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Respiratory Adverse Reactions to Tyrosine Kinase Inhibitors: A Disproportionality Analysis of Spontaneous Reports from European Countries

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Abstract

(1) Background: Tyrosine kinase inhibitors (TKIs) asciminib, bosutinib, dasatinib, imatinib, nilotinib, ponatinib have been approved for the therapy of chronic myelogenous leukemia (CML). Pharmacovigilance reports associated with these drugs are not consistent and homogenous and have been associated with pulmonary toxicity that could limit their utilization. To give a contribution for a more clear definition of TKIs pulmonary risk, we conducted a research investigating on adverse events suspected to be caused by TKIs asciminib, bosutinib, dasatinib, imatinib, nilotinib, ponatinib used for CML, using the european database EudraVigilance. (2) Methods: Suspected adverse reactions to TKIs in the data system EudraVigilance (2020–2024) coming from European countries and United Kingdom were analyzed and compared through a disproportionality analysis. (3) Results: most frequent alerts concerned the respiratory disorders "Pleural effusion" (PE) and Pulmonary arterial hypertension" (PAH) related to dasatinib and bosutinib. Among the category of TKIs, prescription of dasatinib is associated with a higher occurrence of PE and PAH, while prescription of bosutinib induces with minor frequency PE but it exposes at a significant risk for PAH, occurring more often in women. (4) Conclusions: Results indicate that respiratory disorders induced by the TKIs dasatinib and bosutinib need to be punctually and rapidly diagnosed and suggest caution before prescription of these TKIs in patients affected by CML with pulmonary comorbidities.

Keywords: respiratory adverse reactions; tyrosine kinase inhibitors

1. Introduction

Chronic myelogenous leukemia (CML) is a disease that involves myeloproliferation and the Philadelphia chromosome t(9;22)(q34;q11) and/or and/or the breakpoint cluster Region-Abelson (BCR-ABL1) fusion gene, a genetic abnormality representing a hallmark CML and other leukemias. The translocation t(9;22) (q34;q11), results in the formation of the Philadelphia (Ph) chromosome and the BCR-ABL1 fusion gene. This produces a constitutively active tyrosine kinase that drives proliferation, blocks apoptosis and induces genomic instability, key features of CML leukemogenesis (Hochhaus A et al., 2018). The cytogenetic disorder is characterized by the expression of BCR-ABL1 protein activated by tyrosine kinase (TK) [1]. Annual incidence of CML is approximately of two cases per 100,000 people [2]. Clinical presentation is characterized by variable symptoms: while many

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patients are frequently treated with nonspecific symptoms, nearly 40% of patients are diagnosed incidentally through routine laboratory evaluations revealing unexplained leukocytosis. Splenomegaly is the most common physical finding, present in approximately half of newly diagnosed patients [3]. Without treatment, CML typically progresses from chronic phase to accelerated phase and finally to blast crisis, a stage similar to acute leukemia [4]. CML progression is largely attributed to the genetic instability imparted by BCR-ABL1, which facilitates the acquisition of additional cytogenetic and molecular abnormalities driving the transformation from chronic phase to accelerated phase and blast crisis [5]. After the previous use of recombinant interferon-alfa, cytarabine and hematopoietic cell transplantation, currently, people with Philadelphia chromosome/BCR-ABL1 CML are treated with drugs acting through the inhibition of tyrosine kinase (TK) activity. The tyrosine kinase inhibitors (TKIs) asciminib, bosutinib, dasatinib, imatinib, nilotinib, ponatinib have been approved for the therapy of persons affected by CML [6].

A recent pharmacovigilance study, based on the adverse events to TKIs signaled in cancer patients, using the Food and Drug Administration Adverse Event Reporting System (FAERS) database revealed that reports associated with drugs linked to BCR-ABL1 TKIs reveal a safety profile not consistent and homogenous [7]. Although it is considered effective in terms of clinical response, the TKI dasatinib has been associated with potential pulmonary toxicity characterized by pulmonary arterial hypertension (PAH) and pleural effusion (PE), to the point that they can limit its utilization [8]. These adverse events occur at the beginning of therapy and in general they are transitory, even if need special attention, partucularly in the high-risk patients [9]. Furthermore, a disproportionality analysis showed that dasatinib, as well as bosutinib, ponatinib, and nilotinib, had a significant disproportionality signal for PAH induced by PKIs [10]. Cases of bosutinib-induced lung injury potentially causing life-threatening complications have been also reported, suggesting that patients treated with bosutinib should be carefully monitored about pulmonary safety [11].

With the aim to give a contribution for a more clear definition of safety of TKIs and the pulmonary risk associated with these drugs, we conducted a research investigating on respiratory adverse events suspected to be caused by TKIs used for CML using the european database EudraVigilance. A descriptive and a disproportionality analysis were performed on reports of adverse reactions associated with TKIs dasatinib, asciminib, bosutinib, imatinib, nilotinib, ponatinib, used for CML and signaled in the years from 2020 and 2025 and coming from European Union (EU) and United Kingdom (UK).

2. Materials and Methods

EudraVigilance is a database collecting suspected adverse reactions (SARs) related to medicines authorized for the European Union (EU) market. SARs are traceable in individual cases (Individual Case Safety Reports; ICSRs) and are signaled by national drug regulatory authorities in the EU or by marketing authorization holders. EudraVigilance collects reports of “suspected” adverse reactions, meaning unwanted medical events observed following medicine use that are not necessarily related to or caused by the medicine itself [12].

2.1. Design of the Study

ICSRs reporting SARs that occurred following prescription of the TKIs dasatinib, imatinib, nilotinib, ponatinib, bosutinib and asciminib from 1 January 2020 to 31 December 2024, were collected, analyzed and compared among them. The public version of the EudraVigilance database was used, and data collection on SARs was conducted according to the following inclusion criteria: serious SARs and reports sent only from healthcare professionals in cases regarding all ages (from 0 to > 85 years) and those reported from the European Economic Area (EEA), including UK. Uk is mentioned separately because in EudraVigilance, it is included within the EEA. Alerts were excluded from the analysis when they were reported by non-healthcare professionals or came from non-European countries. For all cases, information on patient characteristics (age group and sex), adverse reaction type (often more than one for each ICSR), and the qualification of the primary source was

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provided. Regarding the criteria for data extraction from ICSRs, SAR selection was based on the Medical Dictionary for Regulatory Activities (MedDRA) [13]. MedDRA is used to code cases reporting adverse effects in pharmacovigilance databases and to facilitate searches in databases on adverse drug reactions. Every mentioned SAR was extracted and counted for every single case. Adverse reactions were grouped under the terms of the SOC (System Organ Classification) level in the MedDRA hierarchy, such as, for example "Skin and subcutaneous tissue diorders" or "Cardiac disorders" or "Vascular disorders". The SOC system's organ classification is the highest level in the hierarchy, as it captures the broadest concept useful for data retrieval. It is a way of grouping medical terms based on body systems or functions. The terms "Pleural effusion" and Pulmonary arterial hypertension", used in this study have been used as a so-called "Preferred term" (PT) listed in MedDRA and reported by the National Center for Biomedical Ontology. A PT is a distinct descriptor (single medical concept) for an adverse symptom or sign. We selected all cases reporting of adverse reactions and adverse reactions singularly signaled "Pleural effusion" and Pulmonary arterial hypertension"recorded in the ICSRs, and we counted them all and analyzed their frequency for dasatinib, imatinib, nilotinib, ponatinib, bosutinib and asciminib.

2.2. Data Analysis

Source of data extraction is represented by a a line listing a structured table where each row represents an ICSR and each column represents a specific data point associated with that case. The data were analyzed by aggregating the PTs of individual reports to a higher level of the MedDRA hierarchy by merging individual serious SARs in the SOC level. Serious/Non serious (S/NS) ratio was calculated for each drug. Only reports classified as serious were analyzed. In accordance with the E2D guidelines of the International Council for Harmonization, ICSRs are classified as serious if they are life-threatening, have resulted in death, have resulted or prolonged hospitalization or disability, or are related to a congenital anomaly/birth defect or other medically important conditions. The adequate stratification of alerts by sex and age groups was performed to avoid biases caused by confounding effects and to analyze these two variables separately. The sex distribution was analyzed using the chi-square test. Duplicate and incomplete ICSRs were excluded from the analysis. A duplicate search was conducted of the dataset based on similarity in terms of the adverse reaction, age, sex, suspected/interacting medicinal products, and the EudraVigilance local report number. The statistical analyses used were one-way ANOVAs. A disproportionality analysis of the potential association of the SOC group "Respiratory, thoracic and mediastinal disorders" was performed by the reporting odds ratio (ROR) and comparing the SARs of dasatinib or bosutinib with those signaled for the other TKIs considered for the study. Disproportionality analysis is used to compare the proportions or frequencies of two or more groups and to verify whether the differences are statistically significant. It is a methodology used to detect adverse drug reaction alerts. It is based on the two-by-two contingency table. In this way, the differences between the occurrence frequency and the background frequency for target drugs and target adverse events can be compared [14]. The ROR calculates the odds ratio of a selected drug versus other drugs for a certain adverse event. It is used here to establish the strength of disproportionality by comparing SARs signaled for the combination of amoxicillin/clavulanic with those signaled for amoxicillin alone. ROR equal to 1 indicates the absence of an alert; conversely, an ROR greater than 1 indicates an alert and the existence of an association [15]. All statistical analyses were completed using the SPSS statistical software, version 29.0 (SPSS, IBM, Armonk, NY, USA).

3. Results

3.1. Percentage and Ratio of Serious/Non-Serious Suspected Adverse Reactions of the TKIs dasatinib, imatinib, nilotinib, ponatinib, bosutinib and asciminib.

In Table 1 are shown the total number of ICSRs, the number of serious and non serious and the serious/non serious ratio related to signals of SARs related to the prescription of the TKIs dasatinib,

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asciminib, bosutinib, imatinib, nilotinib, ponatinib. S/NS ratio of all the drugs is less than 1. The highest ratio is linked to dasatinib prescription (Table 1).

Table 1. Serious and non serious Individual Cases Safety Reports (ICSRs) related to the tyrosine kinase inhibitors dasatinib, asciminib, bosutinib, imatinib, nilotinib, ponatinib, signaled in the years 2020-2024 in the European Economic Area and United Kingdom.

Drug	ICSRs (total)	Serious ICSRs	Non serious ICSRs	ICSRs serious/non serious ratio
Dasatinib	703	508	195	0.72
Asciminib	125	79	46	0.63
Bosutinib	337	213	124	0.63
Imatinib	1773	1116	657	0.63
Nilotinib	604	413	191	0.68
Ponatinib	467	326	141	0.70

3.2. Reporting Odds Ratio (ROR) of Serious Suspected Adverse Reactions to dasatinib, asciminib, bosutinib, imatinib, nilotinib, ponatinib, According to the System Organ Class (SOC) Level

In Table 2, are reported the ROR and confidence intervals of SARs grouped according to the SOC level. For each drug can be revealed some differences of the safety profile with respect to the total of TKIs examined. Cardiac and vascular disorders are more signaled with the use of nilotinib and ponatinib. Gastrointestinal disorders are more frequently reported with the prescription of bosutinib. More general disorders were signaled with use of imatinib, nilotinib and dasatinib. Injury, poisoning and procedural complucations with the use of ponatinib, while infections and infestations with asciminib prescription. Investigations and Neoplasms are more frequently reported with the prescription of nilotinib and ponatinib, respectively. These two drugs are also more frequently associated with nervous system disorders, while imatinib use with skin and subcutaneous disorders. The most significant data is undoubtedly the dramatic increase in reporting of Respiratory, thoracic and mediastinal disorders associated with the prescription of dasatinib. This group of disorders is reported as increased also with bosutinib, but to a much lesser extent.

Table 2. Reporting odds ratio (ROR) of signals of serious suspected adverse reactions related to the prescription of the tyrosine kinase inhibitors dasatinib, asciminib, bosutinib, imatinib, nilotinib, ponatinib, signaled in the years 2020-2024 in the European Economic Area and United Kingdom, clustered according to the System Organ Class (SOC) level.

SOC	**Imatinib** *Cases* ROR 95% C.I.	**Nilotinib** *Cases* ROR 95% C.I.	**Ponatinib** *Cases* ROR 95% C.I.	**Dasatinib** *Cases* ROR 95% C.I.	**Bosutinib** *Cases* ROR 95% C.I.	**Asciminib** *Cases* ROR 95% C.I.
Blood and lymphatic system disorders	*208* 1.06 (0.87-1.30)	*80* 1.10 (0.84-1.44)	*54* 0.88 (0.65-1.21)	*93* 1.01 (0.79-1.30)	*31* 0.65 (0.44-0.97)	*15* 1.06 (0.60-1.88)
Cardiac disorders	*109* 0.48 (0.38-0.61)	*85* 2.77 (2.10-3.65)	*68* 1.94 (1.45-2.60)	*80* 1.40 (0.07-1.82)	*34* 1.21 (0.83-1.78)	*15* 1.37 (0.77-2.43)
Gastrointestinal disorders	*273* 1.45 (1.20-1.75)	*57* 0.91 (0.68-1.23)	*57* 1.15 (0.85-1.55)	*103* 1.42 (0.12-1.80)	*52* 1.58 (1.14-2.19)	*12* 0.80 (0.43-1.49)
General disorders and	*393* 2.20	*118* 2.26	*73* 1.17	*130* 1.61	*43* 0.99	*21* 1.35

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administration site conditions	(1.84-2.63)	(1.79-2.85)	(0.89-1.54)	(1.29-2.00)	(0.70-1.39)	(0.81-2.24)
Injury, poisoning and procedural complications	*92* 1.10 (0.83-1.47)	*23* 0.52 (0.33-0.81)	*50* 2.23 (1.59-3.14)	*35* 0.88 (0.60-1.28)	*8* 0.39 (0.19-0.81)	*2* 0.25 (0.06-1.04)
Infections and infestations	*71* 0.86 (0.64-1.17)	*23* 0.59 (0.38-0.93)	*21* 0.77 (0.48-1.24)	*46* 1.43 (1.01-2.03)	*13* 0.75 (0.42-1.33)	*14* 2.49 (1.37-4.53)
Investigations	*136* 0.95 (0.75-1.20)	*82* 2.17 (1.65-2.86)	*30* 0.75 (0.50-1.11)	*47* 0.80 (0.58-1.10)	*25* 0.96 (0.62-1.48)	*12* 1.23 (0.66-2.30)
Neoplasms benign, malignant and unspecified	*133* 1.19 (0.93-1.52)	*44* 0.98 (0.70-1.38)	*46* 1.45 (1.03-2.04)	*41* 0.77 (0.54-1.09)	*12* 0.46 (0.25-0.84)	*14* 1.68 (0.93-3.04)
Nervous system disorders	*109* 0.70 (0.55-0.90)	*80* 2.19 (1.66-2.90)	*57* 1.82 (1.33-2.48)	*41* 0.71 (0.50-1.00)	*16* 0.59 (0.35-1.00)	*11* 1.16 (0.61-2.22)
Respiratory, thoracic and mediastinal disorders	*125* 0.34 (0.27-0.42)	*32* 0.46 (0.31-0.66)	*42* 0.79 (0.56-1.10)	*267* 10.77 (8.69-13.34)	*67* 2.38 (1.76-3.24)	*8* 0.51 (0.24-1.06)
Skin and subcutaneous disorders	*175* 1.63 (1.30-2.06)	*44* 0.89 (0.64-1.25)	*31* 0.78 (0.53-1.14)	*39* 0.63 (0.44-0.89)	*33* 1.36 (0.92-2.01)	*10* 0.99 (0.50-1.94)
Vascular disorders	*54* 0.50 (0.36-0.69)	*60* 2.20 (1.59-3.05)	*37* 1.58 (1.08-2.30)	*25* 0.63 (0.41-0.97)	*9* 0.49 (0.24-0.96)	*11* 1.80 (0.94-3.47)

ROR and confidence intervals (C.I.; in brackets) are reported as the result of the comparison of each drug with the other tyrosine kinase inhibitors.

3.3. Sex Distribution of Serious Suspected Adverse Reactions"Pleural Effusion" and "Pulmonary Arterial Hypertension"Associated with dasatinib and bosutinib Prescription

Sex distribution of signals associated with dasatinib prescription reporting the adverse reactions PE shows an apparent prevalence of males, with a percentage of 55.7%. However, statistical analysis does not confirm this date. "Pulmonary arterial hypertension" is equally reported between the sexes with dasatinib use. An asymmetric sex distribution is observed following bosutinib prescription. PE is more signaled for males, while PAH for females.

PE is reported in the 32.5% of all serious cases associated with dasatinib, and in the percentage of 5.16% for bosutinib. "Pulmonary arterial hypertension" is reported in the percentage of 4.13% and 3.29% of all serious cases signaled for dasatinib and bosutinib, respectively (Table 3). Age distribution shows as PE is more reported in elderly (65-85 years), both for dasatinib and bosutinib. PAH is more signaled for adult age (18-64 years) with dasatinib and in elder patients (65-85 years) with bosutinib (Table 4).

Table 3. Sex distribution of serious suspected adverse reactions to the drugs dasatinib and bosutinib, signaled in the years 2020-2024 with the Preferred Terms "Pleural effusion" and "Pulmonary arterial hypertension" in the European Economic Area and United Kingdom. Total number of Individual Cases Safety Reports (ICRSs) of dasatinib and bosutinib is 508 and 2013, respectively. Total number of serious male and female cases signaled for dasatinib is 267 and 241, respectively. Total number of serious male and female cases signaled for bosutinib is 116 and 97, respectively.

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Drug	Adverse reaction	Male cases number and %	Female cases number and %	Male and female cases	% of all serious ICSRs	Sex distribution significance level (P)
Dasatinib	Pleural effusion	92 (55.7%)	73 (44.3%)	165	32.5%	N.S. 0.3167
	Pulmonary arterial hypertension	17 (50.0%)	17 (50.0%)	34	4.13%	N.S. 0.7570
Bosutinib	Pleural effusion	28 (68.3%)	13 (31.7%)	41	5.16%	0.0478*
	Pulmonary arterial hypertension	4 (22.2%)	14 (77.8%)	18	3.29%	0.0041*

*P = < 0.05 males vs females. N.S. = not significant.

Table 4. Age distribution of serious suspected adverse reactions to the drugs dasatinib and bosutinib, signaled in the years 2020-2024 with the Preferred Terms "Pleural effusion" and "Pulmonary arterial hypertension" in the European Economic Area and United Kingdom. Total number of Individual Cases Safety Reports (ICRSs) for dasatinib = 508.

Drug	Adverse reaction	18-64 (years)	65-85 (years)	>85 (years)
Dasatinib	Pleural effusion	30 (5.9%)	41 (8.1%)	3 (0.6%)
	Pulmonary arterial hypertension	13 (2.5%)	6 (1.2%)	2 (0.4%)
Bosutinib	Pleural effusion	3 (1.4%)	8 (3.75%)	___
	Pulmonary arterial hypertension	2 (0.94%)	5 (2.35%)	-----

In brackets, the percentage of the total number of ICSRs associated with dasatinib or bosutinib prescription.

3.4. Reporting Odds Ratio (ROR) of Individual Cases Safety Reports (ICRSs) Associated with dasatinib and bosutinib Prescription, Reporting "Pleural Effusion" and "Pulmonary Arterial Hypertension" Compared to the Tyrosine Kinase Inhibitors asciminib, imatinib, nilotinib, ponatinib

A disproportionality analysis was carried out through the evaluation of ROR obtained by comparison of the signals "Pleural effusion" and "Pulmonary arterial hypertension" related to

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dasatinib and bosutinib prescription. Data of the two drugs were singularly compared with those regarding the same adverse reactions reported with the other TKIs. Asciminib, imatinib, nilotinib, ponatinib and bosutinib were compared with dasatinib. Asciminib, imatinib, nilotinib, ponatinib and dasatinib were compared with bosutinib. Results show a ROR of 9.55 (95%; C.I. 7.28-12.52) for the adverse reaction PE suspected to be caused by dasatinib and a ROR of 2.32 (95%; C.I. 1.61-3.36) for the same adverse reaction suspected to be caused by bosutinib. ROR for PAH was 4.90 (95%; C.I. 2.98-8.05) for dasatinib and 4.70 (95%; 2.68-8.25) for bosutinib prescription (Table 5).

Table 5. Reporting odds ratio (ROR) of serious Individual Cases Safety Reports (ICRSs) associated with dasatinib and bosutinib prescription, signaled in the years 2020-2024 with the Preferred Terms "Pleural effusion" and "Pulmonary arterial hypertension" in the European Economic Area and United Kingdom, compared to the signals associated with the prescription of the tyrosine kinas inhibitors asciminib, imatinib, nilotinib, ponatinib. Total number of serious Individual Cases Safety Reports (ICRSs) for dasatinib and bosutinib is 508 and 213, respectively.

Drug	Adverse reaction	ICSRs (cases)	All the other TKIs ICSRs (cases)	ROR (95% C.I.)
Dasatinib	Pleural effusion	165	103	9.55 (7.28-12.52)
	Pulmonary arterial hypertension	34	31	4.90 (2.98-8.05)
Bosutinib	Pleural effusion	41	227	2.32 (1.61-3.36)
	Pulmonary arterial hypertension	18	47	4.70 (2.68-8.25)

Dasatinib or bosutinib cases were excluded from "All the other TKIs ICSRs" when calculating the ROR of each of them. C.I. = confidence intervals.

4. Discussion

PE is a condition characterized by abnormal quantity of fluid in the pleural space, the gap between the lungs and the chest wall, which normally contains a small amount of fluid [16]. PAH is another respiratory disorder characterized by high blood pressure in the pulmonary arteries. This condition, characterized by constriction of small arteries, forces the right side of heart to an harder work leading to potential heart failure [17]. These adverse reactions, requiring discontinuing of therapy and initiating a appropriate medical intervention [18], have been associated with the prescription of the TKI dasatinib [8]. The present analysis indicates that the use of TKIs dasatinib and bosutinib, although in a different extent, can expose patients to these respiratory disorders.

Dasatinib is a second-generation TKI, indicated as first-line treatment for patients newly diagnosed with CML and second-line treatment for those who are resistant or intolerant to therapy with imatinib [19]. It has been observed how, despite the superiority of clinical effectiveness of dasatinib versus imatinib, its potential pulmonary toxicity, may limit its clinical use [9]. PE, affecting 14% to 35% of patients who dasatinib has been prescribed, seems to be caused by an imbalance in oncotic and hydrostatic pressures, increased capillary permeability, or impaired lymphatic drainage [20]. Bosutinib is a second-generation TKI indicated for the therapy of patients with Ph-positive chronic-, accelerated-, or blast-phase CML who are intolerant or resistant to other TKIs. Bosutinib

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inhibits a tyrosine kinase oncogene and Src kinases responsible for CML pathogenesis [21]. More recently, another case report, described refractory recurrent PE caused by bosutinib in a 79 old yeras woman. The event started developing worsening dyspnea related to pulmonary toxicity in the form of PE [22].

An early analysis of adverse events using data from FAERS database raised the hypothesis of an association between PE and PAH and prescription of dasatinib, even if these events were considered rare [23]. This concern has been raised about PE, with the publication of a case series reporting chylothorax (condition with chyle in the pleural space) [24] in association with dasatinib use that required treatment including administration of diuretics, steroids, dose reduction and discomtinuing of the drug [25]. About the mechanism underlying chylothorax induced by dasatinib, different hypothesis have been proposed, such as immune factors, block of of T-cell function, inhibition of platelet-derived growth factor receptor expressed in pericytes involved in angio-lymphangiogenesis [26]. A retrospective pharmacovigilance study on TKIs inhibitors based on FAERS databank collecting signals reported from 1 January 2004 to 30 September 2021 and published in the year 2023, revealed that patients aged ≥65 years using dasatinib, imatinib, nilotinib or bosutinib had higher RORs for PE, pericardial effusion and pulmonary oedema [27].

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure $\geq$ 25 mmHg [28]. It is a rare but potentially life-- threatening complication. The pathophysiological mechanism linked to this adverse reaction induced by dasatinib is not clear. Together with endothelial dysfunction and vascular remodelling, inhibition of BCR-ABL and Src family kinases induced by the drug, could give a contribution to PAH development [29,30]. A disproportionality analysis performed in 2019 with data from the World Health Organization pharmacovigilance database VigiBase, using the ROR and 95% confidence interval, found a positive signal indicating the association between dasatinib bosutinib, ponatinib, ruxolitinib, nilotinib and the raising of pulmonary arterial hypertension. The authors found dasatinib safety profile to be dissimilar with respect to the other drugs of the same category and suggested as kinases of the bone morphogenetic protein signalling pathway also seem to play a role in the pathophysiology of PAH induced by TKIs [10].

Our analysis has been conducted by using the european database system EudraVigilance. This is the first time that a post-marketing pharmacovigilance study on potentially adverse reactions induced by TKIs has been designed using data derived exclusively from real-world European data through the analysis of the database EudraVigilance. The use of this database offers a European perspective and allows the early identification and evaluation of potential safety issues (signals) for medicines in the EEA based on pharmacovigilance systems are homogenous among the different european countries and UK. Data of our study, include a descriptive analysis and a disproportionality analysis about adverse reactions, particularly respiratory disorders induced by the TKIs dasatinib, asciminib, bosutinib, imatinib, nilotinib and ponatinib. Calculation of ratio between serious and non serious adverse reactions of all the drugs, shows that the highest ratio, although to a lesser extent, is linked to prescription of dasatinib. A high S/NS ratio acts as a strong indicator of potential underlying toxicity, suggesting the drug carries a greater inherent risk for severe harm, even with fewer total reports and its safety profile warrants closer scrutiny [31]. Data of the TKIs examined in this study show a different profile among the TKIs. Cardiac and vascular disorders are more signaled with the use of nilotinib and ponatinib. Gastrointestinal disorders are frequently reported with the prescription of bosutinib. More general disorders were signaled with use of imatinib, nilotinib and dasatinib. Injury, poisoning and procedural complucations with the use of ponatinib, while infections and infestations with asciminib prescription. Investigations and neoplasms are more frequently reported with the prescription of nilotinib and ponatinib, respectively. These two drugs are also more frequently associated with nervous system disorders, and imatinib use with skin and subcutaneous disorders.

As expected, the most significant data obtained with the disproportionality analysis is the dramatic increase in reporting of respiratory, thoracic and mediastinal disorders associated with the

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prescription of dasatinib (ROR 10.77; 95% C.I. 8.69-13.34). A closer look at respiratory disorders PE and PAH, associated with dasatinib prescription, shows that they are reported in the 32.5% and the 4.13% of all serious cases, respectively. This date confirms previous date indicating that PE is more commonly signaled in comparison to PAH induced by dasatinib. A recent study reported that 17.6% of patients treated with dasatinib developed PE [32], while, as a cause of PAH, the lowest estimated incidence based on French Pulmonary Hypertension registry data, is of 0.45% [33]. In our study, an apparent asymmetric sex distribution, indicating a male prevalence between the patients treated with dasatinib in which these adverse reactions occur, has not been comfirmed by statistical analysis. Age distribution shows as PE is more reported in elderly (65-85 years), while PAH in adults (18-64 years). The disproportionality analysis performed comparing the signals PE and PAH associated with dasatinib and data of the same adverse reactions reported with the the TKIs asciminib, bosutinib, imatinib, nilotinib, ponatinib produced a ROR of 9.55 (95%; C.I. 7.28-12.52) for the adverse reaction PE and a ROR of 4.90 (95%; C.I. 2.98-8.05) for the adverse reaction PAH. Thus indicating for this drug a strong signal for disproportionate reporting compared to the combined odds of that event with other drugs in the same category. It means that prescription of dasatinib is over 10 times more probably linked to the potential occurrence of PE in comparison to other TKIs. Similarly, although to a lesser extent, patients prescribed dasatinib are approximately 5 times more likely to develop PAH than patients prescribed with other TKIs.

Disproportionality analysis about respiratory, thoracic and mediastinal disorders potentially induced by bosutinib shows a ROR of 2.38 (95%; C.I. 1.76-3.24) in comparison with the other TKIs (included dasatinib). Evaluation of ROR about both respiratory disorders PE and PAH, induced by bosutinib shows that these disorders are signaled in the 5.16% and the 3..29% of all serious cases induced by this drug, respectively. The incidence of PE following the use of bosutinib as being reported as largely variable in the percentage of 1–10% of patients [34]. Evaluation of sex distribution of european data shows that there is an asymettric difference between PE and PAH induced by bosutinib, indicating statistically significant male prevalence for PE in males and of PAH in females. The disproportionality analysis performed comparing the signals PE and PAH associated with bosutinib and data of the same adverse reactions reported with the TKIs dasatinib, asciminib, imatinib, nilotinib, ponatinib produced a ROR of 2.32 (95%; C.I. 1.61-3.36) for the adverse reaction PE and a ROR of 4.70 (95%; C.I. 2.68-8.25) for the adverse reaction PAH. These data indicate that prescribing bosutinib exposes patients to a more than two-fold higher risk of developing PE compared to other TKIs and a more than four-fold higher risk for pulmonary arterial pressure. In other words, the risk is present, but lower than that of PE with dasatinib, but almost comparable between the two drugs for pulmonary arterial hypertension. Sex distribution shows a difference characterized by prevalence of male patients experiencing PE and prevalence of females affected by PAH.

Meaning of ROR higher than 1, as observed in our analysis, means the odds for specific adverse events occurring with drugs is more elevated compared to the combined odds of these events (in this case PE and PAH) with other drugs in the same category (or all other drugs), indicating a strong signal for disproportionate reporting [35]. The results produced through our analysis need to be interpreted with care due to the known limitations of pharmacovigilance research using data systems of spontaneous signals for drugs with known adverse reactions. Limitations include the arbitrary choice of the years analyzed (2020-2024), lack of a denominator, under-reporting, lower-quality information, causal relationship uncertainty, and, finally, the difficulty in controlling confounding factors such as comorbidities or, sometimes, the dosage and frequency duration of exposure, which may have an influence on health/pathology conditions. Despite limitation above exposed, these data can be considered an update regarding the problem linked to the occurence of respiratory disorders induced by dasatinib. They confirm that risk is dramatically elevated for dasatinib-induced PE and it is significant also for PAH induced by dasatinib and bosutinib in comparison to other TKI as the disproportionality analysis indicates that the risk of PAH is similar for the two drugs and is almost 5 times higher than for the TKIS considered.

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5. Conclusions

In conclusion, this is the first post-marketing surveillance report conducted through the analysis of data exclusively coming fro European countries and United Kingdom. Results indicate that prescription of dasatinib is associated with a higher occurrence of rate of PE and PAH among the category of TKIs, while prescription of bosutinib induces with minor frequency PE but it exposes at a significant risk for PAH and this disorder seems to occur more often in women. These results indicate that respiratory disorders induced by the TKIs dasatinib and bosutinib need to be punctually and rapidly diagnosed and suggest caution before prescription of TKIs in patients affected by CML.

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Abbreviations

The following abbreviations are used in this manuscript:

TK	Tyrosine kinase
TKIs	Tyrosine kinase inhibitors
SARs	Suspected adverse reactions
FDA	Food and Drug Administration
EMA	European Medicines Agency
EU	European Union
UK	United Kingdom
EEA	European Economic Area
CML	Chronic myelogenous leukemia
BCR-ABL1	Breakpoint cluster Region-Abelson 1
MedDRA	Medical Dictionary for Regulatory Activities
S/NS	Serious/Non serious ratio
PE	Pleural effusion
PAH	Pulmonary arterial hypertension
PT	Preferred Term
FAERS	Food and Drug Administration Adverse Event Reporting System
ICSRs	Individual Cases Safety reports
SOC	System Organ Class
ROR	Reporting odds ratio
N.A.	Not applicable
C.I.	Confidence intervals

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References

1. Minciacchi VR, Kumar R, Krause DS. Chronic Myeloid Leukemia: A Model Disease of the Past, Present and Future. Cells. 2021 Jan 10;10(1):117. doi: 10.3390/cells10010117. PMID: 33435150; PMCID: PMC7827482.
2. Kantarjian H, Breccia M, Haddad FG, Hehlmann R, Issa GC, Malhotra H, Nicolini FE, Sasaki K, Stenke L, Jabbour E. Management of chronic myeloid leukemia in 2025. Cancer. 2025 Jul 15;131(14):e35953. doi: 10.1002/cncr.35953. PMID: 40616814; PMCID: PMC12529753.
3. Jabbour E, Kantarjian H. Chronic Myeloid Leukemia: A Review. JAMA. 2025 May 13;333(18):1618-1629. doi: 10.1001/jama.2025.0220. PMID: 40094679.
4. Hehlmann R, Hochhaus A, Baccarani M; European LeukemiaNet. Chronic myeloid leukaemia. Lancet. 2007 Jul 28;370(9584):342-50. doi: 10.1016/S0140-6736(07)61165-9. PMID: 17662883.
5. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, Wang SA, Bagg A, Barbui T, Branford S, Bueso-Ramos CE, Cortes JE, Dal Cin P, DiNardo CD, Dombret H, Duncavage EJ, Ebert BL, Estey EH, Facchetti F, Foucar K, Gangat N, Gianelli U, Godley LA, Gökbuget N, Gotlib J, Hellström-Lindberg E, Hobbs GS, Hoffman R, Jabbour EJ, Kiladjian JJ, Larson RA, Le Beau MM, Loh ML, Löwenberg B, Macintyre E, Malcovati L, Mullighan CG, Niemeyer C, Odenike OM, Ogawa S, Orfao A, Papaemmanuil E, Passamonti F, Porkka K, Pui CH, Radich JP, Reiter A, Rozman M, Rudelius M, Savona MR, Schiffer CA, Schmitt-Graeff A, Shimamura A, Sierra J, Stock WA, Stone RM, Tallman MS, Thiele J, Tien HF, Tzankov A, Vannucchi AM, Vyas P, Wei AH, Weinberg OK, Wierzbowska A, Cazzola M, Döhner H, Tefferi A. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022 Sep 15;140(11):1200-1228. doi: 10.1182/blood.2022015850. PMID: 35767897; PMCID: PMC9479031.
6. De Novellis D, Cacace F, Caprioli V, Wierda WG, Mahadeo KM, Tambaro FP. The TKI Era in Chronic Leukemias. Pharmaceutics. 2021 Dec 20;13(12):2201. doi: 10.3390/pharmaceutics13122201. PMID: 34959482; PMCID: PMC8709313.
7. Zhao D, Long X, Wang J. Pharmacovigilance study of BCR-ABL1 tyrosine kinase inhibitors: a safety analysis of the FDA adverse event reporting system. BMC Pharmacol Toxicol. 2024 Feb 23;25(1):20. doi: 10.1186/s40360-024-00741-x. PMID: 38395895; PMCID: PMC10885429.
8. Nekoukar Z, Moghimi M, Salehifar E. A narrative review on adverse effects of dasatinib with a focus on pharmacotherapy of dasatinib-induced pulmonary toxicities. Blood Res. 2021 Dec 31;56(4):229-242. doi: 10.5045/br.2021.2021117. PMID: 34776414; PMCID: PMC8721448.
9. Cheng F, Xu Q, Li Q, Cui Z, Li W, Zeng F. Adverse reactions after treatment with dasatinib in chronic myeloid leukemia: Characteristics, potential mechanisms, and clinical management strategies. Front Oncol. 2023 Feb 6;13:1113462. doi: 10.3389/fonc.2023.1113462. PMID: 36814818; PMCID: PMC9939513.
10. Cornet L, Khouri C, Roustit M, Guignabert C, Chaumais MC, Humbert M, Revol B, Despas F, Montani D, Cracowski JL. PAHassociated with protein kinase inhibitors: a pharmacovigilance-pharmacodynamic study. Eur Respir J. 2019 May 9;53(5):1802472. doi: 10.1183/13993003.02472-2018. PMID: 30846469.
11. Watanabe N, Takaku T, Tsukune Y, Yasuda H, Ochiai T, Yamada K, Nakazawa H, Hotta S, Nishimaki T, Takagi H, Takahashi K, Komatsu N, Ando M. Bosutinib-induced lung injury: a report of two cases and literature review. Int J Hematol. 2022 Jun;115(6):902-905. doi: 10.1007/s12185-022-03304-0. Epub 2022 Feb 28. PMID: 35229254; PMCID: PMC8884415.
12. Ammendolia I, Mannucci C, Cardia L, Calapai G, Gangemi S, Esposito E, Calapai F. Pharmacovigilance on cannabidiol as an antiepileptic agent. Front Pharmacol. 2023 Feb 10;14:1091978. doi: 10.3389/fphar.2023.1091978. PMID: 36843933; PMCID: PMC9950105.MedDRA and pharmacovigilance: A complex and little-evaluated tool. Prescrire Int. 2016, 25, 247–250.
13. MedDRA and pharmacovigilance: a complex and little-evaluated tool. Prescrire Int. 2016 Oct;25(175):247-250. PMID: 30645835.
14. Hauben M. Signal detection in the pharmaceutical industry: integrating clinical and computational approaches. Drug Saf. 2007;30(7):627-30. doi: 10.2165/00002018-200730070-00012. PMID: 17604418.
15. Faillie, J.L. Case-non-case studies: Principle, methods, bias and interpretation. Therapies 2019, 74, 225–232.
16. Agrawal V, Sahn SA. Lipid pleural effusions. Am J Med Sci. 2008 Jan;335(1):16-20. doi: 10.1097/MAJ.0b013e31815d2634. PMID: 18195578.

 doi:10.20944/preprints202512.2366.v1

17. Fan T, Li L, Wang Y, Lin M, Wu F. Targeting endothelial cells: the pathological mechanisms and therapeutic innovations in pulmonary arterial hypertension. Front Cell Dev Biol. 2025 Nov 26;13:1690124. doi: 10.3389/fcell.2025.1690124. PMID: 41383397; PMCID: PMC12689994.
18. Özgür Yurttaş N, Eşkazan AE. Dasatinib-induced pulmonary arterial hypertension. Br J Clin Pharmacol. 2018 May;84(5):835-845. doi: 10.1111/bcp.13508. Epub 2018 Mar 6. PMID: 29334406; PMCID: PMC5903230.
19. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, Clark RE, Cortes JE, Deininger MW, Guilhot F, Hjorth-Hansen H, Hughes TP, Janssen JJWM, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Mayer J, Nicolini F, Niederwieser D, Pane F, Radich JP, Rea D, Richter J, Rosti G, Rousselot P, Saglio G, Saußele S, Soverini S, Steegmann JL, Turkina A, Zaritskey A, Hehlmann R. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020 Apr;34(4):966-984. doi: 10.1038/s41375-020-0776-2. Epub 2020 Mar 3. PMID: 32127639; PMCID: PMC7214240.
20. Pura Krishnamurthy K, Mahadevappa M, Srinivasan BR, Jayaprakash Narayan H. Dasatinib Induced Pulmonary Hypertension and Third Space Effusion: A Case Series and Literature Review. Hosp Pharm. 2025 Jul 17:00185787251348384. doi: 10.1177/00185787251348384. Epub ahead of print. PMID: 40688241; PMCID: PMC12271141.
21. Doan V, Wang A, Prescott H. Bosutinib for the treatment of chronic myeloid leukemia. Am J Health Syst Pharm. 2015 Mar 15;72(6):439-47. doi: 10.2146/ajhp140221. PMID: 25736937.
22. Vojjala N, Sami HA, Kotla NK, Peshin S, Goyal K, Kondaveety S, Prabhu RR, Krishnamoorthy G. Bosutinib-Induced PE-Class Effect and Cross-Intolerance to All Tyrosine Kinase Inhibitors. Hematol Rep. 2025 Jan 31;17(1):7. doi: 10.3390/hematolrep17010007. PMID: 39997355; PMCID: PMC11855369.
23. Cortes J, Mauro M, Steegmann JL, Saglio G, Malhotra R, Ukropec JA, Wallis NT. Cardiovascular and pulmonary adverse events in patients treated with BCR-ABL inhibitors: Data from the FDA Adverse Event Reporting System. Am J Hematol. 2015 Apr;90(4):E66-72. doi: 10.1002/ajh.23938. Epub 2015 Jan 30. PMID: 25580915; PMCID: PMC11458256.
24. Armas-Villalba AJ, Jimenez CA. Chylothorax. Clin Chest Med. 2025 Jun;46(2):251-260. doi: 10.1016/j.ccm.2025.02.004. Epub 2025 Mar 29. PMID: 40484500.
25. Al-Abcha A, Iftikhar MH, Abu Rous F, Laird-Fick H. Chylothorax: complication attributed to dasatinib use. BMJ Case Rep. 2019 Dec 16;12(12):e231653. doi: 10.1136/bcr-2019-231653. PMID: 31848139; PMCID: PMC6936595.
26. Molina V, Vañes S, Castelló C, Chiner E. Chylothorax Secondary to Dasatinib. Arch Bronconeumol (Engl Ed). 2020 Sep;56(9):599-601. English, Spanish. doi: 10.1016/j.arbres.2020.05.001. Epub 2020 May 31. PMID: 32493642.
27. Huang J, Cai J, Ye Q, Jiang Q, Lin H, Wu L. Fluid retention-associated adverse events in patients treated with BCR::ABL1 inhibitors based on FDA Adverse Event Reporting System (FAERS): a retrospective pharmacovigilance study. BMJ Open. 2023 Aug 3;13(8):e071456. doi: 10.1136/bmjopen-2022-071456. PMID: 37536976; PMCID: PMC10401248.
28. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015 Oct;46(4):903-75. doi: 10.1183/13993003.01032-2015. Epub 2015 Aug 29. Erratum in: Eur Respir J. 2015 Dec;46(6):1855-6. doi: 10.1183/13993003.51032-2015. PMID: 26318161.
29. Montani D, Seferian A, Savale L, Simonneau G, Humbert M. Drug-induced pulmonary arterial hypertension: a recent outbreak. Eur Respir Rev. 2013 Sep 1;22(129):244-50. doi: 10.1183/09059180.00003313. PMID: 23997051; PMCID: PMC9487364.

 doi:10.20944/preprints202512.2366.v1

30. Guignabert C, Tu L, Le Hiress M, Ricard N, Sattler C, Seferian A, Huertas A, Humbert M, Montani D. Pathogenesis of pulmonary arterial hypertension: lessons from cancer. Eur Respir Rev. 2013 Dec;22(130):543-51. doi: 10.1183/09059180.00007513. PMID: 24293470; PMCID: PMC9639182.
31. Moulis G, Sommet A, Durrieu G, Bagheri H, Lapeyre-Mestre M, Montastruc JL; French Association of PharmacoVigilance Centres. Trends of reporting of 'serious'vs. 'non-serious' adverse drug reactions over time: a study in the French PharmacoVigilance Database. Br J Clin Pharmacol. 2012 Jul;74(1):201-4. doi: 10.1111/j.1365-2125.2012.04185.x. PMID: 22257367; PMCID: PMC3394146.
32. Jain AG, Gesiotto Q, Ball S, Nodzon L, Rodriguez A, Chan O, Padron E, Kuykendall A, Komrokji R, Sallman DA, Lancet JE, Pinilla-Ibarz J, Sweet K. Incidence of PE with dasatinib and the effect of switching therapy to a different TKI in patients with chronic phase CML. Ann Hematol. 2024 Jun;103(6):1941-1945. doi: 10.1007/s00277-024-05760-6. Epub 2024 Apr 18. PMID: 38634915; PMCID: PMC11090947.
33. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubeau P, Girerd B, Natali D, Guignabert C, Perros F, O'Callaghan DS, Jaïs X, Tubert-Bitter P, Zalcman G, Sitbon O, Simonneau G, Humbert M. PAHin patients treated by dasatinib. Circulation. 2012 May 1;125(17):2128-37. doi: 10.1161/CIRCULATIONAHA.111.079921. Epub 2012 Mar 26. PMID: 22451584.
34. Caldemeyer L., Dugan M., Edwards J., Akard L. Long-term side effects of tyrosine kinase inhibitors in chronic myeloid leukemia. Curr. Hematol. Malign. Rep. 2016;11(2):71–79. doi: 10.1007/s11899-016-0309-2.
35. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004 Aug;13(8):519-23. doi: 10.1002/pds.1001. PMID: 15317031.