Investigating the association between ALK receptor tyrosine kinase inhibitors and pulmonary arterial hypertension: a disproportionality analysis from the WHO pharmacovigilance database

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To the Editor:

Awada *et al.* [1] recently published in the *European Respiratory Journal* an interesting pre-clinical study suggesting that crizotinib may exacerbate and predispose to pulmonary arterial hypertension (PAH). Crizotinib is a first-in-class anaplastic lymphocyte kinase (ALK) inhibitor and is now a standard first-line therapy for advanced ALK-positive non-small cell lung cancer (NSCLC) [2]. Its inconsistent efficacy and its limited ability to control brain metastases pushed the development of second-generation ALK tyrosine kinase inhibitors (TKIs) (ceritinib, alectinib and brigatinib), which are characterised by higher selectivity and distribution to the central nervous system. Furthermore, third-generation ALK-TKIs, such as lorlatinib and entrectinib, have been recently developed to overcome acquired resistance due to secondary ALK mutations, which concern more than half of patients treated by second-generation ALK-TKIs [3]. Cases of PAH onset have also been reported in patients with metastatic NSCLC who received other ALK-TKIs, such as brigatinib and lorlatinib [4, 5]. Subsequently, one can ask if this adverse event is specific to crizotinib or a class effect of ALK-TKIs, and whether on-target or off-target tyrosine kinases are implicated in its pathophysiology. To further add knowledge on this potential adverse drug reaction, we aimed to comprehensively characterise PAH reported with ALK-TKI use, using the World Health Organization (WHO) pharmacovigilance database to describe cases' clinical features and to assess its causality.

We first extracted all cases of PAH reported with commercialised ALK-TKIs (crizotinib, ceritinib, brigatinib, lorlatinib, alectinib and entrectinib) from the WHO pharmacovigilance database, VigiBase. VigiBase is the world's largest pharmacovigilance database, collecting reports from among the 150 countries participating in the WHO Programme for International Drug Monitoring since 1968. At the date of extraction (May 2021) more than 25 million cases were reported in this database. We identified cases of PAH using the following search terms of the MedDRA dictionary: "pulmonary arterial hypertension" (preferred term). We also broadened our searches using the high-level term "pulmonary hypertension" and the standardised medical query "pulmonary hypertension". Standardised medical queries are internationally validated, pre-determined collections of MedDRA terms associated with a common disease, allowing for high-sensitivity searches (*e.g.* PAH, right ventricular failure, acute cor pulmonale, tricuspid valve incompetence). Secondly, we performed a disproportionality analysis to compare the proportion of PAH cases reported with ALK-TKIs against other antineoplastic drugs used in NSCLC [6]. Disproportionality analyses are statistical methods that quantify the extent to which an adverse event occurs more than expected with a drug. Such methods are widely used by national drug agencies, industries and researchers for safety signal detection in pharmacovigilance spontaneous reporting systems databases. They compare proportion of reporting of an event between cases exposed and non-exposed to a specific drug to generate safety signals. Therefore, they answer the question: "does the number of observed cases exceed the number of expected cases?". However, they do not provide risk quantification, since the population actually exposed to the drugs is unknown and are scarcely adjusted on drug dosage and duration of exposure. Several frequentists, multivariate and Bayesian disproportionality methods have been developed to date. In

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PAH associated with crizotinib seems to be very rare but cases are reported in pharmacovigilance databases with other ALK tyrosine kinases inhibitors, notably lorlatinib. Therefore, the potential emergence of PAH by ALK-TKI needs to be further explored. https://bit.ly/3k9es94

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this study, we used the Bayesian neural network method, which displays the best sensitivity and specificity among disproportionality analyses, notably for rare events [7, 8]. A signal was deemed significant if the lower boundary of the 95% credibility interval of the information component (IC_{025}) was superior to 0 [7]. Statistical analyses were performed with Python (version 3.7.6) and R (version 3.6.2).

On 15 May, 2021, among the 18 945 adverse drug reactions reported to the WHO pharmacovigilance database with ALK-TKI, we identified 11 cases of PAH and 21 cases of related adverse events. Eight PAH cases were reported with lorlatinib, two with brigatinib and one with crizotinib. These PAH cases were associated with pleural effusion (three cases) and right ventricular failure (two cases), and five were fatal (figure 1a). Median (interquartile range) age of patients was 64 years (48–78 years) and median time to onset was 70 days (62.5–293 days). Moreover, 16 cases of pulmonary hypertension (five alectinib, five crizotinib, three lorlatinib, two entrectinib and one ceritinib), two cases of tricuspid valve incompetence (crizotinib), one case of acute cor pulmonale (crizotinib), one case of pulmonary valve incompetence (crizotinib), and one right ventricular failure (entrectinib) were reported. The number of cases reported by year since commercialisation of each ALK-TKI is presented in figure 1b. Disproportionality analysis showed that ALK-TKIs are associated with a disproportionality signal of PAH and more broadly of PH against other drugs used in NSCLC (figure 1c). However, this signal was almost exclusively driven by lorlatinib and we found no individual signals for crizotinib, ceritinib, brigatinib and alectinib. Affinity of ALK-TKI for ALK kinases and for off targets strongly differs and is represented in figure 1d.

In the WHO pharmacovigilance database, we found only one case of PAH onset during crizotinib therapy. We can therefore assume that PAH associated with crizotinib is a very rare event, and these results raise questions about the clinical translation of the findings of Awada *et al.* [1]. In their study, authors found that R-crizotinib may provoke endothelial cell injury and amplify the response to well-established pulmonary hypertension inducers, but crizotinib was not able to elicit PAH alone [1]. The role of lung cancer in eliciting PAH in combination with crizotinib seems therefore unlikely. However, cases of PAH are reported with other ALK-TKIs, notably lorlatinib and brigatinib, and the disproportionality analysis suggests a potential association between ALK-TKIs and PAH. Beyond ALK inhibition, ALK-TKIs display a very heterogeneous affinity profile for tyrosine kinases [9]. In a phase 3 trial comparing crizotinib and lorlatinib as first-line treatment of patients with ALK-positive NSCLC, the rate of vascular adverse events was superior with lorlatinib (*e.g.* hypertension 18.1%) compared to crizotinib (2.1%), suggesting heterogeneous vascular effects among this class [10]. Thus, it remains hazardous to assume a class effect and a similar pathomechanism for all ALK-TKIs. Awada *et al.* [1] emphasised the role of HGF/c-MET signalling in endothelial cell survival and vascular remodelling [1]. However, other ALK-TKIs, such as lorlatinib or brigatinib, display very low affinity for these tyrosine kinases, and were associated with the largest number of reported cases of PAH, despite a smaller number of exposed patients and fewer reported adverse events in Vigibase [11]. Thus, the replication of the original study with other ALK-TKIs, notably lorlatinib, may bring important results in the understanding of this potential adverse drug reaction and its pathophysiology, notably in the role of ALK-TKI.

In the WHO pharmacovigilance database, the adverse events are spontaneously reported by healthcare professionals and patients from 150 countries, allowing detection of rare adverse drug reactions, but also suffers from heterogeneity in case definition and coding. Moreover, under- and selective reporting of adverse events and the lack of clinical data to ensure the validity of such reactions could result in misclassification of PAH among other pulmonary hypertension aetiologies that are common in comorbid patients receiving ALK-TKIs [12]. While all cases reported in France have been reviewed by our team (75% of PAH cases were confirmed by right heart catheterisation), this validation have not been performed in other reporting countries. Due to the fragile state and the unfavourable prognosis of patients with NSCLC, one can suggest that the duration of follow-up does not allow the occurrence of pulmonary hypertension in these patients and that some patients may not have benefited from an extensive workup, especially invasive right heart catheterisation.

In conclusion, if it does exist, PAH induced by crizotinib seems to be a very rare adverse drug reaction. However, we detected a pharmacovigilance signal for other ALK-TKIs, notably lorlatinib. The association of PAH with these TKIs therefore needs to be further explored, characterised and validated through complementary methods and databases before evoking a causal link. Prescribers should be aware of this possible complication and we encourage them to report cases to pharmacovigilance centres. Patients receiving ALK-TKIs with unexplained dyspnoea should be screened for pulmonary hypertension by echocardiography and for other causes of dyspnoea (*e.g.* pulmonary embolism, interstitial lung disease). In case of suspected pulmonary hypertension, we recommend right heart catheterisation to confirm the diagnosis and determine the haemodynamic profile (pre- or post-capillary pulmonary hypertension) along

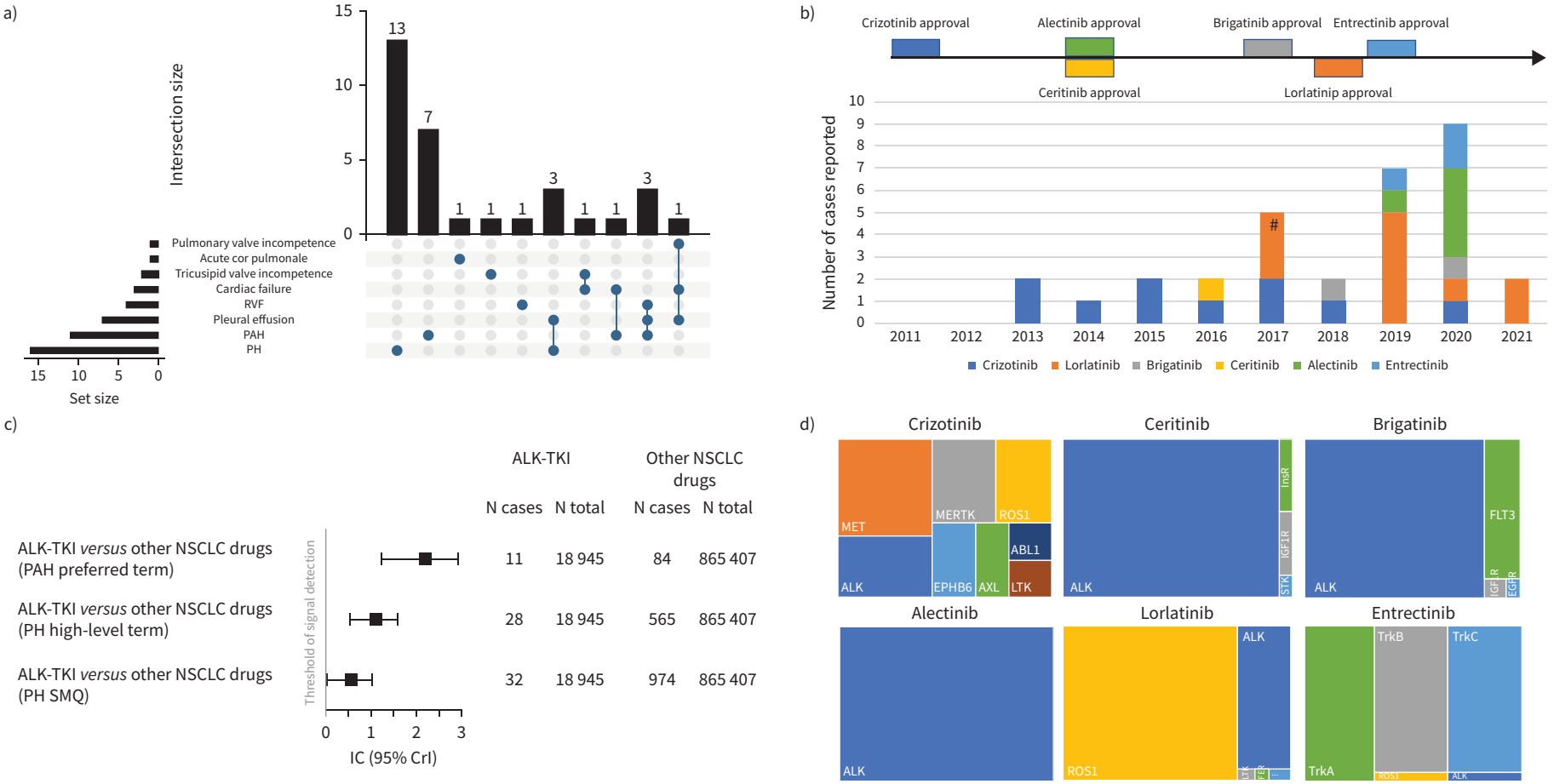

FIGURE 1 Characteristics of cases reported in the World Health Organization (WHO) pharmacovigilance databases, disproportionality analysis and affinity profile of anaplastic lymphocyte kinase (ALK) tyrosine kinase inhibitors (TKIs). a) Upset plot presenting the frequency and the association between selected adverse events related to pulmonary arterial hypertension (PAH) and all ALK-TKIs. b) Temporal evolution of the number of reported cases ("pulmonary hypertension" (PH) as standardised medical query (SMQ)) in the WHO pharmacovigilance database related to the year of US Food and Drug Administration approval for all ALK-TKIs. #: cases reported in France during the temporary use authorisation of lorlatinib delivered by the French health authority in 2015. c) Forest plot presenting disproportionality analysis results, with the information component (IC), 95% credibility intervals (95% CrI), and number of cases. We used three definitions of PAH using different collections of MedDRA terms: one narrow (preferred term "pulmonary arterial hypertension") and two broader definitions ("pulmonary hypertension" high level term and "pulmonary hypertension" SMQ). d) Representation of the relative affinity profile for main targets of ALK-TKI (half maximal inhibitory concentration <100 nM), based on the literature and public databases. RVF: right ventricular failure; NSCLC: nonsmall cell lung cancer.

with a systematic workup to exclude other possible causes of pulmonary hypertension (*e.g.* left heart disease, chronic thromboembolic disease, chronic respiratory disease).

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