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LETTER TO THE EDITOR

Comment on: "Direct Oral Anticoagulants and Interstitial Lung Disease: Emerging Clues from Pharmacovigilance"

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Dear Editor,

We represent the leadership of the largest randomized clinical trials and ongoing registries with edoxaban and wish to comment on the research letter by Raschi et al. [1] that summarized a hypothesis-generating study linking direct oral anticoagulants (DOACs) to interstitial lung disease (ILD), especially with factor-Xa inhibitors, with disproportionality signals between specific anticoagulants.

First, it is critical to underscore that this disproportionality analysis was conducted using the US Food and Drug Administration (FDA) Adverse Event (FAERS) database, which contains adverse event reports voluntarily and unsystematically submitted by healthcare providers and consumers. The FAERS website [2] itself acknowledges several limitations in their data, including an inability to establish causality, incomplete and duplicate reports, unverified data, and inability to establish occurrence rates, and the FDA themselves conclude that "the FAERS data by themselves are not an indicator of the safety profile of the drug or biologic." Thus, accurate numbers for neither the numerator (cases) nor the denominator (exposures) are available from this database.

Furthermore, important limitations of the data presented by Raschi et al. include the lack of evaluation for other potential causes; limited ability to account for very large differences in the regional use of specific DOACs, reporting rates, and of ILD; lack of information regarding diagnostic criteria and thresholds for reporting cases; and uncertain temporality between onset of ILD and timing of initiation of anticoagulation.

Large randomized clinical trials and well-conducted registries avoid many of the limitations enumerated above. The largest randomized clinical trials conducted with DOACs in patients with atrial fibrillation (ENGAGE AF-TIMI 48 [3]) and in patients with venothromboembolism (HOKUSAI-VTE [4]) compared edoxaban ($n = 18{,}212$) with warfarin ($n = 11{,}185$) and had an independent review by a pulmonary expert of 160 suspected cases of ILD. The reviewer concluded there was "No evidence to support a drug-induced ILD was identified in this evaluation of these two Phase 3 global Edoxaban trials" [5].

We believe that the reporting odds ratios calculated by Raschi et al. are difficult to interpret given the elective nature of these reports and are likely biased against edoxaban because it was the last of the DOACs introduced (available for only 4 of the 15 years covered in this analysis) and is most commonly prescribed in Asia where rates of diagnosis of ILD are highest. Table 1 in the letter by Raschi et al. includes a total of 64 estimates of risk for eight therapies (with no adjustments for multiple comparisons) with values of RORs that range from 0.62 to 11.37, and vary widely even among similar therapies (range of RORs for all DOACs, 0.92–2.64, for factor Xa inhibitors only, 1.04–2.89) demonstrating no consistency of the findings across the various sensitivity analyses.

Last, the authors call for data from prospective registries such as the Edoxaban Treatment in routiNe clinical prActice (ETNA) registries. In the ETNA-AF and ETNA-VTE registries, ILD was reported in 5/11,190 (0.04% [95% confidence interval 0.01–0.10] and 0/1702 [upper bound of 95% confidence interval 0.2]) patients after 2 and 1 years, respectively. Thus, the data from these well-conducted global registries

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do not support the authors' hypothesis of a high and disproportionate risk for ILD with edoxaban. We agree with the US FDA that analysis from voluntary adverse event reporting systems should be considered hypothesis generating and extreme caution is needed in interpreting the results.

Declarations

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References

1. Raschi E, Fusaroli M, Diemberger I, Poluzzi E. Direct oral anticoagulants and interstitial lung disease: emerging clues from pharmacovigilance. Drug Saf. 2020;43(11):1191–4. https://doi.org/10.1007/s40264-020-00990-9.
2. US Food and Drug Administration. Questions and answers on FDA's Adverse Event Reporting System (FAERS). 4 June 2018. https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers. Accessed 5 Nov 2020.
3. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, ENGAGE AF-TIMI 48 Investigators, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
4. HOKUSAI-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369:1406–15.
5. Daiichi Sankyo. Internal safety data. Basking Ridge (NJ) (2011).