK inhibitors in atopic dermatitis: a methodological protocol using French medico-administrative database. JAKTER study (JAK-inhibitors and ThromboEmbolic Risk).” We believe the results of the study will be of high scientific quality and will give a better understanding of the possible role of JAKis in the development of thromboembolic events. We recommend BMJ Open to accept the manuscript. At the same time, please find below a few comments which probably could improve the investigation. We will be pleased if you would take them into consideration but, if not, the quality of the study will not be questionned. 1. Formulating of two research questions of “equal significance” may pose some difficulties for further designing of the study, for instance, sample size evaluation, especially for studies with hypothesis. At the same time, the study goals (for instance, “to evaluate whether initiation of a JAKi increasesthe risk of VTE in the following three months”) could be reached by formulating the relevant secondary objective. 2. The research question “Whether JAKis administration increase the risk of VTEs in adults with AD?” could be followed by the primary objective of the study “To assess the risk of VTEs in adults with AD exposed to JAKis comparing to AD adults not exposed to JAKis” and secondary objective “To evaluate the risk of VTEs in adults with AD within three months after administration of JAKis”. 3. The primary hypothesis should include the clinically significant difference in frequency of VTEs. For instance, “OR 2 and above is considered as clinically significant”. At the same time, this kind of research (extended retrospective database search) may not require the clear study hypothesis and may be of explorative/ pilot nature, to find the possible relations between different characteristics and variables.

VERSION 2 – AUTHOR RESPONSE

REVIEWER: 1

Dr. Oleg Melikhov, Institute of Clinical Research, Moscow, the Russian Federation

Comments to the Author:

1. Formulating of two research questions of “equal significance” may pose some difficulties for further designing of the study, for instance, sample size evaluation, especially for studies with hypothesis. At the same time, the study goals (for instance, “to evaluate whether initiation of a JAKi increases the risk of VTE in the following three months”) could be reached by formulating the relevant secondary objective.

2. The research question “Whether JAKis administration increase the risk of VTEs in adults with AD?” could be followed by the primary objective of the study “To assess the risk of VTEs in adults with AD exposed to JAKis comparing to AD adults not exposed to JAKis” and secondary objective “To evaluate the risk of VTEs in adults with AD within three months after administration of JAKis”.

REPLY for points 1 and 2:

Thank you for your comments. This point has been re-worded as follows in the revised manuscript:

- In the abstract section: “our research question is to investigate whether Janus Kinase inhibitors (JAKis) administration increases the risk of venous thromboembolic events (VTEs) in adults with atopic dermatitis (AD). Our primary objective is to assess the risk of VTEs in adults with AD exposed to JAKis comparing to AD adults not exposed to JAKis, and our secondary objective is to evaluate whether JAKis initiation acts as a trigger of VTEs in adults with AD within three months.” Page 4

- In the introduction section: “here, we describe the protocol for the “JAK inhibitors and ThromboEmbolic Risk” (JAKTER) study of the association between JAKis and VTEs in AD, using real-world evidence from an exhaustive French medical-administrative database. We also discuss our methodological choices. Our primary objective is to assess the risk of VTEs in adults with AD exposed to JAKis comparing to AD adults not exposed to JAKis, and our secondary objective is to evaluate whether JAKis initiation acts as a trigger of VTEs in adults with AD within three months, corresponding to two different methodological approaches.” Page 8

3. The primary hypothesis should include the clinically significant difference in frequency of VTEs. For instance, “OR 2 and above is considered as clinically significant”. At the same time,this kind of

research (extended retrospective database search) may not require the clear study hypothesis and may be of explorative/

REPLY:

The definition of a clinically relevant minimum difference is a difficult issue for VTEs (potentially fatal pulmonary embolism and “not serious” distal deep vein thrombosis).

The estimated power calculation has been given in Table 3. A final power calculation will be performed at the end of the study with the final number of adults exposed to JAKis.