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Case report

Drug-induced lung injury associated with combination therapy of daclatasvir and asunaprevir: The first case report

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ABSTRACT

Combination therapy with direct acting antiviral agents (DAAs) without interferon (IFN) has emerged as a treatment for chronic hepatitis C because of its high overall sustained virologic response rates and favorable side effect profile as compared to that with interferon. We report the first case of drug-induced lung injury (DLI) associated with IFN-free therapy with the DAAs, daclatasvir (NS5A inhibitor) and asunaprevir (NS3/4A protease inhibitor).

Although this combination therapy of DAAs has been considered to have fewer side effects than IFN, more attention should be paid to DLI as an important side effect.

1. Introduction

Chronic hepatitis C virus (HCV) infection is associated with significant morbidity and mortality resulting from the progression towards cirrhosis and hepatocellular carcinoma. Interferon (IFN) has played the leading role in treating chronic hepatitis C. Because IFNs have potent immunomodulatory activities, many adverse drug reactions such as myalgia, fever, flu-like symptoms, depression, and cytopenia have been observed in the patients treated with IFNs. Particularly, interstitial pneumonia is an important clinical concern of the lungs [1]. According to the Japanese Welfare Ministry, interstitial pneumonia events have been reported in 0.29% and 0.08% of the patients receiving pegylated (PEG)-IFNα-2A and PEG-IFNα-2B [2], respectively; additionally, 202 patients have developed interstitial pneumonia, and 19 patients have died [2]. Recently, combination therapy with direct-acting antiviral agents (DAAs) has emerged as a treatment for chronic hepatitis C because of its high overall sustained virologic response rates. Additionally, these regimens have a favorable side effect profile compared to IFN-based regimens, and reports of drug-induced lung injury (DLI) have not been cited.

Combination therapy of daclatasvir (NS5A inhibitor) and asunaprevir (NS3/4A protease inhibitor) was first approved

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for treating chronic hepatitis C due to HCV genotype 1 in Japan in July 2014 [3]. To our knowledge, this is the first case report of DLI associated with an IFN-free regimen with DAAs for chronic hepatitis C.

2. Case report

A 60-year-old man, nonsmoker, was presented with nonproductive cough and shortness of breath that he had been experiencing for 10 days previously. He had been treated for chronic hepatitis C due to HCV genotype 1 by administering IFN without ribavirin for 24 weeks in 1993, and since then he had not administered IFN. Other medical history included psoriasis vulgaris that had been cured more than 5 years previously and cerebral infarction that had occurred last year. He had no history of dust inhalation, and he kept no pets. His medications were aspirin, clopidogrel sulfate, lansoprazole, and ursodeoxycholic acid. He had not been receiving other medications including over-the-counter drugs, Chinese herbal medicines, or supplements. However, he had started administering 60 mg of daclatasvir and 200 mg of asunaprevir 2 months previously. On physical examination, fine crackles were heard in both sides of the anterior chest; however, there were no findings of fever, skin eruption, or arthritis. Although chest computed tomography (CT) performed 4 months earlier and chest radiography performed at the start of daclatasvir and asunaprevir treatment did not reveal any abnormality (Fig. 1a), chest radiography on the first follow-up revealed bilateral opacity (Fig. 1b) and chest high-resolution CT revealed bilateral subpleural, peribronchial opacities with bilateral pleural effusion (Fig. 2a). Reversed halo sign was also evident (Fig. 2b). White blood cell count was 11,680/mm^3, with 60% neutrophils, 22% lymphocytes, and 6% eosinophils. The results of routine blood chemistry tests were within normal range, except for lactate dehydrogenase (LDH) levels of 354 IU/L and aspartate aminotransferase (AST) levels of 39 IU/L. The serum levels of C-reactive protein were elevated to 0.9 mg/dl. Additionally, the anti-ss-DNA antibody levels were elevated to 82.2 IU/mL, and the anti-nuclear antibodies were undetectable. Results were negative for all other antibodies. The serum levels of 1-3 β-D glucan and immunoglobulin-E were within normal range. The serum levels of Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D), which are specific biomarkers for interstitial pneumonia, were elevated to 3088 U/mL (normal range: <500 U/mL) and 486.8 ng/ml (normal range: <110 ng/mL), respectively. The arterial blood gas analysis, done with the patient breathing room air, revealed mild hypoxemia (PaO_2, 69.4 Torr) with $PaCO_2$ as 29.8 Torr and pH as 7.46. No blood was observed in the bronchoalveolar lavage fluid (BALF). The cells recovered from the BALF were 3.2×10^5/mL, which comprised 79% lymphocytes, 7% macrophages, 5% neutrophils, and 3% eosinophils. The ratio of CD4/CD8 was 0.72. Transbronchial lung biopsy was not performed because the patient had administered aspirin and clopidogrel sulfate for cerebral infarction. Microorganisms including fungi were not identified in the BALF culture. Because the patient's clinical course suggested DLI associated with daclatasvir and/or asunaprevir, he was hospitalized, and the treatment with both the drugs was discontinued. The serum drug lymphocyte stimulation test (DLST) showed negative results for daclatasvir and asunaprevir with [H^3]-thymidine uptakes of 117% and 163% (normal range<180%), respectively. After the discontinuation of daclatasvir and asunaprevir administration, cough lessened, room air oxygen saturation of the peripheral artery rose from 90% to 93%, and LDH levels decreased to 303 IU/L. Because there was no apparent improvement in the chest CT findings, administration of 0.5 mg/kg body weight/day of prednisolone (30 mg/day) was started on day 8. Subsequently, the subjective symptoms remitted; on day 18, chest radiographs revealed clear improvement; the levels of LDH, KL-6, and SP-D decreased to 215 IU/L, 2531 U/mL, and 258.1 ng/mL, respectively. Oral prednisolone administration was decreased by 5 mg every 2 weeks, and the chest CT on day 62 revealed evident improvement in opacities, and pleural effusion was cured (Fig. 2c, d).

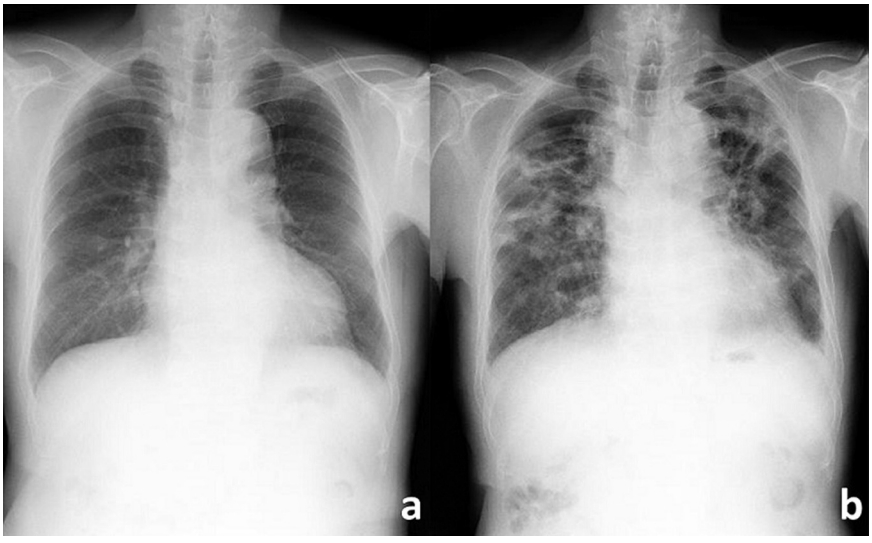

Fig. 1 – The chest radiograph at the start of daclatasvir and asunaprevir treatment does not reveal any abnormality (a). The chest radiograph on the first follow-up reveals bilateral opacities (b).