【Summary of Vanishing Bile Duct Syndrome 1 (Recovering case)】

Patient Background		Clinical course and treatment	
Sex Age Weigh	Reason for use [complication]		
Female 70's 34.4 kg	Granulomatosis with polyangiitis (Remission induction) [Hypertension] [Spinal osteoarthritis] [Sudden hearing loss]	Day 1 of administration	Started to receive this drug (30 mg twice daily).
		Less than 1 month of administration	Noticed subjective symptoms such as malaise, but observed them at home.
		Day 34 of administration: (date of onset, date of discontinuation)	Had increases in bilirubin and hepatobiliary enzymes, which suggested drug-induced liver disorder. Had jaundice and malaise. Discontinued this drug and sulfamethoxazole/trimethoprim.
		Day 6 of onset	Still had increased bilirubin, with prominent jaundice. Started to receive ursodeoxycholic acid 900 mg/day for drug-induced liver disorder.
		Day 8 of onset	Had no dilation of the bile duct on contrast-enhanced CT. Underwent liver biopsy. Started to receive STRONGER NEO-MINOPHAGEN C Inj. Syringe 60 mL/day for the above condition.
		Day 10 of onset	Underwent simple plasma exchange (FFP 24 units) due to prolonged high bilirubin levels (Total bilirubin: 23.0 mg/dL). Completed with no adverse events.
		Day 13 of onset	Total bilirubin level was improved from 23.0 to 16.3 mg/dL with plasma exchange. Jaundice and pruritus slightly improved.
		Day 15 of onset	Liver biopsy results: Presence of cholestasis in hepatocytes or bile canaliculi. Presence of inflammatory cell infiltration mainly consisting of lymphocytes, with disappearance of the interlobular bile duct and bile duct-like reaction, in the portal region. These findings are consistent with cholestatic drug-induced liver injury when the medical history is taken into consideration, and disappearance of the interlobular bile duct suggests the pathology of vanishing bile duct syndrome. No neoplastic lesions cannot be found, with no findings suggestive of malignancy.
		Day 16 of onset	The diagnosis of vanishing bile duct syndrome was made based on the liver biopsy results.
		Day 17 of onset	Continued to receive prednisolone for the treatment of drug-induced liver disorder, at a dose of 30 mg/day, which was decreased to 20 mg/day. Underwent simple plasma exchange (FFP 24 units). Completed with no adverse events.
		Day 20 of onset	Total bilirubin level was improved from 16.3 to 8.2 mg/dL with plasma exchange. Jaundice, pruritus, and malaise also tended to improve.
		Day 23 of onset	Discontinued STRONGER NEO-MINOPHAGEN C Inj. Syringe because of further improvement of total bilirubin. Continued ursodeoxycholic acid only.
		Day 32 of onset	Prednisolone dose was reduced to 15 mg/day.
		Day 37 of onset	Total bilirubin level was improved to 2.4 mg/dL. The next day, ursodeoxycholic acid dose was reduced from 900 mg to 300 mg/day.
		Less than 2 months of onset	Vanishing bile duct syndrome was resolving.

Laboratory test value

Test item	(unit)	14 days after administration	34 days after administration (Date of onset/discontinuation)	Day 4 of onset	Day 8 of onset	Day 13 of onset	Day 23 of onset	Day 37 of onset
AST	[IU]/L	17	215	174	119	57	29	24
ALT	[IU]/L	15	635	401	345	122	50	30
γ-GTP	[IU]/L	29	1126	1339	1373	316	278	361
ALP	[IU]/L	71	536	487	537	202	188	243
T-Bil	mg/dL	-	5.5	9.9	23.8	16.3	6.3	2.4

-: No data available

Concomitant drugs（Suspected drug）： sulfamethoxazole/trimethoprim, prednisolone, alfacalcidol, vonoprazan fumarate, amlodipine besylate, lemborexant, amphotericin B

【Summary of Vanishing Bile Duct Syndrome 2 (Fatal case)】

Patient Background		Clinical course and treatment	
Sex Age Weigh	Reason for use [complication]		
Male 60's 59 kg	Microscopic polyangiitis (Re-induction of remission at relapse) [Hypertension] [Dyslipidemia]	Day 1 of administration	Started to receive this drug (30 mg twice daily).
		Day 46 of administration	Had orange urine.
		Day 50 of administration (Date of onset/discontinuation)	Originally had normal hepatobiliary enzymes, but had increased biliary enzymes. Had minimal inflammatory response. Complained of hematuria. Developed drug-induced liver injury. Admitted to the hospital due to bilirubinuria and severe jaundice. Discontinued administration of this drug due to suspected drug-induced liver injury. Given the possibility of concurrent cholangitis, received ENBD drainage under ERCP. Started to receive cefoperazone sodium/sulbactam sodium.
		Day 4 of onset	Started to receive ursodeoxycholic acid 300 mg three times daily for drug-induced liver injury.
		Day 7 of onset	Underwent liver biopsy.
		Day 8 of onset	Started to receive Inchinkoto (Japanese traditional herbal medicine) 2.5 g three times daily for drug-induced liver injury.
		Day 18 of onset	Liver biopsy results: Presence of inflammation in the portal area, with decreased bile duct and cholestasis around the central vein. These findings are consistent with drug-induced liver injury, but other causes cannot be ruled out. Presence of bile duct loss. These findings are clinically and pathologically consistent with vanishing bile duct syndrome caused by TAVNEOS Capsules, which has been reported previously.
		Day 20 of onset	Prednisolone dose was increased to 40 mg/day for drug-induced liver injury.
		Day 28 of onset	Prednisolone dose was reduced to 30 mg/day due to suspected lung abscess.
		Day 40 of onset	Supportive therapy with phenobarbital 120 mg once daily was added for drug-induced liver injury.
		Day 48 of onset	Complications such as infections caused by Nocardia, etc. Prednisolone dose was reduced to 15 mg/day.
		Day 53 of onset	Tested positive for cytomegalovirus antigen. Had pyrexia and diarrhea.
		Day 56 of onset	Completed phenobarbital.
		Day 59 of onset	Completed Inchinkoto.
		Day 61 of onset	Switched prednisolone to prednisolone sodium succinate for injection 20 mg/day.
		Day 62 of onset	Tested positive for cytomegalovirus antigen. Started to receive ganciclovir.
		Day 63 of onset	Completed ursodeoxycholic acid.
			Despite supportive therapy, the condition continued to be aggravated, with an increased bilirubin level to approximately 20.
		Day 68 of onset	Tested negative for cytomegalovirus antigen.
		Day 71 of onset	Started to receive palliative care intervention, with administration of fentanyl citrate.
		Day 83 of onset	Liver disorder did not improve, and died from progressive multiple organ failure.
			Autopsy was performed. It revealed marked organ jaundice. This suggested decreased circulating blood flow due to hepatic failure.

Laboratory test value

Test item	(unit)	18 days after administration	41 days after administration	50 days after administration (Date of onset/discontinuation)	Day 18 of onset	Day 46 of onset	Day 67 of onset	Day 78 of onset
AST	[IU]/L	17	-	134	36	84	86	57
ALT	[IU]/L	42	25	442	91	92	30	31
γ-GTP	[IU]/L	43	-	597	270	316	411	395
ALP	[IU]/L	59	-	353	244	500	539	401
T-Bil	mg/dL	0.8	-	7.9	19.4	27.6	24	20.1

-: No data available

Concomitant drugs（Suspected drug）： prednisolone, rituximab (recombinant), atovaquone, lansoprazole, repaglinide, alendronate sodium hydrate, lemborexant, ifenprodil tartrate, rosuvastatin calcium, mirabegron

List of Fatal Cases of Hepatic Dysfunction

No.	Onset year/month	Age	Sex	Reason for use	Hepatic dysfunction-related adverse reaction (PT)	No. of days to onset	Other adverse events (PT) (Underlined: Events not related to this drug)
1	2022.10	70's	Female	MPA	*Vanishing bile duct syndrome	45 days	Pneumocystis jirovecii pneumonia
2	2023.5	70's	Female	MPA	*Vanishing bile duct syndrome	36 days	Hypercholesterolaemia, Pneumocystis jirovecii pneumonia, *multiple organ dysfunction syndrome
3	2023.7	70's	Female	MPA	*Vanishing bile duct syndrome	28 days	*Shock haemorrhagic, ascites
4	2023.7	70's	Female	MPA	*Vanishing bile duct syndrome	49 days	*Septic shock
5	2023.10	70's	Female	MPA	*Hepatic function abnormal	72 days	*Diffuse large B-cell lymphoma, *acute kidney injury, COVID-19
6	2024.3	80's	Male	MPA	*Vanishing bile duct syndrome	42 days	*Klebsiella bacteraemia, cytomegalovirus infection, emphysematous cystitis
7	2024.1	80's	Female	GPA	*Hepatic function abnormal	245 days	Pneumonia, gastrointestinal inflammation, hyperlipidaemia, *general physical health deterioration, *bronchopulmonary aspergillosis, *renal failure, *cytomegalovirus infection reactivation, *granulomatosis with polyangiitis, steroid diabetes, hyponatraemia, cognitive disorder, white blood cell count decreased
8	2022.11	90's	Female	MPA	*Hepatitis fulminant	27 days	Herpes zoster
9	2024.11	80's	Female	MPA	*Vanishing bile duct syndrome	42 days	
10	2023.11	70's	Male	GPA	*Vanishing bile duct syndrome	54 days	*Infection
11	2024.12	80's	Female	MPA	*Acute hepatic failure	27 days	*Sepsis
12	2025.1	70's	Female	MPA	*Drug-induced liver injury	43 days	*Pneumocystis jirovecii pneumonia
13	2024.12	70's	Male	MPA	*Vanishing bile duct syndrome	78 days	*Pneumonia
14	2025.3	60's	Male	MPA	*Vanishing bile duct syndrome	43 days	*Multiple organ dysfunction syndrome
15	2025.4	70's	Male	MPA	*Vanishing bile duct syndrome *Acute hepatic failure	77 days	Herpes zoster, *pneumonia
16	2025.5	80's	Female	MPA	*Drug-induced liver injury	28 days	*Staphylococcal infection, neutrophil count decreased, *peptic ulcer, *haematemesis, *bacterial sepsis, *cytomegalovirus infection
17	2025.7	80's	Male	MPA	*Vanishing bile duct syndrome	55 days	
18*	2025.9	60's	Male	MPA	*Vanishing bile duct syndrome	50 days	*Nocardiosis, *cytomegalovirus infection
19	2025.9	70's	Male	MPA	*Cholestasis	49 days	Interstitial lung disease
20	2025.8	70's	Male	MPA	*Vanishing bile duct syndrome	31 days	*Intestinal perforation, *pneumocystis jirovecii pneumonia, *peritonitis

* Outcome: Death

MPA = microscopic polyangiitis, GPA = granulomatosis with polyangiitis

Adverse reaction/adverse event terms are described in preferred terms (PT) according to MedDRA/J Version 28.1.

*Case listed on Page 3