Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2740-19
Intern Med 58: 2501-2505, 2019
http://internmed.jp

【 CASE REPORT 】

Immune-mediated Drug-induced Liver Injury Caused by Laninamivir Octanoate Hydrate

Toshihiro Kawaguchi[1], Teruko Arinaga-Hino[1], Motoki Shimizu[2], Ken Tanikawa[3], Takahiko Tokushige[4], Shingo Hirai[4], Hiroaki Nagamatsu[2], Hideo Tateishi[4], Akio Takata[5], Tatsuya Ide[1] and Takuji Torimura[1]

Abstract:
We herein report the first case of immune-mediated drug-induced liver injury that may have been caused by laninamivir. A 15-year-old girl was diagnosed with influenza and prescribed 40 mg laninamivir. Six weeks later, she was admitted to our hospital because of jaundice and fatigue. Laboratory examinations revealed elevated levels of hepatobiliary enzymes, and acute liver injury was suspected. Laboratory examinations and histological findings were characteristic of autoimmune hepatitis. Steroid treatment was ineffective, and azathioprine was added to the treatment. Twenty-two months after the onset, a second biopsy revealed the absence of inflammatory infiltrations, and the drugs were withdrawn. Liver function tests remained normal nine months after withdrawal.

Key words: immune-mediated drug-induced liver injury, laninamivir, autoimmune hepatitis, drug-induced liver injury, drug-induced autoimmune hepatitis

(Intern Med 58: 2501-2505, 2019)
(DOI: 10.2169/internalmedicine.2740-19)

Introduction

Laninamivir octanoate hydrate (laninamivir) is a neuraminidase inhibitor (NAI) for the treatment of influenza (1). Laninamivir is used as a single inhalation, which is convenient and improves compliance. Commonly reported adverse drug reactions are psychiatric disorders, such as abnormal behavior, and most adverse drug reactions emerge within three days of inhalation (2).

Drug-induced autoimmune hepatitis (AIH) occurs in 9.2% of AIH (3), and several drugs have been identified. Minocycline (4) and nitrofurantoin (5) are well-known drugs that cause drug-induced autoimmune hepatitis, and others have also been reported such as methyldopa, atorvastatin, infliximab, and isoniazid (6). Weiler-Normann et al. (7) reported drug-induced liver injury (DILI) and its relationship to AIH and proposed three classifications: 'AIH with DILI', 'drug-induced AIH', and 'immune-mediated DILI'. In this classification, it is difficult to distinguish 'drug-induced AIH' and 'immune-mediated DILI', and sustained remission after the cessation of treatment helps diagnose 'immune-mediated DILI'. This diagnosis is important, especially for young people, as life-long prednisone (PSL) therapy causes serious side effects.

We herein report a 15-year-old girl with immune-mediated DILI that may have been caused by laninamivir.

Case Report

The patient was a 15-year-old girl (height 162.3 cm; weight 46.9 kg; body mass index 17.8). In May 2016, she was referred to our hospital because of jaundice, general malaise, and abnormal liver function tests. She was a high school student and originally healthy.

At admission, her laboratory examinations revealed ele-

[1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Japan, [2]Department of Gastroenterology, Juntendo University School of Medicine, Japan, [3]Department of Diagnostic Pathology, Yame General Hospital, Japan, [4]Department of Gastroenterology, Yame General Hospital, Japan and [5]Department of Gastroenterology, Asakura Medical Association Hospital, Japan
Received: January 25, 2019; Accepted: February 27, 2019; Advance Publication by J-STAGE: May 22, 2019
Correspondence to Dr. Toshihiro Kawaguchi, kawaguchi_toshihiro@med.kurume-u.ac.jp

Table. Laboratory Data on Admission.

WBC (/μL)	7,600	TP (g/dL)	7.3
Neutrophilis (%)	66.9	ALB (g/dL)	3.7
Lymphocytes (%)	25	T-Cho (mg/dL)	145
Eosinophils (%)	1.2	Glu (mg/dL)	85
Monocytes (%)	6.4	UN (mg/dL)	8.9
RBC (/μL)	425×10^4	Cre (mg/dL)	0.64
Hemoglobin (g/dL)	12.8	Ammonia (μg/dL)	47
Hematocrit (%)	35.2		
Platelets (/μL)	34×10^4	PT (%)	54.3
CRP (mg/dL)	0.14	PT INR	1.33
IgG (mg/dL)	2,046		
IgM (mg/dL)	114	IgM anti-HAV	(-)
IgE (IU/mL)	903	HBsAg	(-)
Anti-nuclear antibody	<40	IgM anti-HBc	(-)
Anti-mitochondria M2	<1.5	HBV DNA	(-)
Anti-smooth muscle	negative	HCV RNA	(-)
Anti- LKM1	negative	IgM anti-HEV	(-)
HLA	DR4	IgM anti-EBV VCA	(-)
T.Bil (mg/dL)	10.3	IgG anti-EBV VCA	(-)
D.Bil (mg/dL)	8.0	EBNA	(-)
AST (U/L)	848	IgM anti-CMV	(-)
ALT (U/L)	1,115	IgM anti-HSV	(-)
LDH (U/L)	366		
ALP (U/L)	979		
GGT (U/L)	75		
Ch-E (U/L)	155		

WBC: white blood cell count, RBC: red blood cell count, CRP: c-reactive protein, Ig: immunoglobulin, Anti-LKM1: anti-liver-kidney microsome type 1 antibody, HLA: human leukocyte antigen, T. Bil: total bilirubin, D. Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transpeptidase, Ch-E: cholinesterase, TP: total protein, ALB: albumin, T-Cho: total cholesterol, Glu: glucose, UN: urea nitrogen, Cre: creatinine, PT: prothrombin time, INR: international normalized ratio, anti-HAV: anti-hepatitis A virus antibody, HBsAg: hepatitis B virus surface antigen, anti-HBc: hepatitis B virus core antibody, HBV: hepatitis B virus, HCV: hepatitis C virus, HEV: hepatitis E virus, anti EBV VCA: anti-Epstein-Barr virus capsid antigen antibody, EBNA: Epstein-Barr virus nuclear antigen, CMV: cytomegalovirus, HSV: herpes simplex virus

vated levels of hepatobiliary enzymes including aspartate aminotransferase (AST) 848 U/L, alanine aminotransferase (ALT) 1,115 U/L, alkaline phosphatase (ALP) 979 U/L, total bilirubin 10.3 mg/dL, direct bilirubin 8.0 mg/dL, total protein 7.3 g/dL, albumin 3.7 g/dL, c-reactive protein 0.14 mg/dL, WBC 7,600/μL, eosinophils 1.2%, Hb 12.8 g/dL, platelet count 34×10^4/μL, ammonia 47 μg/dL, and prothrombin time-international normalized ratio (PT-INR) 1.33 (PT: 54.3%) (Table). Viral serological tests for viral hepatitis A, B, C, E, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus were negative. Levels of anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, and anti-liver-kidney microsome type 1 antibody were negative. Serum copper levels and ceruloplasmin levels were within normal ranges. The level of serum IgG was elevated to 2,046 mg/dL. Computed tomography showed only hepatomegaly and excluded biliary obstruction and malignancy.

Six weeks before she was referred to our hospital, she was diagnosed with influenza A and prescribed 40 mg laninamivir and 200 mg acetaminophen. Three weeks later she became aware of jaundice. She did not go to the hospital until she felt fatigued because she was busy with school activities. A drug-induced lymphocyte stimulation test (DLST) for laninamivir was positive with a stimulation index of 186%. A DLST for acetaminophen was negative. The association between laninamivir and liver injury was deemed "probable" using the criteria of the Roussel Uclaf Causality Assessment Method (RUCAM) scale (score of 5) (8, 9). Based on these findings, she was diagnosed with severe DILI that may have been caused by laninamivir.

Due to severe hepatitis (10) (PT <60%, ALT >200 U/L, T. Bil >5 mg/dL), oral PSL 50 mg/day (1 mg/kg/day) was initiated from the 7th day of hospitalization. PSL was reduced to 40 mg/day 7 days after the initiation. On the 26th day of hospitalization, a liver biopsy was performed. The histopathological findings of the liver indicated moderate-to-severe interface hepatitis and infiltration of marked inflammatory cells with plasma cells and a few eosinophil granulocytes in the portal area. Hepatic rosette formation, partial ballooning, and phlebitis in the central veins of the liver were observed (Fig. 1A). These histopathological findings were similar to the characteristics of AIH. Human leukocyte antigen (HLA) DR4 was positive. The score of the revised international diagnostic scoring system of AIH was 12 points (11), and that of the simplified diagnosis criteria was 6 points (12). AIH was diagnosed as "probable" using these scoring systems. Based on the biochemical data and the histopathological findings of the liver, we diagnosed the patient with 'drug-induced AIH' or 'immune-mediated DILI' that may have been caused by laninamivir.

Elevated liver function test findings persisted for 3 weeks after the initiation of PSL and azathioprine (AZA) 50 mg/day was added to the treatment. Liver function tests gradually improved. Therefore, PSL was gradually tapered. Liver function tests normalized two months after AZA initiation. The clinical and therapeutic course of the patient during hospitalization and after discharge is shown (Fig. 2). Eighteen months after PSL initiation, PSL was withdrawn. A second biopsy was performed 22 months after the onset. These pathological findings revealed the absence of interface hepatitis and inflammatory infiltrations in some portal areas (Fig. 1B). AZA was withdrawn based on these results two years after the onset.

Her liver function test results have remained normal in the nine months since withdrawing the immunosuppressant, so we diagnosed her with 'immune-mediated DILI' caused by laninamivir.

Discussion

To our knowledge, this is the first case of immune-mediated DILI that may have been caused by laninamivir. Laninamivir is often prescribed for young patients in Japan.

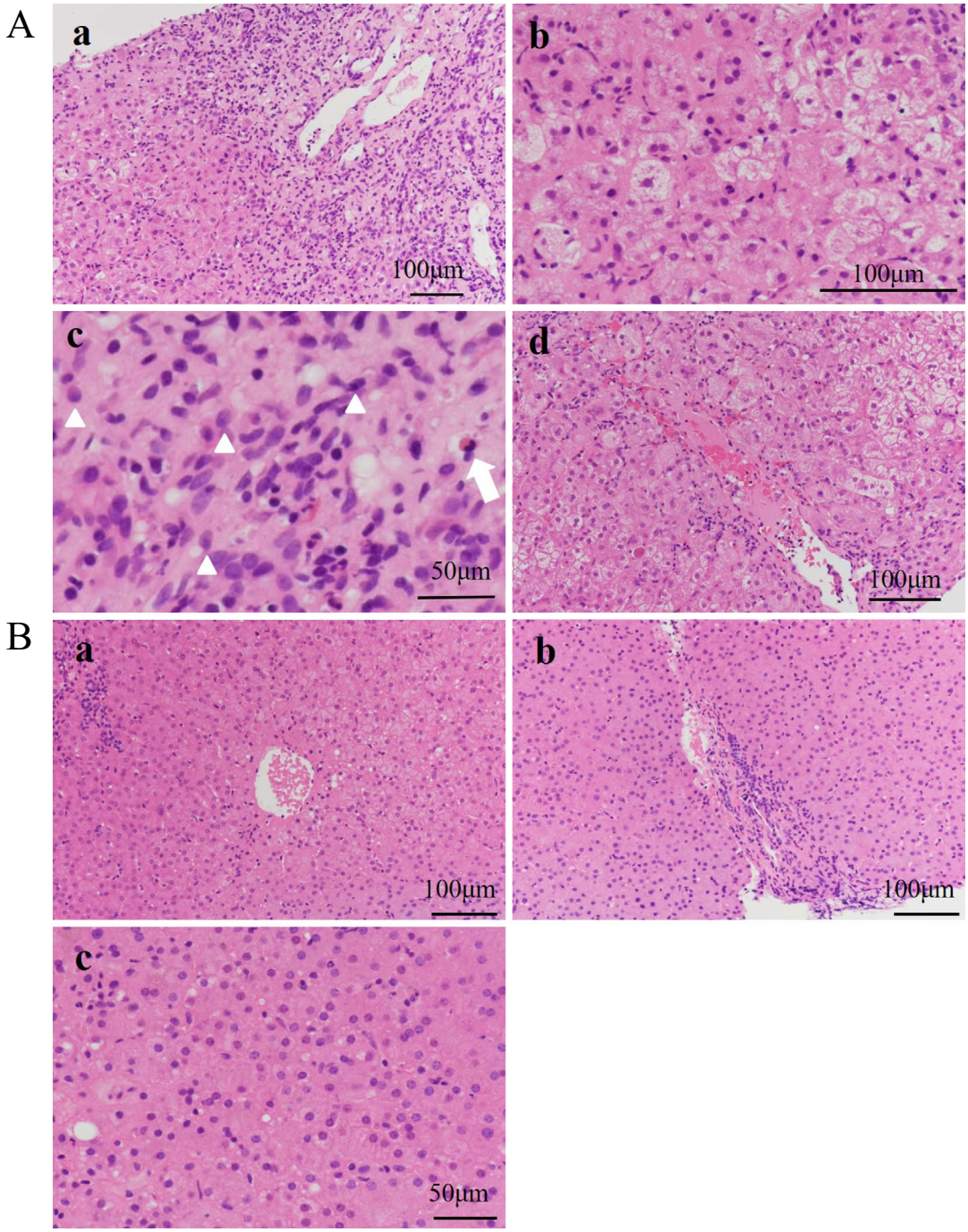

Figure 1. **A: The first liver biopsy (a-d). (a) The liver biopsy showed severe portal hepatitis with infiltration of inflammatory cells. (b) A hepatic rosette-like formation of ballooning hepatocytes is shown. (c) Presence of plasma cells (white arrowhead) and rare eosinophils (white arrow). (d) Phlebitis in the hepatic central veins are shown. B: The second biopsy performed 22 months after onset (a-c). Liver biopsy showed remission of inflammatory infiltrates and an almost normal portal tract.**

Kashiwagi et al. reported the results of a post-marketing surveillance study of laninamivir (2). The most common adverse drug reactions (ADRs) were psychiatric disorders (0.48%), such as abnormal behavior and delirium, but no serious or delayed ADRs occurred, and hepatobiliary disorders occurred in 0.13% of patients. ADRs emerged within 3 days after inhalation in ≥90% of adversely affected patients. In our case, jaundice became noticeable about three weeks after the administration of laninamivir, and the association between laninamivir and liver injury was deemed "probable" using the criteria of the RUCAM scale (score of 5) (8, 9). These findings suggest that laninamivir may cause delayed liver injury.

The possibility of 'autoimmune hepatitis' not related to laninamivir cannot be excluded. There is a report of AIH following influenza virus vaccination (13) and the virus itself may cause AIH. The present patient had received an influenza virus vaccine more than five months prior to presen-

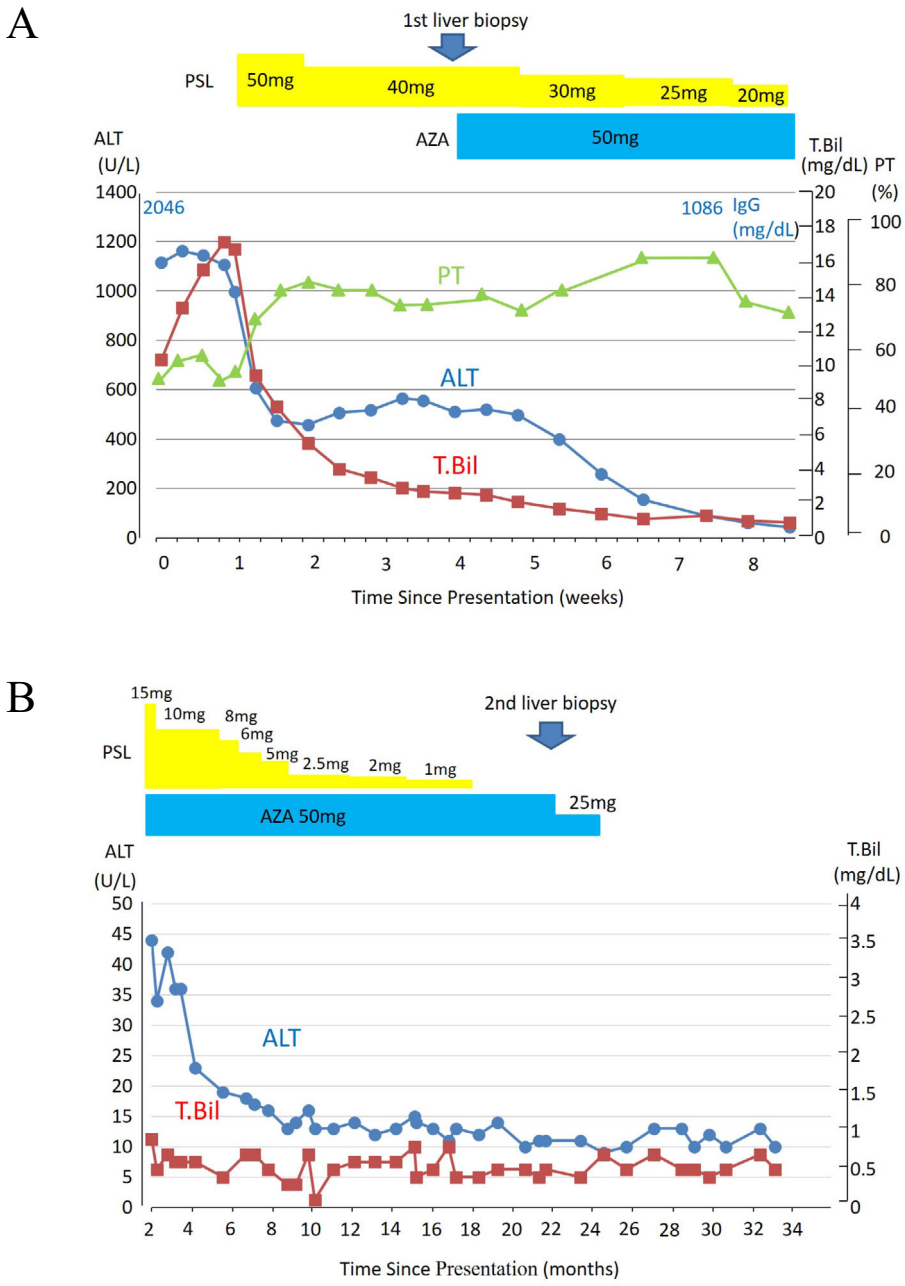

Figure 2. **A: Clinical and therapeutic course of the patient during hospitalization. B: Clinical and therapeutic course after discharge.**

tation. We believe that the possibility of AIH related to influenza virus vaccination is low.

Weiler-Normann et al. (7) reported on DILI and its relationship to AIH and proposed three classifications: 'AIH with DILI', 'drug-induced AIH', and 'immune-mediated DILI'. Our case had characteristics of AIH based on the clinical data and hepatopathological findings, and the patient was diagnosed with 'drug-induced AIH' or 'immune-mediated DILI'. It is difficult to distinguish 'drug-induced AIH' and 'immune-mediated DILI'. If remission is maintained after the successful withdrawal of steroids, 'immune-mediated DILI' should be considered. In our case, the liver function was normalized by adding AZA to PSL, and the treatment was discontinued after two years. Therefore, it was diagnosed as 'immune-mediated DILI'.

The risk factors for immune-mediated DILI include advanced age, female gender, and an abnormal hepatic drug metabolism (14). The patient was female, but she did not have either of the other risk factors. In addition, HLA-DR4 was positive, which may be a factor related to AIH.

Life-long PSL therapy is required in AIH patients and has various side effects. There are serious problems, especially for young patients. Therefore, it is better to perform a second biopsy after remission in order to determine whether or not treatment can be discontinued.

In conclusion, this was the first case of immune-mediated DILI that may have been caused by laninamivir. A second biopsy after remission may help decide if treatment can be

discontinued.

The authors state that they have no Conflict of Interest (COI).

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 **51**: 1167-1175, 2010.
2. Kashiwagi S, Yoshida S, Yamaguchi H, et al. Safety of the long-acting neuraminidase inhibitor laninamivir octanoate hydrate in post-marketing surveillance. Int J Antimicrob agents **40**: 381-388, 2012.
3. Bjornsson E, Talwalkar J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology **51**: 2040-2048, 2010.
4. Bhat G, Jordan J Jr, Sokalski S, Bajaj V, Marshall R, Berkelhammer C. Minocycline-induced hepatitis with autoimmune features and neutropenia. J Clin Gastroenterol **27**: 74-75, 1998.
5. Stricker BH, Blok AP, Claas FH, Van Parys GE, Desmet VJ. Hepatic injury associated with the use of nitrofurans: a clinicopathological study of 52 reported cases. Hepatology **8**: 599-606, 1988.
6. Czaja AJ. Drug-induced autoimmune-like hepatitis. Dig Dis Sci **56**: 958-976, 2011.
7. Weiler-Normann C, Schramm C. Drug induced liver injury and its relationship to autoimmune hepatitis. J Hepatol **55**: 747-749, 2011.
8. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs-II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol **46**: 1331-1336, 1993.
9. Danan G, Benichou C. Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol **46**: 1323-1330, 1993.
10. Onji M, Zeniya M, Yamamoto K, et al. Diagnosis and treatment guide for autoimmune hepatitis in Japan, 2013. Kanzo **54**: 723-725, 2013.
11. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol **31**: 929-938, 1999.
12. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology **48**: 169-176, 2008.
13. Sasaki T, Suzuki Y, Ishida K, et al. Autoimmune hepatitis following influenza virus vaccination: two case reports. Medicine **97**: e11621, 2018.
14. Lucena MI, Andrade RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. Hepatology **49**: 2001-2009, 2009.