

ORIGINAL RESEARCH

Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA Adverse Event Reporting System (FAERS)

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Background: Inhibitors of the anaplastic lymphoma kinase (ALK) gene mutation are highly effective treatments for ALK-positive lung cancer. We conducted this pharmacovigilance analysis using the Food and Drug Administration Adverse Event Reporting System (FAERS).

Patients and methods: FAERS files from 2012 to 2020 were used. Reports for crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib were filtered. We used the Medical Dictionary for Regulatory Activities (MedDRA version 22.1). Further, we searched for adverse events on the preferred term (PT) level based on case reports in the literature. After filtering duplicate reports, disproportionality analysis was used to detect safety signals by calculating proportional reporting ratios (PRRs), reporting odds ratios (RORs), empirical Bayesian geometric mean, and information component. Reports were considered statistically significant if the 95% confidence interval did not contain the null value.

Results: Within the system organ classes, significant safety signals were found, including those for crizotinib [eye disorders (PRR 2.09, ROR 2.12)], ceritinib [gastrointestinal disorders (PRR 2.19, ROR 2.41), hepatobiliary disorders (PRR 4.4, ROR 4.52), respiratory disorders (PRR 1.96, ROR 2.08)], alectinib [hepatobiliary disorders (PRR 2.60, ROR 2.63)], brigatinib [respiratory disorders (PRR 2.15, ROR 2.31)], and lorlatinib [metabolism disorders (PRR 3.34, ROR 3.53)]. For adverse events on the PT level, we found several significant signals, including pneumothorax with crizotinib (PRR 3.29, ROR 3.29), ceritinib (PRR 3.13, ROR 3.13), and alectinib (PRR 4.88, ROR 4.89); myasthenia gravis with lorlatinib (PRR 6.05, ROR 6.05); photosensitivity reactions with crizotinib (PRR 2.20, ROR 2.20), ceritinib (PRR 4.30, ROR 4.31), alectinib (PRR 20.43, ROR 20.51), and brigatinib (PRR 20.97, ROR 21.05); pulmonary arterial hypertension with brigatinib (PRR 2.92, ROR 2.92) and lorlatinib (PRR 9.2, ROR 9.24); and rectal perforation with crizotinib (PRR 7.83, ROR 7.83). All the detected safety signals were confirmed using Bayesian methods.

Conclusion: ALK inhibitors differed in their safety profile reports. We found several significant safety signals that matched previously published case reports, including pulmonary arterial hypertension, rectal perforation, myasthenia gravis, and photosensitivity. These signals require further regulatory investigation to determine their significance and potentially update the product labels to inform patients and clinicians.

Key words: ALK inhibitors, pharmacovigilance, adverse events, post-marketing surveillance, pharmacoepidemiology, lung cancer

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer, accounting for 11.6% of new cancer cases, and the highest cancer-related mortality worldwide.¹ Historically, the

treatment of advanced lung cancer was dependent on platinum-based chemotherapy.² The landscape of treatment changed after the advances in our understanding of the driving mutations in lung cancer.³

Patients with stage IV lung adenocarcinoma are usually assessed for different types of mutations including anaplastic lymphoma kinase (ALK) gene rearrangements, because patients harboring a rearranged ALK gene/fusion protein are highly sensitive to therapy with ALK-targeted inhibitors.⁴

The currently approved ALK-targeted (tyrosine kinase) inhibitors include the following: crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib.⁵ These drugs have shown differences in terms of their efficacy and safety profiles.⁶

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Alectinib is favored to be the first-line therapy, where treatment is continued until there is disease progression or unacceptable toxicity.⁷

Crizotinib is the first approved tyrosine kinase inhibitor for ALK-positive advanced non-small-cell lung cancer,⁸ and considered first-line treatment in centers where alectinib is not available. Moreover, newer more potent ALK inhibitors with greater systemic and central nervous system efficacy have since been developed and are preferred over crizotinib. Ceritinib and brigatinib are approved for metastatic non-small-cell lung cancers with ALK-positive tumors in second-line setting after progression on alectinib or crizotinib,^{9,10} whereas lorlatinib is used as a salvage treatment after using at least two lines of ALK inhibitor.¹¹

Treatment with ALK inhibitors is usually well tolerated; however, there are common class adverse events such as nausea, vomiting, diarrhea, pneumonitis, and cardiac toxicity.¹² Some less common adverse events have been reported as well including rectal perforation,¹³ cataract, macular edema or blindness,^{14,15} osteitis,¹⁶ ventricular fibrillation,^{17,18} pulmonary arterial hypertension,¹⁹ pancreatitis,²⁰ cholestasis,²¹ alopecia,²² proteinuria,²³ myasthenia gravis,²⁴ toxic epidermal necrolysis,²⁵ sarcoid-like reaction,²⁶ and photosensitivity.²⁷

Treatment discontinuation due to adverse events among different ALK inhibitors were as follow: 12% with crizotinib as in the PROFILE 1014 trial,²⁸ 5% with ceritinib as in the ASCEND 4 trial,²⁹ 11% with alectinib as in the ALEX trial,³⁰ 12% with brigatinib as in the ALTA-1L trial,¹⁰ and 7% with lorlatinib as in the CROWN trial.³¹

Better understanding of the real-world safety profile of ALK inhibitors in patients with lung cancer will lead to better compliance, decrease interruptions, and reflect on the desirable progression-free survival and overall survival.³²⁻³⁵ With the wide use of ALK inhibitors in clinical practice, and scarcity in evaluations of their adverse effects in real-world cohorts, we conducted this pharmacovigilance analysis to evaluate the safety profile of the available ALK inhibitors in the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

METHODS

FAERS is a database used by the Food and Drug Administration (FDA) in the United States to collect postmarketing safety data on approved drugs and therapeutic biologic products. Drug manufacturers are required to send any safety reports to the FDA, while health care professionals and consumers may voluntarily do so.

The FDA regularly analyzes the received reports for potential safety signals, which would warrant further evaluation and regulatory actions if necessary.³⁶

Publicly available files from 2012Q1 to 2020Q2 were downloaded from the FDA website.³⁶ We used a two-step deduplication process to prevent counting the same report twice, first by filtering unique row variables, and then by using unique case ID values.³⁶

The agents under study were filtered if they were found under either 'PROD_AI' or 'DRUGNAME' column. As the FAERS database may contain uppercase or lowercase values, all values were recoded to lowercase values. Reports for the following terms representing ALK inhibitors were used: 'Crizotinib', 'Xalkori', 'Ceritinib', 'Zykadia', 'Alectinib', 'Alecensa', 'Brigatinib', 'Alunbrig', 'Lorlatinib', and 'Lorbrena'. Moreover, to detect any missed reports, we used terms that reflect the active chemical compound or trade names outside the United States (e.g. 'LDK378' and 'Spexib' for ceritinib).

To focus our results on the drug most likely to have caused the adverse event, we limited our analysis to reports in which the drug was considered the primary suspect, using results with the role code 'PS'.³⁷ Adverse events in FAERS are described using the preferred term (PT) of the standardized Medical Dictionary for Regulatory Activities (MedDRA) terminology,³⁸ which contains 27 system organ classes (SOCs). Further, MedDRA is characterized by 'multiaxiality', where a PT can be linked to more than one SOC. Accordingly, we used MedDRA (version 22.1) to classify adverse events in each report to the corresponding SOC levels. Within each SOC significant safety signal, we reported counts of each adverse event found using PTs, to describe the most frequent adverse events in each SOC for every drug. We also searched PubMed for case reports on adverse events associated with at least one of the ALK inhibitors that are not mentioned in their package label. Our search yielded 17 adverse events, which were then matched to their corresponding MedDRA codes on the PT level to run safety signal analysis in FAERS.

We also included information on age, weight, sex, reporter occupation, and patient outcome in our analysis, if they were available. To study the outcomes of detected safety signals, we grouped them using outcome code 'OUTC_COD' to produce the four categories: Death (using the term 'DE'); major events comprising Life Threatening, Hospitalization, and Disability (using terms 'LT', 'HO', and 'DS', respectively); Congenital Anomaly (using terms 'CA'), and other important medical events (using the term 'OT').

Disproportionality analysis was used to detect safety signals for the drugs under study. We calculated proportional reporting ratios (PRRs)³⁹ and reporting odds ratios (RORs).⁴⁰ Safety signals were considered significant if the PRR or ROR were ≥ 2.0 and the 95% confidence interval values exceeded 1.0 (null value). Furthermore, we used Bayesian analysis methods, empirical Bayesian geometric mean,⁴¹ and information component⁴² with 95% confidence interval to confirm our findings and decrease false-positive safety signals. Importing and analysis were performed using PostgreSQL (version 12),⁴³ and Python 3.6⁴⁴; our code used to generate the analysis is publicly available on a GitHub repository.⁴⁵

RESULTS

Over the 8-year study period, there were 58 471 reports for ALK inhibitors, with 35 202, 11 248, 6173, 2772, and 3076

Table 1. Characteristics of studied safety reports

	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib	P value*
Total number of adverse events reports attributed to drug	35 202	11 248	6173	2772	3076	
Age (years), mean \pm SD	61.1 \pm 16.85	55.9 \pm 14.99	61.6 \pm 14.03	59.1 \pm 12.81	59.2 \pm 17.06	<0.001
Weight (kg), mean \pm SD	65.6 \pm 19.82	64.2 \pm 17.12	68.5 \pm 17.0	69.3 \pm 15.57	68.8 \pm 20.46	<0.001
Sex, n (%)						<0.001
Male	13 349 (37.92)	4545 (40.41)	2164 (35.06)	948 (34.2)	1136 (36.93)	
Female	19 997 (56.81)	6010 (53.43)	3666 (59.39)	1624 (58.59)	1666 (54.16)	
Missing	1856 (5.27)	693 (6.16)	343 (5.56)	200 (7.22)	274 (8.91)	
Report source, n (%)						<0.001
Consumer	10 654 (30.27)	2392 (21.27)	3054 (49.47)	1138 (41.05)	664 (21.59)	
Physician	13 198 (37.49)	5488 (48.79)	2079 (33.68)	1026 (37.01)	1358 (44.15)	
Pharmacist	3657 (10.39)	538 (4.78)	596 (9.65)	234 (8.44)	419 (13.62)	
Other	7239 (20.56)	1796 (15.97)	322 (5.22)	284 (10.25)	328 (10.66)	
Missing	184 (0.52)	895 (7.96)	36 (0.58)	4 (0.14)	61 (1.98)	

SD, standard deviation.

* P values for analysis of variance when comparing continuous variables and chi-square when comparing categorical variables.

attributed to crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib, respectively, as the primary suspect.

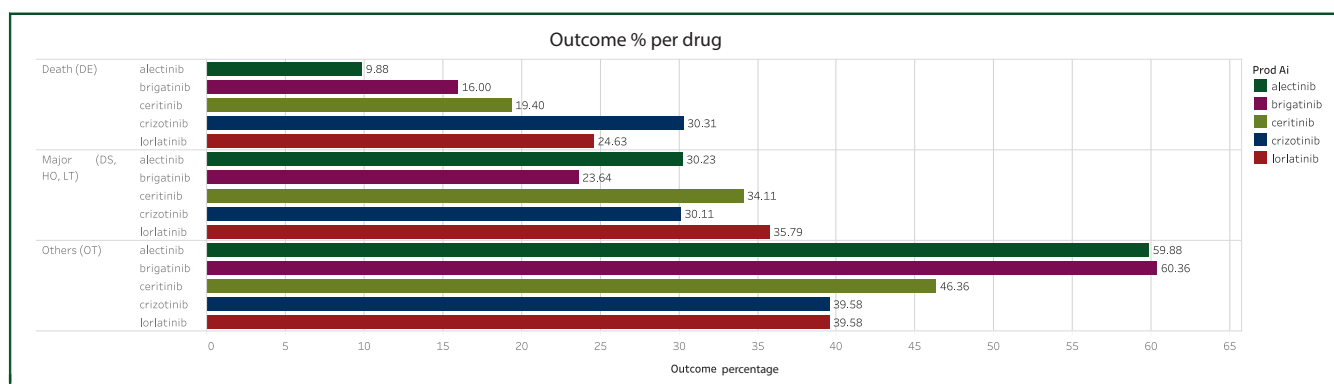
The average age and weight reported for ALK inhibitor users were different, with the highest mean age of 61.6 years for alectinib, the lowest mean age of 59.1 years for brigatinib, the highest mean weight of 69.3 kg for brigatinib, and the lowest mean weight of 64.2 kg for ceritinib. Moreover, there were a higher percentage of female patients for all five drugs under study compared with male patients. Most of the reports were submitted by either the consumer or physician: physicians contributed to the highest percentage of reports for crizotinib (37.49%), ceritinib (48.79%), and lorlatinib (44.15%), whereas consumers contributed to the highest percentage of reports for alectinib (49.47%) and brigatinib (41.05%; Table 1).

Within the SOCs, significant safety signals using disproportionality analysis were two for crizotinib [eye disorders (PRR 2.09, ROR 2.12) and neoplasms (PRR 4.26, ROR 4.57)], five for ceritinib [gastrointestinal disorders (PRR 2.19, ROR 2.41), hepatobiliary disorders (PRR 4.4, ROR 4.52), neoplasms (PRR 9.31, ROR 10.53), respiratory disorders (PRR 1.96, ROR 2.08), investigations (PRR 2.05, ROR 2.15)], two for alectinib [hepatobiliary disorders (PRR 2.60, ROR 2.63), neoplasms (PRR 2.03, ROR 2.06)], two for brigatinib

[neoplasms (PRR 8.43, ROR 9.41) and respiratory disorders (PRR 2.15, ROR 2.31)], and two for lorlatinib [metabolism disorders (PRR 3.34, ROR 3.53), neoplasms (PRR 3.26, ROR 3.36)]. Moreover, all the detected safety signals were significant when the Bayesian methods were used (Table 2).

Regarding outcomes of the detected safety signals, crizotinib had the highest percentage of death among the studied drugs (30.31%), and alectinib had the lowest (9.88%). Lorlatinib had the highest percentage of major outcomes (35.79%), and brigatinib the lowest (23.64%; Figure 1). Moreover, our analysis found no adverse event reports with the outcome of congenital anomaly except for ceritinib ($n = 11$).

Further analysis of the detected safety signals showed that the most frequently reported adverse events were the following: for crizotinib, visual impairment in eye disorders ($n = 404$) and neoplasm progression in neoplasms ($n = 778$). For ceritinib, diarrhea in gastrointestinal disorders ($n = 446$), liver disorder in hepatobiliary disorders ($n = 65$), malignant neoplasm progression in neoplasms ($n = 491$), non-small-cell lung cancer in respiratory disorders ($n = 310$), and increased alanine aminotransferase in investigations ($n = 91$). For alectinib, abnormal hepatic function in hepatobiliary disorders ($n = 17$) and metastases

**Figure 1. Outcomes for adverse events associated with ALK inhibitors at the level of system organ classes.**

ALK, DE, death; DS, disability; HO, hospitalization; LT, life threatening; OT, other.

Table 2. Detected significant safety signals on the system organ class level

System organ class	Proportional reporting ratio (95% CI)	Reporting odds ratio (95% CI)	Information component (95% CI)	Empirical Bayesian geometric mean (95% CI)
Crizotinib				
Eye disorders	2.09 (1.97-2.21)	2.12 (2.0-2.26)	70.05 (65.97-74.37)	2.09 (1.97-2.22)
Neoplasms benign, malignant, and unspecified	4.26 (4.09-4.45)	4.57 (4.27-4.67)	70.81 (67.73-74.04)	4.25 (4.07-4.45)
Ceritinib				
Gastrointestinal disorders	2.19 (2.1-2.29)	2.41 (2.29-2.54)	71.27 (67.72-75.01)	2.19 (2.08-2.31)
Hepatobiliary disorders	4.4 (3.99-4.86)	4.52 (4.08-5.01)	65.88 (59.47-72.98)	4.40 (3.97-4.87)
Neoplasms benign, malignant, and unspecified	9.31 (8.87-9.77)	10.53 (9.96-11.13)	68.65 (64.95-72.56)	9.29 (8.79-9.82)
Respiratory, thoracic, and mediastinal disorders	1.96 (1.86-2.07)	2.08 (1.96-2.20)	70.42 (66.35-74.73)	1.96 (1.85-2.08)
Investigations	2.05 (1.93-2.18)	2.15 (2.01-2.30)	69.62 (65.14-74.41)	2.05 (1.92-2.19)
Alectinib				
Hepatobiliary disorders	2.60 (2.18-3.09)	2.63 (2.20-3.14)	63.39 (53.02-75.78)	2.60 (2.17-3.10)
Neoplasms benign, malignant, and unspecified	2.03 (1.76-2.36)	2.06 (1.77-2.40)	64.73 (55.64-75.29)	2.03 (1.75-2.37)
Brigatinib				
Neoplasms benign, malignant, and unspecified	8.43 (7.61-9.34)	9.41 (8.38-10.57)	64.47 (57.39-72.41)	8.43 (7.50-9.47)
Respiratory, thoracic, and mediastinal disorders	2.15 (1.94-2.38)	2.31 (2.06-2.59)	66.51 (59.29-74.61)	2.15 (1.92-2.41)
Lorlatinib				
Metabolism and nutrition disorders	3.34 (2.95-3.78)	3.53 (3.09-4.04)	64.89 (56.81-74.13)	3.34 (2.92-3.82)
Neoplasms benign, malignant, and unspecified	3.26 (2.77-3.83)	3.36 (2.83-3.99)	63.39 (53.44-75.20)	3.26 (2.74-3.86)

CI, confidence interval.

to the central nervous system in neoplasms ($n = 48$). For brigatinib, progression of neoplasms in neoplasms ($n = 154$) and cough in respiratory disorder ($n = 40$). For lorlatinib, hypercholesterolemia in metabolism disorder ($n = 36$) and progression of neoplasms in neoplasms ($n = 125$).

Of the 17 adverse events found in our PubMed search, we found no matched reports in FAERS for two (sarcoid-like reactions and osteitis). For the remaining 15 adverse events, we found the following significant safety signals: two for cholestasis, three for pneumothorax, one for fulminant hepatitis, one for myasthenia gravis, one for pancreatitis, four for photosensitivity reactions, one for proteinuria, two for pulmonary arterial hypertension, one for toxic epidermal necrolysis, and one for rectal perforation (Figure 2 and Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2021.100315>).

DISCUSSION

Our study demonstrates that ALK inhibitors differ in their safety profile based on FAERS reports. In terms of organ systems, ceritinib was the only agent to show a significant signal in gastrointestinal disorders and abnormal laboratory values. Ceritinib and alectinib both showed a significant signal in hepatobiliary disorders, and ceritinib and brigatinib both showed a significant signal in respiratory disorders. Lorlatinib was the only agent to show a significant signal in metabolism and nutrition disorders, and crizotinib was the only agent to show a significant safety signal in eye disorders.

Some of our findings are consistent with previous published studies that compared the safety of different ALK inhibitors. Costa et al. reported that ceritinib had a higher percentage of gastrointestinal toxicity, as it caused 5.7% of grade 3/4 diarrhea, compared with 0.6% for alectinib, 0.5% for brigatinib, and 1.7% for crizotinib ($P < 0.001$). Moreover, they found that ceritinib caused 22.8% of grade 3/4 alanine aminotransferase elevations, compared with 4% for alectinib and 9.1% for crizotinib ($P < 0.001$).⁶ Kassem et al.⁴⁶ reported that gastrointestinal toxicity was highest in ceritinib, with 72%-86% for diarrhea and 52%-67% for vomiting, and lowest in alectinib with 4%-20.7% for diarrhea and 4%-11.5% for vomiting. Almost all of visual disorders found in their meta-analysis was attributed to crizotinib, ranging from 54.8% to 82%.

In terms of MedDRA PT level adverse events reported in the literature, we found safety signals in FAERS for multiple adverse events including pneumothorax, rectal perforation, myasthenia gravis, pulmonary arterial hypertension, and photosensitivity.

We found three significant signals for pneumothorax associated with the ALK inhibitors under study, including crizotinib, ceritinib, and alectinib. Crizotinib is known to be associated with pulmonary side-effects, mainly interstitial lung disease and pneumonitis.²⁸ However, Gennatas et al.⁴⁷ reported a rare pulmonary side-effect in a 48-year-old male with stage IV lung adenocarcinoma who developed dyspnea due to pneumothorax 4 weeks after starting crizotinib. The pneumothorax resolved after chest tube insertion and the patient was discharged. This highlights the consideration of

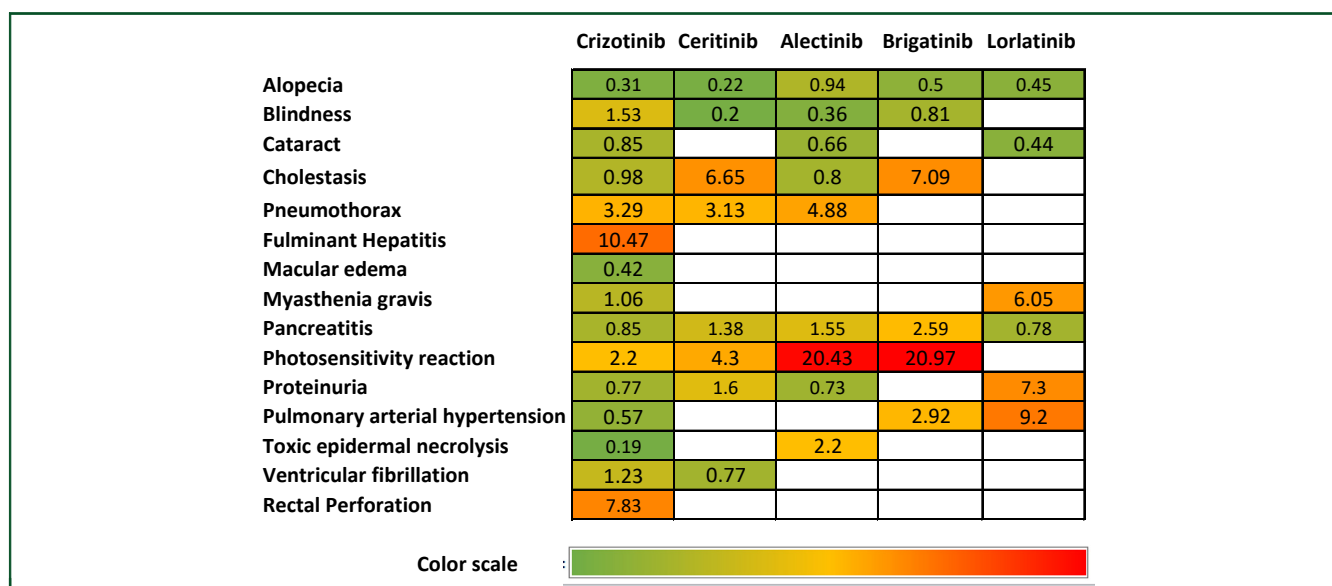


Figure 2. Heatmap for safety signals based on proportional reporting ratio for selected adverse events found in literature review.

pneumothorax in the differential diagnosis of newly developed dyspnea in patients on crizotinib.

Our analysis found a significant signal for rectal perforation with crizotinib, but not with the other ALK inhibitors. Yanagisawa et al.¹³ reported a case of a 86-year-old male with stage IV lung adenocarcinoma who developed rectal perforation associated with crizotinib.

For myasthenia gravis, we found a significant signal with only lorlatinib. Although lorlatinib is not known to be associated with autoimmune diseases such as myasthenia gravis,⁴⁸ Desai et al.²⁴ published a case report in which a 56-year-old male with stage IV non-small-cell lung adenocarcinoma developed myasthenia gravis after starting lorlatinib, who clinically improved after treatment with pyridostigmine. The author suspected lorlatinib because the patient was previously treated with other ALK inhibitors, crizotinib and ceritinib, without developing this autoimmune reaction.

For pulmonary arterial hypertension, our analysis found significant signals with two ALK inhibitors: lorlatinib and brigatinib. Chabrol et al.¹⁹ reported two cases of pulmonary arterial hypertension developed after starting lorlatinib; however, both clinically improved upon lorlatinib withdrawal. Tabbò et al.⁴⁹ reported a case which developed pulmonary arterial hypertension after starting brigatinib.

Moreover, tyrosine kinase inhibitors used in the treatment of other malignancies have been associated with pulmonary arterial hypertension including dasatinib, lapatinib, and bosutinib.⁵⁰

Among ALK inhibitors, alectinib is the only agent for which the product label contains precautions to avoid photosensitivity.⁵¹ However, our analysis of the FAERS databases found four significant signals for photosensitivity reactions associated with brigatinib, alectinib, crizotinib, and ceritinib. Morgado et al.²⁷ reported a case in which a 70-year-old female with metastatic lung cancer developed a

photosensitivity reaction while on brigatinib, which warranted treatment interruption; the same adverse event reoccurred upon reintroduction. Although brigatinib is associated with some skin-related adverse events such as rash or pruritus, it is not known to be a photosensitizing drug that requires precautions to sun exposure.⁵² The previously reported safety signals warrant investigating the photosensitizing ability of other ALK inhibitors with the potential to update the product labels, if the association was determined to be causal, to guide patients for taking necessary sun exposure precautions.

Our findings should be interpreted while considering the limitations of the FAERS database. As the FDA does not require a proof of causal relationship for submitted reports, we cannot infer causation from the observed associations in the database.⁵³ Further, we cannot calculate the incidence of a specific adverse event because FAERS does not contain every adverse event that occurred in the population. Moreover, spontaneous reporting systems such as FAERS can be subjected to the Weber effect, where reporting of adverse events for a certain drug tends to increase within the first 2 years of approval and then decreases with more time in the market.⁵⁴ They are also subjected to confounding by age, indication, and interacting medications.⁵⁵ Nevertheless, the FAERS database remains an important tool that the FDA continues to use for postmarketing surveillance.

Conclusion

ALK inhibitors constitute an important part of the pharmacotherapy for non-small-cell lung cancer. Agents belonging to this group have different safety profiles, with some resulting in severe adverse events that may lead to lack of compliance or treatment discontinuation. Clinicians should be aware of such differences to tailor their agent choice and monitor

their patients accordingly. We found multiple postmarketing safety signals similar to what had been reported in clinical trials, as well as other reports that require further regulatory investigation to determine their significance.

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DISCLOSURE

AAA is an employee of Astellas Pharma Global Development. All other authors have declared no conflicts of interest.

DATA SHARING

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
- Carbone DP, Minna JD. Chemotherapy for non-small cell lung cancer. *BMJ*. 1995;311(7010):889.
- Sabari JK, Santini F, Bergagnini I, Lai WV, Arbour KC, Drilon A. Changing the therapeutic landscape in non-small cell lung cancers: the evolution of comprehensive molecular profiling improves access to therapy. *Curr Oncol Rep*. 2017;19(4):24.
- McCusker MG, Russo A, Scilla KA, Mehra R, Rolfo C. How I treat ALK-positive non-small cell lung cancer. *ESMO Open*. 2019;4(suppl 2):524.
- Pirker R, Filipits M. From crizotinib to lorlatinib: continuous improvement in precision treatment of ALK-positive non-small cell lung cancer. *ESMO Open*. 2019;4(5):548.
- Costa RB, Costa RLB, Talamantes SM, et al. Systematic review and meta-analysis of selected toxicities of approved ALK inhibitors in metastatic non-small cell lung cancer. *Oncotarget*. 2018;9(31):22137-22146.
- Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet*. 2017;390(10089):29-39.
- Shaw AT, Kim D-W, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.
- Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(7):874-886.
- Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2027-2039.
- Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654-1667.
- Hou H, Sun D, Liu K, et al. The safety and serious adverse events of approved ALK inhibitors in malignancies: a meta-analysis. *Cancer Manag Res*. 2019;11:4109-4118.
- Yanagisawa A, Hayama N, Amano H, et al. Crizotinib-induced rectal perforation with abscess. *Intern Med*. 2017;56(23):3211-3213.
- Chelala E, Hoyek S, Arej N, et al. Ocular and orbital side effects of ALK inhibitors: a review article. *Futur Oncol*. 2019;15(16):1939-1945.
- Chun SG, Iyengar P, Gerber DE, Hogan RN, Timmerman RD. Optic neuropathy and blindness associated with crizotinib for non-small-cell lung cancer with EML4-ALK Translocation. *J Clin Oncol*. 2015;33(5):e25-e26.
- Guisier F, Piton N, Bellefleur M, et al. Crizotinib-induced osteitis mimicking bone metastasis in a stage IV ALK-rearranged NSCLC patient: a case report. *BMC Cancer*. 2020;20(1):14.
- Oyakawa T, Muraoka N, Iida K, et al. Crizotinib-induced simultaneous multiple cardiac toxicities. *Invest New Drugs*. 2018;36(5):949-951.
- Mandal AKJ, Stokes SA, Missouri CG. Implantable cardioverter defibrillator for alectinib induced ventricular fibrillation. *Clin Toxicol*. 2020;58(7):781-784.
- Chabrol A, Mayenga M, Hamid AM, et al. Lorlatinib-induced pulmonary arterial hypertension. *Lung Cancer*. 2018;120:60-61.
- Rao A, Reddy A, Dinunno C, Elali I. Life-threatening hypertriglyceridemia-induced pancreatitis related to alectinib successfully treated by plasmapheresis: a review of the literature on metabolic toxicities associated with anaplastic lymphoma kinase inhibitors. *J Oncol Pharm Pract*. 2020;26(6):1533-1537.
- Hirano T, Yamada M, Ichinose M. Chronic cholestasis with dilation of intrahepatic bile duct related to administration of ceritinib. *J Thorac Oncol*. 2017;12(8):e123-e125.
- Koizumi T, Fukushima T, Gomi D, et al. Alectinib-induced alopecia in a patient with anaplastic lymphoma kinase-positive non-small cell lung cancer. *Case Rep Oncol*. 2016;9(1):212-215.
- Lee C-S, Wanchoo R, Seetharamu N. Lorlatinib induced proteinuria: a case report. *J Oncol Pharm Pract*. 2021;27:1037-1039.
- Desai A, Sriwastava S, Gadgeel SM, Lisak RP. New onset myasthenia gravis in a patient with non small cell lung cancer treated with lorlatinib a novel anti-cancer agent. *J Neurol Sci*. 2018;392:100-101.
- Yang S, Wu L, Li X, Huang J, Zhong J, Chen X. Crizotinib-associated toxic epidermal necrolysis in an ALK-positive advanced NSCLC patient. *Mol Clin Oncol*. 2018;8(3):457-459.
- Facchinetti F, Gnetti L, Balestra V, et al. Sarcoid-like reaction mimicking disease progression in an ALK-positive lung cancer patient receiving lorlatinib. *Invest New Drugs*. 2019;37(2):360-363.
- Morgado F, Calvão J, Barata F, Gonçalves M. Phototoxic reaction to brigatinib — a new photosensitizing drug. *J Eur Acad Dermatol Venerol*. 2019;33(12):e491-e492.
- Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167-2177.
- Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017;389(10072):917-929.
- Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-838.
- Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med*. 2020;383(21):2018-2029.
- Lebovits AH, Strain JJ, Messe MR, Schleifer SJ, Tanaka JS, Bhardwaj S. Patient noncompliance with self-administered chemotherapy. *Cancer*. 1990;65(1):17-22.
- Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin*. 2009;59(1):56-66.
- Schneider MP, Jeanneret LA, Chevaux B, et al. A novel approach to better characterize medication adherence in oral anticancer treatments. *Front Pharmacol*. 2019;9:1567.
- Hershman DL, Shao TS, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat*. 2011;126(2):529-537.

36. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). 2018. Available at <https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers>. Accessed April 11, 2021.
37. Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. *Drug Saf*. 2018;41(4):357-361.
38. Medical Dictionary for Regulatory Activities. *Welcome to MedDRA. Medical Dictionary for Regulatory Activities*. 2018. Available at <https://www.meddra.org/>. Accessed April 11, 2021.
39. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf*. 2001;10(6):483-486.
40. Van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection is spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf*. 2002;11(1):3-10.
41. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Safety*. 2002;25(6):381-392.
42. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol*. 1998;54(4):315-321.
43. PostgreSQL: The world's most advanced open source database. 2013. Available at <https://www.postgresql.org/>. Accessed April 11, 2021.
44. van Rossum G. *Python Release Python 3.6.0* | *Python.org*. 2016. Available at <https://www.python.org/downloads/release/python-360/>. Accessed April 11, 2021.
45. GitHub - MarwaEshra/FAERS-Database. *OpenSource FAERS Database Cleansing, Merging and Analysis using postgresql*. Available at <https://github.com/MarwaEshra/FAERS-Database>. Accessed April 11, 2021.
46. Kassem L, Shohdy KS, Lasheen S, Abdel-Rahman O, Ali A, Abdel-Malek RR. Safety issues with the ALK inhibitors in the treatment of NSCLC: a systematic review. *Crit Rev Oncol Hematol*. 2019;134:56-64.
47. Gennatas S, Stanway SJ, Thomas R, et al. Early pneumothorax as a feature of response to crizotinib therapy in a patient with ALK rearranged lung adenocarcinoma. *BMC Cancer*. 2013;13(1):207.
48. Lorlatinib Package Insert. Highlights of prescribing information. Available at www.pfizer.com. Accessed April 11, 2021.
49. Tabbò F, D'Aveni A, Tota D, et al. Pulmonary arterial hypertension in ALK receptor tyrosine kinase-positive lung cancer patient: adverse event or disease spread? *J Thoracic Oncol*. 2019;14(2):e38-e40.
50. Preda M, Seferian A, Jutant E-M, et al. Tyrosine kinase inhibitor-induced pulmonary arterial hypertension. *Adv Pulm Hypertens*. 2018;17(2):69-74.
51. Alectinib Package Insert. *Highlights of Prescribing Information*. Available at <http://www.fda.gov/CompanionDiagnostics>. Accessed April 12, 2021.
52. Brigatinib Package Insert. *Highlights of Prescribing Information*. Available at www.alunbrig.com. Accessed April 12, 2021.
53. FDA FAERS Public Dashboard. Available at <https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html>. Accessed April 12, 2021.
54. Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM. The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. *Drug Saf*. 2014;37(4):283-294.
55. Michel C, Scosyrev E, Petrin M, Schmouder R. Can disproportionality analysis of post-marketing case reports be used for comparison of drug safety profiles? *Clin Drug Investig*. 2017;37(5):415-422.