J Infect Chemother 25 (2019) 1043–1046

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case Report

Drug-induced pneumonitis following the administration of laninamivir octanoate: The first two reported cases☆

Takunori Ogawa [a, b], Kyuto Tanaka [b, *], Keiko Ohgino [b], Nao Omori [b], Tomoko Betsuyaku [a], Koichi Sayama [b]

[a] Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
[b] Kawasaki Municipal Hospital, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 2 September 2018
Received in revised form
15 April 2019
Accepted 15 May 2019
Available online 6 June 2019

Keywords:
Influenza
Neuraminidase inhibitor
Laninamivir
Laninamivir octanoate
Drug-induced pneumonitis

ABSTRACT

Laninamivir, a neuraminidase inhibitor (NAI), has been used for the treatment and prophylaxis of influenza A/B. To date, pneumonia has not been reported as an adverse effect of NAIs. Here, we report the first 2 cases of drug-induced pneumonitis after the administration of laninamivir octanoate (LO), a pro-drug of laninamivir.

Case 1 reports a 20-year-old healthy woman presenting with LO-induced pneumonitis so severe that it was necessary for endotracheal intubation and administration of mechanical ventilator support. Steroids were used for the treatment of pneumonitis and rapid improvement was observed. Case 2 reports a 35-year-old healthy woman presenting with less severe LO-induced pneumonitis that improved without any treatment. In both cases, drug-induced lymphocyte stimulation tests (DLSTs) were positive. In the bronchoalveolar lavage (BAL) fluid, the proportion of eosinophils to lymphocytes was higher in Case 1. Conversely, the proportion of lymphocytes to eosinophils was higher in Case 2.

Collectively, we determined 3 clinical issues: (1) LO could cause pneumonia; (2) BAL and DLST could be helpful in the diagnosis of LO-induced pneumonitis; and (3) LO-induced pneumonia could become severe, though steroids were effective in improving it.

1. Introduction

Laninamivir is a long-acting neuraminidase inhibitor (NAI). A single inhalation of laninamivir octanoate (LO), a pro-drug of laninamivir, has been shown to be effective in the treatment and prophylaxis of influenza A/B [1–4]. Gastrointestinal events, such as diarrhea, nausea, and vomiting, as well as dizziness were reported as adverse effects of LO [1–4]. Pneumonia has not been reported as an adverse effect of any NAIs, including oseltamivir, zanamivir, peramivir, and laninamivir. Herein, we report the first 2 cases presenting with LO-induced pneumonia.

2. Case report

Case 1: A 20-year-old healthy woman used zanamivir for the treatment of influenza in January 2016. The patient was not allergic to lactose and was a non-smoker. She complained of fever and nausea in February 2017. The patient had no history of contact with patients with influenza. The symptoms disappeared two days after the symptoms first occurred, and she consulted a local doctor. The patient tested negative for influenza virus antigen with a rapid diagnosis kit. Still, the doctor clinically diagnosed the patient with influenza and, subsequently, prescribed LO. Dyspnea, cough, and chest pain occurred about an hour after the first inhalation of LO and gradually worsened. The patient had used herbal medicine Goreisan for headaches once or twice a year in the past, but she did not use Goreisan prior to the symptoms occurring.

Abbreviations: AEP, acute eosinophilic pneumonitis; BAL, bronchoalveolar lavage; CT, computed tomography; CTD-ILD, connective tissue disease associated with interstitial lung disease; DLST, Drug-induced lymphocyte stimulation test; GGO, ground-glass opacities; HP, hypersensitivity pneumonitis; LO, laninamivir octanoate; NAI, neuraminidase inhibitors; PCR, polymerase chain reaction.

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author. Division of Pulmonary Medicine, Department of Medicine, Kawasaki Municipal Hospital, 12-1 Shinkawa-Dori, Kawasaki, Kanagawa, 210-0013, Japan.
E-mail address: cutetanaka@yahoo.co.jp (K. Tanaka).

https://doi.org/10.1016/j.jiac.2019.05.008
1341-321X/

On day 3 after the initial symptoms presented, the patient was admitted to our hospital, where endotracheal intubation and mechanical ventilator support had to be administered due to respiratory failure. Laboratory data demonstrated elevations in serum c-reactive protein. Serum anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were at normal levels. The chest X-ray and computed tomography (CT) scan revealed wide-spread centrioloblar ground-glass opacities (GGO) with lung consolidation along the bronchovascular bundles, thickening of the interlobular septa, and bilateral pleural effusions (Fig. 1). The patient began taking methylprednisolone (1 g/day, for 3 days) and subsequently prednisolone (40 mg/day). 4 days after the initial symptoms occurred, we performed bronchoalveolar lavage (BAL) and extubated the patient after having confirmed that her respiratory status had improved. In the patient's BAL-fluid, the proportion of eosinophils to lymphocytes was high (eosinophils 19%, lymphocytes 6%, neutrophils 1%, macrophages 74%, basophils 0%, CD4/8 ratio 1.38). No infectious pathogens or malignant cells were detected. 7 days after the initial symptoms appeared, all opacities and pleural fluids disappeared in the follow-up CT scan. We gradually reduced prednisolone and was administered for 26 days. At 14 days after completion with the prednisolone therapy, drug-induced lymphocyte stimulation tests (DLSTs) were positive (stimulation index 2.57) for LO. The clinical course for Case 1 is shown in Fig. 2.

Case 2: A 32-year-old healthy woman, non-smoker and without allergy to lactose. She complained of a fever in January 2017. On the second day of experiencing the symptom, she consulted a local doctor. The patient tested positive for influenza A with a rapid diagnosis kit for influenza virus antigen, and was prescribed LO and inhaled it on the same day. No drugs or supplements were co-administered with LO. The patient's fever disappeared on day 4 following the initial symptoms.

However, 5 days after presenting with the initial symptoms, the patient had a cough, left chest pain, and bloody sputum; hence, she reported to the hospital. The chest X-ray and CT revealed a left dominant bilateral GGO that was mixed with lung consolidation as shown by an air bronchogram (Fig. 3). Laboratory data demonstrated elevations in serum c-reactive protein levels. Serum anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were at normal levels. On day 9 after initial symptoms, we performed BAL, and the BAL-fluid indicated a higher proportion of lymphocytes (eosinophils 4.5%, lymphocytes 32%, neutrophils 1%, macrophages 61%, basophils 1.5%, CD4/8 ratio 0.46). No infectious pathogens or malignant cells were detected. The symptoms and the opacities disappeared gradually without use of steroids, yet the DLST was positive (stimulation index 2.43) for LO.

The results of all the laboratory examinations—including analysis for complete blood cell profiles, blood chemistry, BAL fluid, and the lymphocyte stimulation test—for both cases are shown in Table 1.

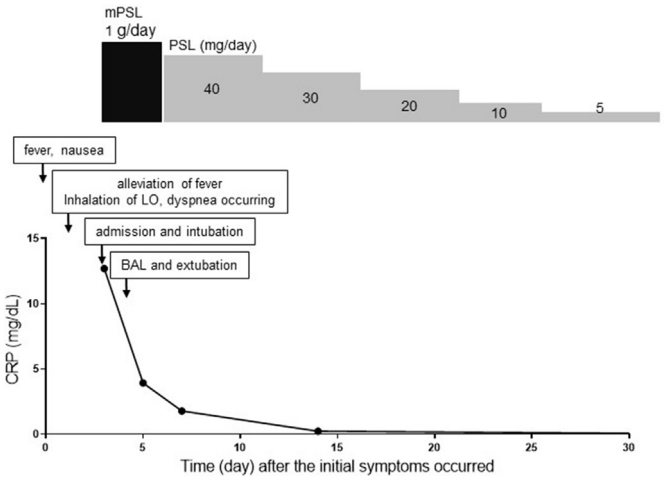

Fig. 2. Clinical course for Case 1. LO = laninamivir octanoate; CRP = serum c-reactive protein; mPSL = methylprednisolone; PSL = prednisolone.

3. Discussion

We determined 3 clinical issues regarding the adverse effects caused by LO and pneumonia: (1) LO could cause pneumonia; (2) BAL and DLST could be helpful in the diagnosis of LO-induced pneumonia; and (3) LO-induced pneumonia could become severe, though steroids were effective in treating it.

To the best of our knowledge, there had not been previous reports of pneumonia induced by NAI, including LO. These are the first two cases of LO-induced pneumonia. In both these cases, no other drugs were taken by the patients. In Case 1, the opacities observed in the CT scan were distributed in the centrioloblar zone along the bronchovascular bundles. Inhaled LO spreads in airways, therefore, it can create this distribution in the CT scan. The results of BAL-fluid differential cell counts showed increases in eosinophils or lymphocytes, which does not contradict with past reports of drug-induced pneumonia [5]. In Case 1, drug-induced acute eosinophilic pneumonitis (AEP) was suspected due to the observed eosinophilic BAL-fluid. The CT images were consistent with the past reported images of AEP [6]. In Case 2, cryptogenic organizing pneumonitis (COP) was suspected in the CT images, which does not contradict with the lymphocytic BAL-fluid result [7]. The reasons for the different forms of lung toxicity in two cases were likely due to differences in the drug metabolism system and/or an immune-

Fig. 1. Chest radiograph (left) and CT imaging (right) for Case 1. The chest X-ray and CT scan revealed wide-spread ground-glass opacities along the bronchovascular bundles and bilateral pleural effusions.

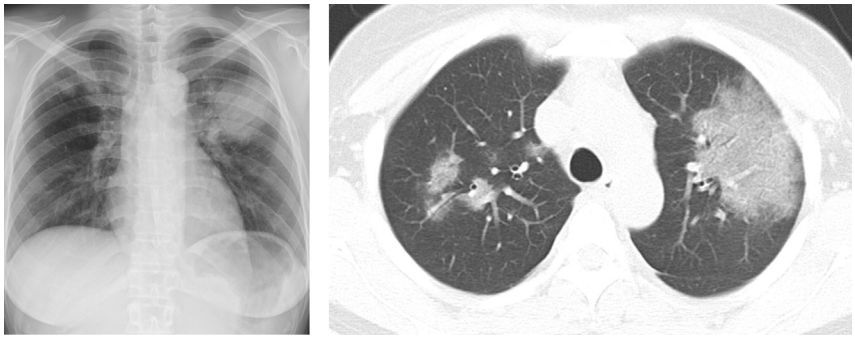

Fig. 3. Chest radiograph (left) and CT imaging (right) for Case 2. The chest X-ray and CT scan revealed left dominant bilateral grand-grass opacities.

Table 1
Laboratory examinations for Case 1 and 2.

	Case 1	Case 2
CBC		
WBC ($\times 10^3/\mu L$)	19.4	9.54
Neut (%)	90	66
Lym (%)	4	27
Mo (%)	4	6
Eo (%)	2	1
Hb (g/dL)	15	12.2
PLT ($\times 10^4/\mu L$)	20.2	30.2
Blood Chemistry		
TP (g/dL)	6.1	7.6
AST (IU/L)	9	14
ALT (IU/L)	7	12
LDH (IU/L)	139	147
BUN (mg/dL)	7	8
Cre (mg/dL)	0.5	0.4
CRP (mg/dL)	12.7	1.8
BNP (pg/mL)	51.2	
KL-6 (U/mL)	114	
SP-D (ng/mL)	263	
ACE (IU/L)	5.9	
procalcitonin (ng/mL)	0.12	0.08
βD-glucan (pg/mL)	5	
HIV screenig test	(—)	
Mycoplasma [PA] (titers)	<40	<40
CMV-Ag [C7-HRP]	(—)	
ANA (U/mL)	1	1
anti-SS-A Ab (U/mL)	1	1
anti-SS-B Ab (U/mL)	1	1
MPO-ANCA (U/mL)	1	1
PR3-ANCA (U/mL)	1	1
anti-GBM Ab (U/mL)	2	
anti-ARS Ab (INDEX)	5	
RF (IU/mL)	3	
IgE-RIST (IU/mL)	101	
BALF		
WBC ($\times 10^3/\mu L$)	1.45	0.72
Neut (%)	1	1
Lym (%)	6	32
Mo (%)	0	0
Eo (%)	19	4.5
Macrophage (%)	74	61
CD4/CD8	1.38	0.46
Pneumocystis PCR	(—)	(—)
DLST		
LO	2.57	2.43

CBC = complete blood cell; CRP = c-reactive protein; BNP = brain natriuretic peptide; ACE = serum angiotensin-converting enzyme; ANA = anti-nuclear antibody; Ab = antibody; ANCA = anti-neutrophil cytoplasmic antibody; RF = rheumatoid factor; HIV screening test = combination HIV antigen and antibody tests; CMV = cytomegalovirus; Ag = antigen; BALF = bronchoalveolar lavage fluid; PCR = polymerase chain reaction; DLST = drug lymphocyte stimulation test; LO = laninamivir octanoate; S.I. = stimulation index.

mediated gene, because there were no major changes in age, gender, the use of other drugs, underlying diseases and the dose of LO. There have been several reports of Amiodarone—well known for lung toxicity—linked to various forms of drug-induced pneumonia: interstitial pneumonitis-fibrosis, acute respiratory distress syndrome, bronchiolitis obliterans with organizing pneumonia, and a solitary pulmonary mass [8].

The inhalational LO kit includes lactose as an additive. In both our cases, the patients did not have an allergy to lactose. In Case 1, the patient had a history of inhaling zanamivir, which includes lactose, however drug-induced pneumonia did not occur at that time. The DLST results of LO lacking lactose support that LO induced pneumonia.

To definitively diagnose these cases with LO-induced pneumonitis, we have to rule out the possibility of connective tissue disease associated with interstitial lung disease (CTD-ILD), other drug-induced pneumonitis, idiopathic AEP, hypersensitivity pneumonitis (HP), as well as bacterial-, viral- (especially influenza), and fungal-pneumonitis.

Both cases did not show eruption, arthralgia, myalgia, or neuropathy, which are indicative of connective tissue disease. All the experienced patient symptoms took relatively acute courses, which would be atypical for connective tissue diseases. In Case 1, the serological tests used, which included tests for anti-nuclear antibody and anti-neutrophil cytoplasmic antibody, to support the diagnosis of connective tissue diseases were negative.

As noted above, there were no co-administered drugs and supplements in both cases. AEP and HP are can be caused by extrinsic antigens; however, there were no episodes of smoking or inhaling any antigens except for LO in both cases.

There were no bacterial or fungal pathogens, polymerase chain reaction (PCR) assays of *Pneumocystis* were negative in both BAL-fluid samples, indicating that bacterial or fungal pneumonitis were unlikely.

Case 1 tested negative with a rapid diagnosis kit for influenza virus antigen and was determined to be clinically inconclusive regarding contracting influenza. Therefore, the lung injury observed in Case 1 was less likely caused by influenza pneumonitis. Conversely, we could not rule out influenza pneumonitis in Case 2. PCR assay of influenza virus for the BAL-fluid sample could rule out influenza pneumonitis.

In Case 1, the pneumonia was so severe that it was necessary for endotracheal intubation and mechanical ventilator support. The pneumonia improved rapidly after administration of steroids. Laninamivir has been shown to be retained in the respiratory tract for a long time [9]. Accordingly, a study of healthy volunteers showed that laninamivir is slowly eliminated from the epithelial lining fluid and is effective for 240 hours after

inhalation [10]. We determined the steroid dose period to be 26 days, which, therefore, was longer than the known effective duration of laninamivir.

Declaration of interest statement

The authors have no conflict of interest in the subject matter.

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

References

[1] Watanabe A, Chang SC, Kim MJ, Chu DW, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: a double-blind, randomized, noninferiority clinical trial. Clin Infect Dis 2010;51:1167–75.

[2] Sugaya N, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate (cs-8958) versus oseltamivir as treatment for children with influenza virus infection. Antimicrob Agents Chemother 2010;54:2575–82.

[3] Kashiwagi S, Watanabe A, Ikematsu H, Awamura S, Okamoto T, Uemori M, et al. Laninamivir octanoate for post-exposure prophylaxis of influenza in household contacts: a randomized double blind placebo controlled trial. J Infect Chemother 2013;19:740–9.

[4] Kashiwagi S, Watanabe A, Ikematsu H, Uemori M, Awamura S. Long-acting neuraminidase inhibitor laninamivir octanoate as post-exposure prophylaxis for influenza. Clin Infect Dis 2016;63:330–7.

[5] Prasad R, Gupta P, Singh A, Goel N. Drug induced pulmonary parenchymal disease. Drug Discov Ther 2014;8:232–7.

[6] Price M, Gilman MD, Carter BW, Sabloff BS, Truong MT, Wu CC. Imaging of eosinophilic lung diseases. Radiol Clin North Am 2016;54:1151–64.

[7] Cordier JF. Cryptogenic organising pneumonia. Eur Respir J 2006;28:422–46.

[8] Kanji Z, Sunderji R, Gin K. Amiodarone-induced pulmonary toxicity. Pharmacotherapy 1999;19:1463–6.

[9] Koyama K, Takahashi M, Oitate M, Nakai N, Takakusa H, Miura S, et al. Cs-8958, a prodrug of the novel neuraminidase inhibitor r-125489, demonstrates a favorable long-retention profile in the mouse respiratory tract. Antimicrob Agents Chemother 2009;53:4845–51.

[10] Ishizuka H, Toyama K, Yoshiba S, Okabe H, Furuie H. Intrapulmonary distribution and pharmacokinetics of laninamivir, a neuraminidase inhibitor, after a single inhaled administration of its prodrug, laninamivir octanoate, in healthy volunteers. Antimicrob Agents Chemother 2012;56:3873–8.