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Treatment of lorlatinib induced hypercholesterolemia with PCSK9 inhibitors; A new solution to an emerging need in non-small cell lung cancer therapy

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Abstract

Lorlatinib is a third generation ALK inhibitor used in the treatment of non-small cell lung cancer. Lorlatinib invariably causes hypercholesteremia, though most patients respond to statin therapy. For patients with cardiovascular comorbidity, refractory elevated cholesterol may represent a particular risk.

Case presentation: We report on such a NSCLC ALK patient, a 47-year-old Caucasian man already receiving high dose statins originally for early onset heart disease (NSTEMI), who achieved significant additional lipid reduction from an PCSK9 inhibitor. To our knowledge the PCSK9 inhibition has not been reported previously as an adjunct to lorlatinib treatment.

Conclusion: This report demonstrates that this new class of lipid lowering agents can be used with statin therapy to significantly improve blood lipid profiles in patients treated with lorlatinib.

Keywords

ALK; Hypercholesteremia; Lorlatinib; Statin; PCSK9 inhibitor; Case Report.

Background

Anaplastic Lymphoma Kinase positive non-small cell lung cancer (ALK+ NSCLC) accounts for approximately 3-7% of NSCLC. The third generation ALK inhibitor lorlatinib can give renewed responses to patients resistant to earlier generation ALK inhibitors. Lorlatinib commonly causes hypercholesteremia [1]; elevated Low-Density Lipoprotein (LDL) in particular is a cardiovascular risk factor. Reducing LDL levels, particularly with statins improves the risk of cardiovascular events [2,3]. Here, we describe a case of a long term ALK patient with a history of early onset aggressive atherosclerosis with hypercholesteremia reoccurring subsequent to lorlatinib treatment. Following treatment with high dose (40 mg) rosuvastatin, cholesterol remained elevated to grade 2 and further lipid lowering strategies were considered.

Case Presentation

Prior Clinical History

In November 2003, the patient presented as a physically fit man (age 38 yr) with chest discomfort during running. ECG showed no ST elevation but troponin I levels were elevated. Angiogram revealed the right posterior descending artery to be fully occluded and immediately relieved by percutaneous thrombectomy, followed by insertion of a bare metal stent. The patient was administered 100 mg aspirin q.d., 75 mg clopidogrel q.d., and long acting sublingual GTN before returning after 4 weeks for the insertion of 4 more (sirolimus-coated) metal stents. Subsequent investigations showed hypercholesteremia (total cholesterol 8.4 mmol/L). The patient was started on 40 mg q.d., simvastatin escalating to 80 mg q.d., successfully stabilising total cholesterol at 2-3 mmol/L over several months.

Oncology History

In July 2013, the patient presented with persistent cough and chest discomfort during exercise. An ECG stress test conducted during the workup to diagnosis of lung cancer showed no evidence of ischaemia due to obstructive coronary artery. Total cholesterol was slightly elevated (4-5 mmol/L) and the patient was switched from simvastatin to 80 mg q.d. atorvastatin. Investigations revealed lung adenocarcinoma with multiple bilateral pulmonary metastases and mediastinal lymphadenopathy with lower left lobe atelectasis, EGFR mutation negative. The patient underwent first-line platinum doublet chemotherapy, with no effect seen after three cycles. Second-line chemotherapy was commenced with docetaxel (5 cycles). In December 2013, ALK gene rearrangement was detected using FISH, and in February 2014 the patient commenced crizotinib, which he remained on with good oncological response and minimal adverse effects for over 5 years.

In June 2019 he presented with waking headaches; MRI head scan showed multiple cerebral, cerebellar and leptomeningeal metastases with measurable lesions in the right superior posterior frontal lobe (18 mm), and left anterior frontal lobe (14 mm). CT of the body showed a stable infiltrative mass around the left lower lobe bronchus, along with longstanding stable partial left lower lobe collapse. The patient commenced corticosteroids in July 2019, discontinued crizotinib, and commenced alectinib 600 mg b.i.d. Baseline blood tests showed grade 1 ALT increase and normal bilirubin. Tests later in July 2019 showed grade 2 bilirubin and ALT increases. Alectinib was withheld in August 2019 and bilirubin and ALT elevation improved to grade 1. Following a series of bilirubin elevations and dose interruptions, stable bilirubin was eventually achieved with alectinib sustained at 150 mg b.i.d. from July 2020. Contrast enhanced CT head scan indicated stable disease.

In September 2020 MRI spine showed previously undetected upper thoracic intraspinal metastasis and in December 2020 MRI scan showed progressive disease in the upper thoracic spinal cord and cerebellum despite increasing alectinib from 150 mg b.i.d. to 300 mg b.i.d. From December 2020 to January 2021, radiotherapy was administered to posterior fossa and C7-T3 spine 20 Gray in 5 fractions to both sites. Alectinib was discontinued in January 2021 and lorlatinib 100 mg commenced. MRI brain and spine in

February 2021 showed strong response in both the irradiated and non-irradiated CNS metastatic disease regions. In May 2021 MRI brain and spine showed ongoing response in all areas of CNS metastatic disease and CT body showed stable disease. The patient continued to feel symptomatically well with no symptoms, currently working full-time and unlimited in his normal activities, running several times a week.

Concurrent Cardiovascular History

In May 2019 the patient again presented with angina and in April 2019 underwent coronary angioplasty with stenting of the left anterior descending artery, with resolution of symptoms. Blood test taken in April 2019 showed normal cholesterol, but 16 days after commencement of lorlatinib this had increased to LDL 4.0 mmol/L (Details in Table 1). As lorlatinib causes moderate CYP3A4 induction and atorvastatin is a CYP3A4 substrate the patient switched to 40 mg rosuvastatin, but subsequent tests showed further elevation in LDL to 5.7 mmol/L. Because of the patient's cardiovascular history, in June 2021 the patient received 150 mg alirocumab by subcutaneous injection pen, and later the same month blood tests showed that lipids had significantly decreased (LDL 2.5 mmol/L). Further testing on in July 2021 showed stable effect with continuing alirocumab treatment with 2.6 mmol/L LDL and a total cholesterol to HDL ratio of 3.5.

Table 1: Blood lipid test results following treatment with lorlatinib and alirocumab.

Date	Comments	Total Cholesterol (mmol/L)	LDL (mmol/L)	HDL (mmol/L)	Triglyceride (mmol/L)	Total Cholesterol/ HDL ratio
April 2019	Pre-lorlatinib	2.7	1.5	0.9	0.7	2.9
Feb 2021	16 days after start of lorlatinib	6.1	4.0	1.2	1.8	4.9
April 2021	Rosuvastatin 40mg q.d. present	8.3	5.7	1.5	2.5	5.6
June 2021	Alirocumab 150mg added					
June 2021		4.6	2.5	1.3	1.7	3.5
July 2021		4.8	2.6	1.4	1.9	3.5

Discussion

Alirocumab is a long-acting monoclonal PCSK9 inhibitor which increases cellular uptake and hepatic metabolism of LDL. Binding of LDL to its receptor (LDL-R) results in endocytosis and PCSK9 interacts with the LDL-R at the plasma membrane preventing normal recycling of LDL-Rs to the plasma membrane. Alirocumab is administered 75–150 mg subcutaneously once every two to four weeks. Elimination half-life is 17–20 days and in hyperlipidaemic patients on statins, alirocumab further decreases LDL-C levels and reduces the risk of future cardiovascular events [4,5].

Conclusion

In a patient with lung cancer and cardiovascular co-morbidities receiving lorlatinib, alirocumab was able to reduce LDL levels by 56% beyond that achieved by statin treatment alone.

Declarations

Ethical approval and consent to participate: The authors declare that the patient has given informed consent to publish. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of supporting data: All data generated or analysed during this study are included in this published article.

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IAS: project management, writing - review and editing.

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