

[CASE REPORT]

Infliximab Was Found to Be Effective for Treating Immunosuppressive Drug-resistant Hepatitis due to Durvalumab

Koki Nakashima^{1,2}, Yoshiki Demura¹, Masahiro Oi¹, Mio Tabata¹, Toshihiko Tada¹, Kohei Shiozaki¹, Masaya Akai¹ and Tamotsu Ishizuka²

Abstract:

A 69-year-old man with stage III lung squamous cell carcinoma developed immune-related hepatitis following treatment with durvalumab, and was given high-dose corticosteroids and immunosuppressive drugs (mycophenolate mofetil, azathioprine, tacrolimus) but without demonstrating any improvement. Two cycles of infliximab (5 mg/kg) were then administered and thereafter the hepatitis improved. At the time of writing (9 months after the initiation of first course of durvalumab), the patient is alive without either any hepatitis symptoms nor any lung cancer progression.

Infliximab may be effective for treating non-small cell lung cancer (NSCLC) patients who develop immunosuppressive drug-resistant immune-related hepatitis caused by durvalumab.

Key words: non-small-cell lung cancer, immune checkpoint inhibitor, durvalumab, immune-related adverse event, hepatitis, infliximab

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Introduction

Immune checkpoint inhibitors (ICIs) have become the treatment options for several types of cancers (1, 2), including non-small cell lung cancer (NSCLC). Durvalumab, a human IgG1 monoclonal antibody that blocks programmed death 1 (PD1), is an ICI given to patients with stage III NSCLC following chemoradiotherapy (3, 4). However, ICIs can cause immune-related adverse events (irAEs), including hepatitis. The American Society of Clinical Oncology (ASCO) recommends that a corticosteroid at 1 to 2 mg/kg should be administered to patients with severe hepatitis, while mycophenolate mofetil (MMF) or azathioprine (AZA) should be used for those resistant to corticosteroid therapy (5), while tacrolimus has also been recommended (6).

However, effective treatments for patients with immune-related hepatitis who are resistant to those immunosuppressive drugs remain unclear. While several reports (7, 8) have

shown the efficacy of infliximab for melanoma patients with immune-related hepatitis due to combination therapy with nivolumab and ipilimumab, no such report has been presented in regard to those with NSCLC.

To the best of our knowledge, this is the first case report showing the efficacy of infliximab for immunosuppressive drug-resistant immune-related hepatitis due to durvalumab administration. Our findings suggest that infliximab may be an effective treatment option for such cases.

Case Report

The present patient provided his informed consent to publish the pertinent details regarding this case, including images.

A 69-year-old man with a 50-year history of smoking was referred to our hospital for an evaluation of abnormal chest radiograph findings. He was a regular drinker, approximately 20 grams of alcohol daily, but had no medical history of

¹Department of Respiratory Medicine, Japanese Red Cross Fukui Hospital, Japan and ²Third Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Japan

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Correspondence to Dr. Koki Nakashima, kouk0527@yahoo.co.jp

Table 1. Laboratory Findings.

[Hematology]		[Biochemistry]	Onset (38th days)	Peak value	
RBC	327×10 ⁴ /μL	T-Bil	7.5	10.2 (44th days)	mg/dL
Hgb	12.9 g/dL	D-Bil	6.1	8.8 (44th days)	mg/dL
WBC	9,000 /mm ³	AST	260	385 (64th days)	IU/L
Neu	88 %	ALT	337	615 (64th days)	IU/L
Lym	3 %	ALP	3,196	4,780 (48th days)	IU/L
Mono	8 %	γ-GTP	1,462	1,888 (62nd days)	IU/L
Eo	1 %	LDH	298		IU/L
PLT	28.8×10 ⁴ /μL	Amy	74		IU/L
		BUN	16		mg/dL
		Cre	0.61		mg/dL
[Coagulation]		ChE	193		IU/L
PT	110 %	TP	5.6		g/dL
APTT	85 %	Alb	2.6		g/dL
Fibrinogen	400 mg/dL				
FDP	3.1 μg/dL	[Viral marker]			
D-Dimer	1.3 μg/dL	IgM-HA	Negative		
		HBsAg	Negative		
[Serology]		HBcAb	Negative		
CRP	4.3 mg/dL	HBsAb	Negative		
ANA	Negative	HCV-Ab	Negative		
AMA	Negative	IgM-EB-VCA	Negative		
AMA-M2	Negative	IgM-CMV	Negative		
ASMA	Negative	IgM-HSV	Negative		
IgG	635 mg/dL				
IgA	161 mg/dL				
IgM	50 mg/dL				
IgE	37 mg/dL				
βD-glucan	<6 pg/mL				

PLT: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, ANA: anti-nuclear antibody, AMA: anti-mitochondrial antibody, ASMA: anti-smooth muscle antibody, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cre: creatine, ChE: cholinesterase, Alb: albumin, IgM-HA: immunoglobulin M hepatitis A, HBsAg: hepatitis B virus antigen, HBcAb: hepatitis B virus antibody, HCV: hepatitis C virus, IgM-EB-VCA: immunoglobulin M Epstein-Barr virus-viral capsid antigen antibody, IgM-CMV: immunoglobulin M cytomegalovirus, IgM-HSV: immunoglobulin M herpes simplex virus

liver disease including viral hepatitis. The examination results led to a diagnosis of squamous cell lung cancer (cT4N0M0: Stage IIIA), with a PD-L1 tumor proportion score of less than 1%. Chemoradiotherapy with carboplatin and paclitaxel was administered, and a partial response was achieved.

Within 2 days after the end of chemoradiotherapy, radiation pneumonitis (grade 2) developed and prednisolone (PSL) treatment (1 mg/kg) was started. After tapering PSL to 10 mg, chemotherapy with durvalumab was initiated. At a follow-up examination, the prolongation of a slight fever and a high level of C-reactive protein (CRP) (4-5 mg/dL) were noted, thus the next course of durvalumab was not administered. At 38 days following the initiation of the first course of durvalumab, liver dysfunction appeared (Table 1). There was no evidence of liver disease, such as viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis in blood test (Table 1). Contrast enhanced computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and abdominal ultra-

sound also showed no abnormality in the liver, gall bladder or biliary tract. According to these results, immune-related hepatitis due to durvalumab was diagnosed. Liver biopsy was not performed because the patient was receiving antithrombotic agents for internal carotid artery stenosis and arteriosclerosis obliterans with an artificial blood vessel.

Treatments with methylpredonolone (mPSL) at 80 mg/day + MMF at 2 g/day, mPSL at 80 mg/day + AZA at 2 mg/kg/day, mPSL at 80 mg/day + AZA at 2 mg/kg/day + tacrolimus at 2.5 mg/day (blood trough level 5 ng/mL) were given to treat the severe hepatitis. Furthermore, we also performed steroid half-pulse therapy on days 38 to 40 and steroid pulse therapy on days 66 to 68 during the course. However, despite these strong immunosuppressive treatments, liver dysfunction remained at Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 3. The peak values related to liver dysfunction during the course were as follows: aspartate aminotransferase (AST) 385 IU/L (grade 3) (day 64), alanine aminotransferase (ALT) 615 IU/L (grade 3) (day 64), alkaline phosphatase (ALP) 4,780 IU/L

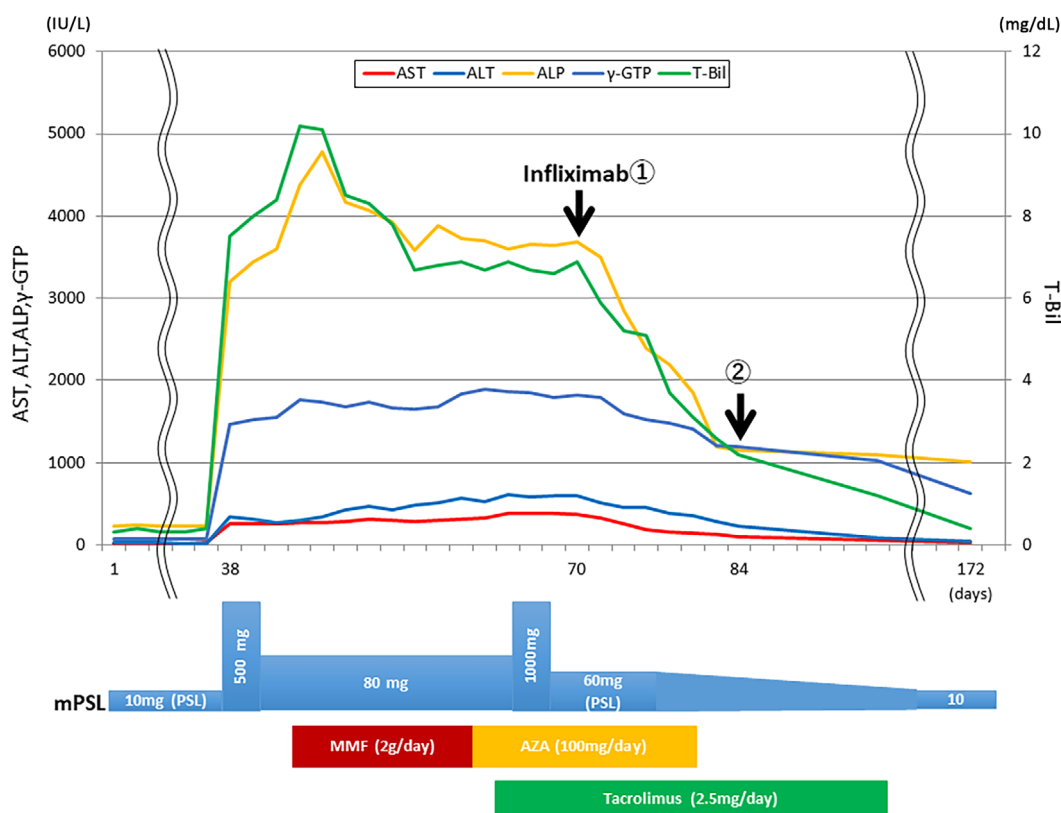


Figure. Patient clinical course. MMF: mycophenolate mofetil, AZA: azathioprine

(grade 3) (day 48), T-Bil 10.2 mg/dL (grade 3) (day 44), γ -glutamyl transpeptidase (GTP) 1,888 IU/L (day 62). Therefore, 2 cycles of infliximab (5 mg/kg) were administered 2 weeks apart, on days 70 and 84, following informed consent and ethics committee approval. At the start of infliximab therapy, the blood test results were as follows: AST 375 IU/L (grade 3), ALT 602 UI/L (grade 3), ALP 3,692 IU/L (grade 3), T-Bil 6.9 mg/dL (grade 3), γ -GTP 1,823 IU/L. Following the administration of infliximab, the hepatitis ameliorated and all related results improved to CTCAE grade 2 within 14 days. On day 172, normal levels of AST, ALT, and T-Bil were noted, whereas those of ALP and γ -GTP remained abnormal, as follows: AST 28 IU/L, ALT 37 UI/L, ALP 1,155 IU/L (grade 2), T-Bil 0.4 mg/dL, γ -GTP 1,189 IU/L. The clinical course is shown in Figure.

At the time of writing (9 months after initiation of first course of durvalumab), the patient is alive without hepatitis relapse nor lung cancer progression. The treatment with tacrolimus was discontinued at day 172. Treatment with PSL at 10 mg/day is continuing.

Discussion

In the PACIFIC study (3), a clinical study of durvalumab, grade 3 or higher hepatitis was seen in only 1.9% of the enrolled patients. Furthermore, there were no cases of immunosuppressive drugs-resistant immune-related hepatitis due to durvalumab administration. For severe immune-related hepatitis, a corticosteroid at 1 to 2 mg/kg, as well as

mycophenolate mofetil, azathioprine and tacrolimus are recommended, while effective treatments for affected patients who are resistant to those drugs are unknown (5, 6), though needed.

It is generally considered that most irAE including hepatitis are caused by cytotoxic T lymphocytes activated by treatment with an ICI (9, 10), and some studies have reported liver biopsy findings of immune-related hepatitis due to ICI treatment showing infiltrating cells mainly comprised of CD8-positive lymphocytes (8, 11-13). Thus, immunosuppressive drugs, including corticosteroids, mycophenolate mofetil, azathioprine, and tacrolimus, are usually effective for immune-related hepatitis (14, 15).

Some reports (7, 8) of immune-related hepatitis cases resistant to corticosteroid and mycophenolate mofetil therapy among melanoma patients treated with a combination of nivolumab and ipilimumab have been presented. Those findings indicated the presence of other mechanisms of irAE in patients with hepatitis who are resistant to those drugs. Other studies (16, 17) have reported a high concentration of mucosal tumor necrosis factor (TNF)- α observed in cases of ICI-related colitis. In addition, Kim et al. (18) noted the presence of irAE subtypes, such as those related to CD8, Th17, Treg, and TNF. These findings indicated that TNF was one of the factors associated with irAEs, although the mechanisms have yet to be elucidated. Immunosuppressive drugs, including corticosteroids, MMF, AZA, and tacrolimus, may be resistant to TNF-related irAEs, while a TNF- α blockade may be effective. Notably, some re-

Table 2. Clinical Data of Patients Who Received Infliximab for Liver Dysfunction Due to ICIs.

No.	Sex	Age	Cancer	Drugs (cycles)	Days until onset	Liver biopsy	Peak AST (IU/L)	Peak ALT (IU/L)	Peak T-Bil (mg/dL)	Peak ALP (IU/L)	Peak γ -GTP (IU/L)	Other treatments	Effect of infliximab	Ref
1	F	46	melanoma	Ipi+Niv (1)	30 days	No	-	2,854	-	-	-	mPLS, PSL, MMF	improve	7
2	F	53	melanoma	Ipi+Niv (3)	81 days	Yes	-	1,200<	29<	857	-	mPSL, PLS, MMF	improve	8
present case	M	69	NSCLC	Durvalumab (1)	38 days	No	385	615	10.2	4,780	1,888	mPSL, PSL, MMF, AZA, tacrolimus	improve	

AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ -GTP: γ -glutamyl transpeptidase, Ipi: ipilimumab, Niv: nivolumab, NSCLC: non-small cell lung cancer, PSL: prednisolone, MMF: mycophenolate mofetil, AZA: azathioprine

ports (7, 8) have shown the efficacy of infliximab for melanoma patients with immunosuppressive drug-resistant hepatitis caused by combination therapy with nivolumab and ipilimumab (Table 2). In present case, persistent liver dysfunction did not improve with corticosteroids, MMF, AZA, and tacrolimus, although each drug was continued for at least 7 days. In contrast, liver dysfunction improved immediately after the initiation of infliximab. This clinical course was similar to other reports which indicated the efficacy of infliximab for immune-related hepatitis (7, 8). Therefore, we considered that the effect which led to an improvement of his hepatitis was not due to corticosteroids, MMF, AZA, and tacrolimus, but instead was due to infliximab in the present case. We performed maintenance therapy with PSL and tacrolimus referring to the case presented by Corrigan. et al (8), although the efficacy remains unknown. At present, tacrolimus was discontinued and PSL 10 mg/day is continuing without any hepatitis relapse. We are going to continue to carry out a careful follow-up.

Several reports (19, 20) presented immune-related cholangitis with non-obstructive dilation of the bile ducts. In the present case, a blood test demonstrated the presence of cholestatic liver dysfunction. However, imaging findings showed no abnormality of bile duct such as non-obstructive dilation of bile ducts was in the present case. Therefore, we diagnosed immune-related hepatitis due to durvalumab, although a pathological evaluation with liver biopsy could not be performed due to various comorbidities. Immunohistochemistry with anti TNF- α antibody may promote an understanding of immunosuppressive drug-resistant hepatitis. Furthermore, measurement of the serum ferritin level may be helpful to understand the association between TNF- α and immunosuppressive drug-resistant hepatitis, although we did not measure it. Further accumulation of the number of cases of immunosuppressive drug-resistant hepatitis due to ICIs is necessary to confirm these findings.

To the best of our knowledge, this is the first report to present findings indicating the efficacy of infliximab for immunosuppressive drug-resistant immune-related hepatitis due to durvalumab. Infliximab may be considered to be an effective treatment option for such cases. Further studies are needed to elucidate the mechanism of immunosuppressive drug-resistant immune-related hepatitis.

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

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