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SHORT REPORT

Ceritinib-associated hyperglycemia in the Japanese Adverse Drug Event Report Database

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ABSTRACT

Genetic rearrangements of anaplastic lymphoma kinase contribute to the pathogenesis of non-small-cell lung cancer; the anaplastic lymphoma kinase inhibitor, ceritinib, is widely used, as it is effective even in patients with non-small-cell lung cancer resistant to other anaplastic lymphoma kinase inhibitors. Although a case of possible ceritinib-induced hyperglycemia was reported, the association of ceritinib with hyperglycemia remains to be investigated. Disproportionality analysis was carried out using the Japanese Adverse Drug Event Report database, which contains all pharmacovigilance data based on spontaneous reports of adverse events between April 2004 and November 2018 to the Pharmaceuticals and Medical Devices Agency. The reporting odds ratio of ceritinib for hyperglycemia was 2.25 (95% confidence interval [CI] 1.24–4.08], whereas those of crizotinib and alectinib were 0.07 (95% CI 0.01–0.40) and 0.94 (95% CI 0.30–2.94), respectively. Among reported events without antidiabetes agent use, the reporting odds ratio of ceritinib was still 2.54 (95% CI 1.27–5.12). Thus, the possibility of hyperglycemia should be carefully monitored in patients receiving ceritinib.

INTRODUCTION

Genetic alterations in anaplastic lymphoma kinase (ALK), a member of the insulin receptor protein-tyrosine kinase superfamily, are implicated in the pathogenesis of several human cancers[1,2]. In non-small-cell lung cancer (NSCLC), ALK rearrangement occurs in approximately 3–7% of patients[3]. NSCLC harboring ALK rearrangements is sensitive to ALK inhibitors (ALKIs), including crizotinib and alectinib; invariable ALK resistance to these drugs remains a clinical issue. Recently, ceritinib, a second-generation ALKI, has been proven effective for patients having disease progression during crizotinib and/or alectinib treatment[3,4]. However, systemic metabolisms affected by ceritinib have not been fully investigated.

Recently, a case of possible ceritinib-induced hyperglycemia was reported[5]. The association between ceritinib and hyperglycemia remains controversial. In the previous clinical trials of ceritinib, the occurrence of hyperglycemia was not noted in a phase 3 trial. In contrast, a limited number of hyperglycemia cases were reported in phase 1 and 2 trials; however, the adverse events were summarized regardless of the exact relationship between cause and effect[6–8]. Furthermore, it is recognized that crizotinib and alectinib have no effect on patients' glucose tolerance[5], whereas the prescribing information of crizotinib and alectinib showed that hyperglycemia occurred in 1.1% of patients who received crizotinib and in <5% of patients who received alectinib, respectively. The exact relationship between each ALK inhibitor and hyperglycemia remains a clinical issue to be resolved, which can benefit the better choice for lung cancer and diabetes treatment.

We therefore carried out disproportionality analysis using the Japanese Adverse Drug Event Report (JADER) database, which contains all pharmacovigilance data based on spontaneous reports to the Pharmaceuticals and Medical Devices Agency[9]. In the present study, potential signals of ceritinib with hyperglycemia were analyzed using the reporting odds ratio (ROR), a well-established parameter in pharmacovigilance research, especially for rare and severe adverse events[10–12].

METHODS

As of March 2019, the database contained 887,636 reports of adverse drug reactions. We extracted cases of "suspected medicine" for adverse effects. For the present study, ethics approval was unnecessary, as the JADER database is open access and the data were downloaded from the website (http://www.pmda.go.jp) according to the Pharmaceuticals and Medical Devices Agency's instructions[12,13]. The potential signals of ALKIs (ceritinib, crizotinib, alectinib) with hyperglycemia and other

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hyperglycemia-related events were assessed with categories using the ROR. The signals of acetaminophen and corticosteroids (prednisolone and dexamethasone), the associations of which with hyperglycemia are well established[13], were also analyzed. The ROR was calculated using a two-by-two contingency table. The ROR was considered significant when the lower bound of the two-sided 95% confidence interval (CI) for the risk of hyperglycemia was >1.0, as previously reported[10–13]. The 51 terms indicating hyperglycemia or diabetes in the Standardized MedDRA Queries 20000041 or antidiabetes agents were selected, as previously described[13]. The data were analyzed using JMP Pro (version 14.3; SAS Institute, Tokyo, Japan).

RESULTS

Analysis of RORs in the entire data of JADER

In the database, 7,837 cases of hyperglycemia-related events were found in 887,636 reports of adverse drug reactions. Only ceritinib showed significant ROR of the three ALKIs (Table 1). In the ceritinib-associated reports, 429 patients started ceritinib use before September 2017, and four of them showed hyperglycemia. In contrast, 132 patients started ceritinib use after September 2017, and seven of them had hyperglycemia. The RORs of initial ceritinib use before and after September 2017 were 1.06 (95% CI 0.39–2.83) and 6.29 (95% CI 2.94–13.5), respectively.

Analysis of RORs in the antidiabetes agent-excluded data of JADER

We additionally analyzed the data in which antidiabetes agents were excluded as suspected medicine according to previous reports[12,13]. Subsequently, 4,744 cases of hyperglycemia-related events were found in 814,273 reports of adverse drug reactions. Of ALKIs, the ROR was found to be significant only in ceritinib; in both crizotinib and alectinib, the RORs were insignificant (Table 2).

Characteristics of cases reported as ceritinib-associated hyperglycemia in JADER

A total of 11 cases of hyperglycemia suspected to be associated with ceritinib were reported in the JADER database. Their detailed clinical characteristics are described in Table 3. All of the cases harbored NSCLC. Eight of them had diabetes mellitus as a comorbidity, and three of them underwent insulin treatment. No cases were reported under treatment of corticosteroids.

DISCUSSION

Targeting of tyrosine kinases is a major cancer therapeutic strategy today[1,2,14]. At the same time, unexpected endocrine and metabolic adverse effects of such therapies have been observed, and heightened vigilance is required[15,16]. Because of the remarkable sensitivities of NSCLCs to selective ALKIs, ALKIs have become promising therapies[14]. Ceritinib was approved in 2014 for ALK-positive metastatic NSCLC for patients who had progressed or were intolerant to crizotinib by the US Food and Drug Administration and in 2016 by the Ministry of Health, Labor and Welfare of Japan[7]. Expanded use as first-line treatment for patients with metastatic NSCLC was approved in 2017 by both the US Food and Drug Administration and Ministry of Health, Labor and Welfare of Japan [17]. As common adverse events of ceritinib, gastrointestinal reactions, such as diarrhea and nausea, as well as liver enzyme elevations have been reported, whereas its involvement in hyperglycemia remains to be clarified [6–8,17].

In the present study, we comprehensively overviewed the occurrence of hyperglycemia associated with ALKIs using the JADER database. As a result, ceritinib was found to show a significant ROR in both entire and antidiabetes agent-excluded analyses, which showed an association with hyperglycemia in clinical settings. The discrete time period analysis based on the expanding application of ceritinib in Japan showed that the ROR in the cases with initial ceritinib use before September 2017 was insignificant, although the RORs after September 2017 and during the entire period were significant. The insignificant ROR before September 2017 might be biased because of the limited case application and/or possible prior use of crizotinib or alectinib[7,17]. In contrast, crizotinib and alectinib showed insignificant RORs, consistent with the results of their clinical trials[18–21].

ROR is a useful statistical method for the evaluation of association between a specific drug and rare adverse events[10–12,22]. Although the number of reported cases treated with ceritinib

Table 1 | Number of reports and reporting odds ratio of hyperglycemia

Drug	No. cases	No. non-cases	Total no. reports	ROR	95% CI
Ceritinib	11	550	561	2.25	1.24–4.08
Crizotinib	1	1,983	1,984	0.056	0.008–0.40
Alectinib	3	357	360	0.94	0.30–2.94
Crizotinib and alectinib	4	2,340	2,344	0.19	0.07–0.18
Prednisolone	855	27,690	28,545	3.77	3.51–4.05
Dexamethasone	124	10,135	10,259	1.38	1.15–1.65
Acetaminophen	13	4,774	4,787	0.30	0.18–0.53

95% CI, 95% confidence interval; ROR, reporting odds ratio.

Table 2 | Number of reports and reporting odds ratio of hyperglycemia without antidiabetes agents use

Drug	No. cases	No. non-cases	Total no. reports	ROR	95% CI
Ceritinib	8	537	545	2.54	1.27–5.12
Crizotinib	1	1,858	1,859	0.092	0.013–0.65
Alectinib	3	318	321	1.61	0.52–5.02
Crizotinib and alectinib	4	2,176	2,180	0.31	0.12–0.84
Prednisolone	670	25,534	26,204	5.05	4.65–5.48
Dexamethasone	87	9,364	9,451	1.60	1.29–1.98
Acetaminophen	9	4,581	4,590	0.33	0.17–0.64

95% CI, 95% confidence interval; ROR, reporting odds ratio.

Table 3 | Clinical characteristics of cases with ceritinib-associated hyperglycemia

Case	Sex	Age	Comorbidity	Concomitant drugs
1	M	70s	DM	Loperamide hydrochloride, Metoclopramide, bifidobacterium
2	F	60s	DM, HT, dyslipidemia, subclavian vein thrombosis	Amlodipine besylate, edoxaban tosilate hydrate, metoclopramide
3	M	80s	N/R	N/R
4	M	NA	DM, valvular disease	N/R
5	M	NA	DM, HT	N/R
6	F	80s	N/R	N/R
7	F	70s	DM	Insulin
8	F	70s	DM, HT, CKD	Insulin aspart, degludec
9	F	70s	DM, HT, CKD	Insulin aspart, degludec
10	F	NA	NR	NR
11	M	70s	DM	NR

CKD, chronic kidney disease; DM, diabetes mellitus; F, female; HT, hypertension; M, male; NA, not available; NR, not reported.

was limited, the present results show reasonable statistical associations between ceritinib and hyperglycemia. In the previous study of drug-induced hyperglycemia using JADER, ceritinib was not mentioned, but the present findings on corticosteroids and acetaminophen are consistent[13]. Considering that we used the same candidate terms and antidiabetes agents for the analysis, this discrepancy might be due to the fact that we used the newer dataset of JADER and that was ceritinib relatively recently released on the market.

The underlying mechanism of ceritinib-associated hyperglycemia remains unclear. Generally, selectivity of tyrosine kinase inhibitors depends on the structure of the adenosine triphosphate-binding sites, Asp-Phe-Gly motif-1 and gatekeepers (Figure 1a,b)[23,24]. As shown Figure 1a, the amino acid residues in the adenosine triphosphate-binding sites and Asp-Phe-Gly motif-1 of ALK are similar to that of the insulin receptor (INSR). Actually, according to the prescribing information, ceritinib blocked INSR with greater potency than crizotinib and alectinib (IC50: 7 vs 290 vs 550 nmol/L)[5]. Thus, the potency of the INSR block might account for ceritinib-associated hyperglycemia. In this context, the efficacy of ceritinib on the ALK L1196M mutant that is resistant to crizotinib and alectinib can provide an additional key to clarify the differing influence on glucose tolerance among the ALKIs (Figure 1c). Ceritinib accessibility to the ALK L1196M gatekeeper mutation might lead to possible inhibition of INSR, the gatekeeper of which is the same amino acid residue, methionine.

Finally, spontaneous reporting systems, including the JADER database, have limitations in terms of inherent biases and lack of data on controls[9]. Therefore, we note that ROR does not reflect the exact prevalence rate[12,13]. The contribution of coexisting illnesses, drug dose, the exposure period or the prior use of anticancer drug were not investigated; additional clinical monitoring and analytical observational studies are required. In the present study, most affected patients had prior diabetes mellitus, and some received insulin therapy. The descriptions of antidiabetes agents were not found for some diabetes patients (Table 3). However, it is difficult to judge whether they did not use any antidiabetes drugs or if the information was lacking. Although ceritinib might be likely to affect diabetes patients lacking compensatory insulin secretion capacity, further studies to clarify this susceptibility are warranted.

In conclusion, ROR analysis using the JADER database shows that ceritinib might be significantly associated with hyperglycemia in clinical settings. Clinicians including diabetologists and oncologists should emphasize vigilance for ceritinib-associated hyperglycemia.

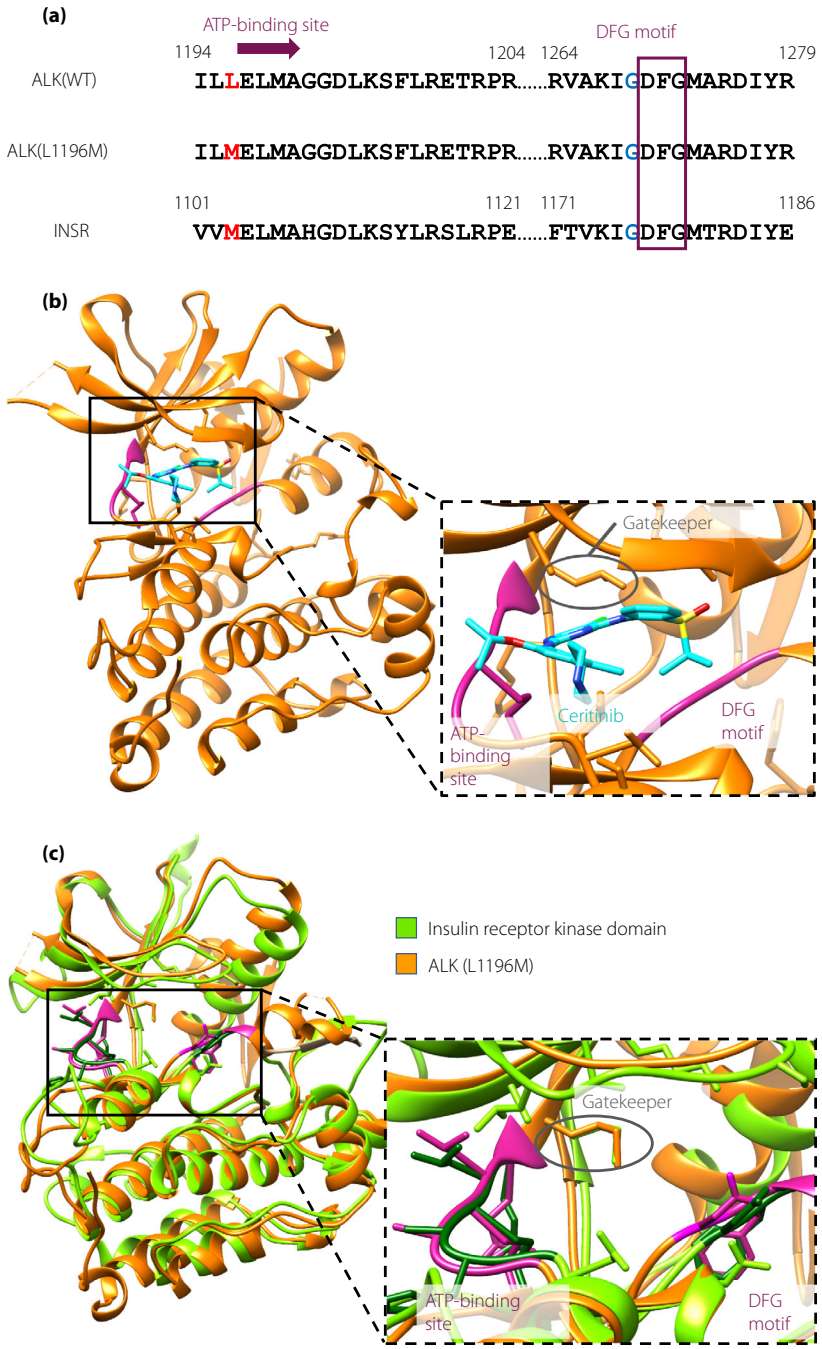

Figure 1 | The structure comparison on ceritinib affinity between anaplastic lymphoma kinase (ALK) and insulin receptor (INSR). (a) The amino acid residues in the adenosine triphosphate (ATP)-binding and Asp-Phe-Gly (DFG) motif sites of wild-type ALK (ALK[WT]), ALK(L1196M) and INSR. Gatekeeper, red; DFG motif-1, blue. (b) Ribbon diagram of the structure of the ALK (WT) catalytic domain obtained from the Protein Data Bank (ID: 4mkc) was visualized with UCSF Chimera version 1.13.1, University of California, San Francisco, CA, USA. The model of the ceritinib-binding domain is shown in the black square[24]. ALK (WT), orange; ceritinib, sky blue; gatekeeper, gray circle; DFG motif and ATP-binding site of ALK, purple. (c) The structural similarities between INSR and ALK (L1196M) might be related to their susceptibilities to ceritinib. Gatekeeper M is shown in the gray circle. The ribbon diagram structures of the INSR kinase domain (Protein Data Bank ID: 1ir3) and ALK (L1196M) catalytic domain (ID: 4cd0) were visualized with UCSF Chimera version 1.13.1. The model of the ceritinib-binding domains is shown in the black square. INSR, light green; ALK (L1196M), orange; gatekeeper, gray circle; DFG motif and ATP-binding site of ALK, purple.

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DISCLOSURE

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