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Early View

Research letter

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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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Awada and colleagues recently published in the *European Respiratory Journal* an interesting pre-clinical study suggesting that crizotinib may exacerbate and predispose to pulmonary arterial hypertension (PAH) [1]. 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 (TKI) (ceritinib, alectinib and brigatinib) which are characterized by higher selectivity and distribution to the central nervous system. Furthermore, third-generation ALK-TKI such as lorlatinib or 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-TKI [3]. Cases of PAH onset have also been reported in patients with metastatic NSCLC who received other ALK-TKI 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-TKI, and whether on-target or off-target tyrosine kinases are implicated in its pathophysiology. To further add knowledge on this potential adverse drug reaction (ADR), we aimed to comprehensively characterize PAH reported with ALK-TKI use, using the WHO pharmacovigilance database to describe cases clinical features and to assess its causality.

Methods

We first extracted all cases of PAH reported with commercialized ALK-TKI (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 millions of 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 (HLT) “Pulmonary Hypertension (PH)” and the Standardized Medical Query (SMQ) “pulmonary hypertension”. SMQs are internationally validated, pre-determined collections of MedDRA terms associated with a same 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-TKI 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 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).

Results

On 15th 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, 2 with brigatinib and 1 with crizotinib. These PAH cases were associated with pleural effusion (3 cases) and right ventricular failure (2 cases), and 5 were fatal (**Figure 1A**). Median age of patients was 64 years (IQR25-75 48-78) and median time to onset was 70 days (IQR25-75 62.5-293). Moreover, 16 cases of PH (5 alectinib, 5 crizotinib, 3 lorlatinib, 2 entrectinib, 1 ceritinib), 2 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 commercialization of each ALK-TKI is presented in **Figure 1B**. Disproportionality analysis showed that ALK-TKI 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**.

Discussion

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 and colleagues. In their study, authors found that R-crizotinib may provoke endothelial cell injury and amplify the response to well-established PH inducer, 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-TKI, notably lorlatinib and brigatinib, and the disproportionality analysis suggests a potential association between ALK-TKI and PAH. Beyond ALK inhibition, ALK-TKI 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-TKI. Awada and colleagues emphasized the role HGF/c-MET signaling in endothelial cell survival and vascular remodeling [1]. However, other ALK-TKI 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-TKI, notably lorlatinib, may bring important result 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 ADR, but also suffers from heterogeneity in cases 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 PH aetiologies that are common in comorbid patients receiving ALK-TKI. [12] While all cases reported in France have been reviewed by our team (75% of PAH cases were confirmed by right heart catheterization), 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 PH in these patients and that some patients may not have benefited from an extensive workup, especially invasive right heart catheterization. In conclusion, if it does exist, PAH induced by crizotinib seems to be a very rare ADR. However, we detected a pharmacovigilance signal for other ALK-TKI, notably lorlatinib. The association of PAH with these TKI therefore needs to be further explored, characterized 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 centers. Patients receiving ALK-TKI with unexplained dyspnea should be screened for PH by echocardiography and for other causes of dyspnea (e.g. pulmonary embolism, interstitial lung disease…). In case of suspected PH, we recommend right heart catheterization to confirm the diagnosis and determine the haemodynamic profile (pre- or post-capillary PH) along with a systematic workup to exclude other possible causes of PH (e.g. left heart disease, chronic thromboembolic disease, chronic respiratory disease…).

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The data supplied to VigiBase come from a variety of sources and the likelihood of a causal relationship is not the same in all reports. The information does not represent the opinions of the UMC or the World Health Organization.

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LEGENDS

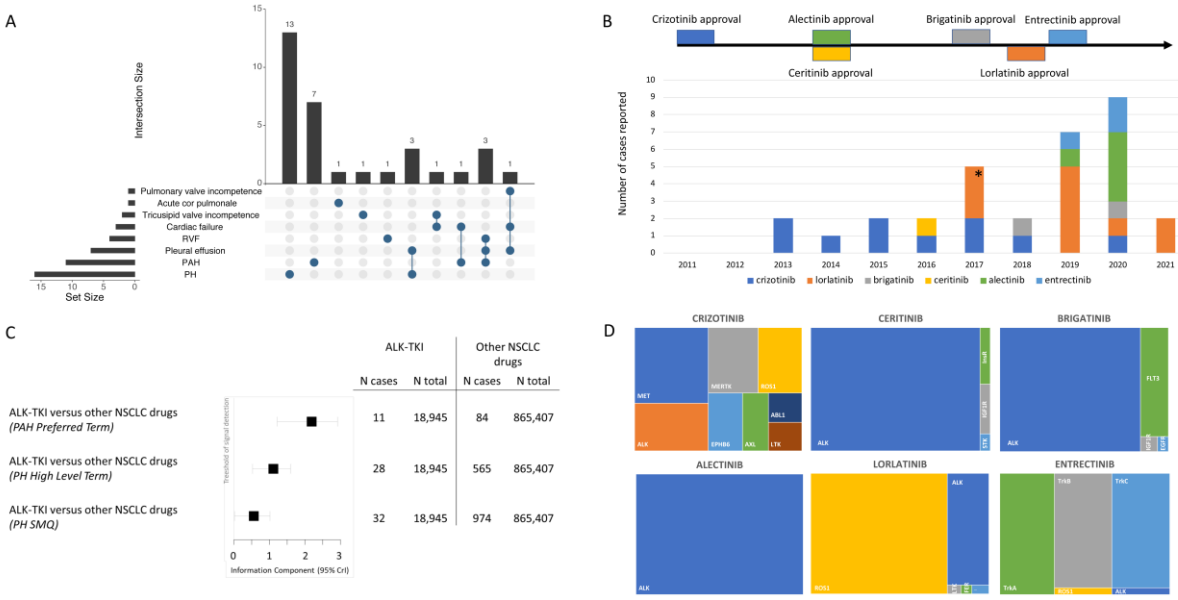

Figure 1. Characteristics of cases reported in the WHO pharmacovigilance databases, disproportionality analysis and affinity profile of ALK tyrosine kinase inhibitors.

A. Upset plot presenting the frequency and the association between selected adverse events related to pulmonary arterial hypertension (PAH) and all ALK-Tyrosine kinase inhibitors. PH: pulmonary hypertension, RVF: right ventricular failure.

B. Temporal evolution of the number of reported cases ('Pulmonary hypertension' Standardized Medical Query) in the WHO pharmacovigilance database related to the year of FDA approval for all ALK-TKI. *Cases reported in France during the temporary use authorization of lorlatinib delivered by the French health authority in 2015.

C. Forest plot presenting disproportionality analysis results, with the Information Component (IC), credibility Intervals (95%CrI), and number of cases. We used 3 definition of pulmonary arterial hypertension using different collection of MedDRA terms: one narrow (Preferred Term PAH) and two broader definitions (PH High level Term HLT and PH standard medical query (SMQ)).

D. Representation of the relative affinity profile for main targets of ALK-TKI (IC_{50}<100nM), based on the literature and public databases.

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