Case Details

Case 1

Patient		Daily dose /Treatment duration	Adverse reactions
Gender /Age	Reason for Use (complications)	100 mg /67 days	Clinical course and Treatment
Male 40s	Chronic hepatitis C (unknown)		No history of liver disorder, no complication of biliary tract disease, no previous treatment, and no history of alcohol consumption. Approximately 5 years before administration Chronic hepatitis C was diagnosed. 44 days before administration Hepatitis C virus-ribonucleic acid (HCV-RNA) was 5.70 log IU/mL (detected by real-time polymerase chain reaction). 12 days before administration Platelet count was 9.0 X 10^4/μL Day 1 of administration: Combination therapy with simeprevir sodium (100 mg/day), peginterferon alfa-2b (120 μg/week), and ribavirin (800 mg/day) was started. Date unknown: Hyperthyroidism occurred. Day 57 of administration Total bilirubin was 3.3 mg/dL. Day 63 of administration Administration of peginterferon alfa-2b was discontinued. Day 67 of administration (day of discontinuation) Administration of simeprevir sodium and ribavirin was discontinued. 3 days after discontinuation (10 weeks after combination therapy started) The patient visited a hospital with general malaise. He was admitted to hospital on this day because laboratory tests showed increased total bilirubin of 25.7 mg/dL. Hyperbilirubinaemia occurred. Imaging test showed no biliary obstruction but revealed ascites. Other findings included gallbladder enlargement, and hepatic cirrhosis. Hepatitis B virus test result was negative. 4 days after discontinuation All of the test results of hepatitis A virus, cytomegalovirus, Epstein-Barr virus, antinuclear antibody, antimitochondrial antibody, and smooth muscle antibody were negative. 7 days after discontinuation Drug lymphocyte stimulation tests showed negative for simeprevir sodium, peginterferon alfa-2b, and olopatadine hydrochloride and positive for ribavirin. The stimulation index (SI) for ribavirin was the highest, and the SI for simeprevir sodium was the second highest. Methylprednisolone sodium succinate 1 g/day was administered from this day through 9 days after discontinuation of simeprevir sodium. 10 days after discontinuation Methylprednisolone sodium succinate 80 mg/day was administered from this day through 15 days after discontinuation of simeprevir sodium. Antibiotic cefazolin sodium was administered to treat for sepsis from this day through 19 days after discontinuation of simeprevir sodium. 15 days after discontinuation Computed tomography scan showed hepatic atrophy, increased ascites, increased levels of mesenteric adipose tissue, gallbladder atrophy, and gallbladder wall thickening. Serious hepatitis was diagnosed (Hepatitis fulminant was suspected). 16 days after discontinuation Methylprednisolone sodium succinate 60 mg/day was administered from this day through 17 days after discontinuation of simeprevir sodium. 18 days after discontinuation Hepatic failure occurred. The cause of hepatic failure was drug treatment. Jaundice, fatigue, disorientation or confusion, encephalopathy, and ascites were found when hepatic failure occurred. Artificial ventilation, haemodialysis, steroid pulse therapy, and plasmapheresis were conducted as ancillary therapy. Prothrombin time activity was below 40%. 19 days after discontinuation Aspartate aminotransferase (AST) was 2300 IU/L. Disturbed consciousness, severe jaundice, and hepatocellular necrosis occurred. HCV-RNA was not detected.

			20 days after discontinuation Blood culture from artery revealed that the pathogen was *Serratia marcescens*. Bacterial sepsis was diagnosed. Clinical findings were shock, hepatic failure, and disseminated intravascular coagulation. 21 days after discontinuation The patient died of bacterial sepsis, hepatic failure, serious hepatitis (suspected hepatitis fulminant), hepatic cirrhosis, and peritonitis. The condition of the patient's liver was changed compared to that before administration of simeprevir sodium, and resulted in hepatic failure. The causes of death were bacterial sepsis resulting from immunological deterioration, hepatic failure, and peritonitis. The autopsy showed hepatic cirrhosis, hepatocellular necrosis, peritonitis, and acute pancreatitis.
Concomitant drugs: peginterferon alfa-2b, ribavirin, rosuvastatin calcium, olopatadine hydrochloride			

Laboratory Examination (Hepatobiliary function tests)

	12 days before administration	Day 1 of administration	Day 14 of administration	Day 28 of administration	Day 56 of administration	3 days after discontinuation	10 days after discontinuation	15 days after discontinuation	19 days after discontinuation	21 days after discontinuation
T-Bil (mg/dL)	1.4	1.0	1.1	1.8	3.3	25.7	37.2	44.1	26.8	20.2
D-Bil (mg/dL)	0.2	－	0.2	0.5	1.9	16.7	24.5	34.5	18.3	13.0
AST (IU/L)	72	63	41	49	56	80	52	59	2300	557
ALT (IU/L)	120	95	54	57	59	51	46	39	1028	320
ALP (IU/L)	248	236	253	294	324	431	505	515	245	284
γ-GTP (IU/L)	39	34	34	36	48	32	27	24	17	21

－: not available

Case 2

Patient		Daily dose /Treatment duration	Adverse reactions
Gender /Age	Reason for Use (complications)	100 mg /91 days	Clinical course and Treatment
Male 60s	Chronic hepatitis C (Type 2 diabetes mellitus and duodenal ulcer)		No history of allergy, no diabetic nephropathy, no history of alcohol consumption. 28 days before administration Platelet count was 9.0 X 10^4/μL Day 1 of administration: Combination therapy with simeprevir sodium (100 mg/day), peginterferon alfa-2a (45 μg/week), and ribavirin (800 mg/day) was started in another hospital. Day 57 of administration Total bilirubin was 4.0 mg/dL. Creatinine was 0.96 mg/dL. Day 72 of administration Creatinine was 0.88 mg/dL. Approximately Day 80 of administration Abnormalities had not been specified before this day. However, general malaise, anorexia, and weight decreased (decreased by 7kg in 3 weeks to 63kg) were noted. The urine output also began to decrease. Day 91 of administration (day of completion) Administration of simeprevir sodium was completed. 8 days after completion Administration of peginterferon alfa-2a and ribavirin was discontinued. 15 days after completion Drug-induced cholestatic hepatic disorder and acute renal failure developed. Creatinine and total bilirubin increased, and cholestasis and acute renal failure concurrently developed. Because advanced cholestatic liver disorder was considered to have induced acute renal failure, intensive care such as plasmapheresis, haemodiafiltration, and steroid pulse therapy was performed. However, the patient did not respond to intensive care. Diagnostic imaging showed no biliary dilatation. The clinical signs and symptoms associated with drug-induced cholestatic hepatic disorder included jaundice, fatigue, nausea, malaise, anorexia, and renal failure. The clinical signs and symptoms associated with acute renal failure included oliguria, general malaise, impaired appetite and disturbed consciousness. 18 days after completion Creatinine was 1.70 mg/dL. 46 days after completion There was no improvement in the laboratory data after 3 weeks of admission to the hospital. The patient did not want to continue haemodialysis. In the afternoon, the patient died of multi-organ failure. Causes of death were drug-induced cholestatic hepatic disorder, renal failure acute, and multi-organ failure. Autopsy was not performed. Plasmapheresis, haemodiafiltration and steroid pulse therapy were performed before death. DLST was positive for simeprevir.
Concomitant drugs: ribavirin, peginterferon alfa-2a, loxoprofen sodium hydrate, and fexofenadine hydrochloride			

Laboratory Examination (hepatobiliary and renal function tests)

	28 days before administration	Day 1 of administration	Day 29 of administration	15 days of completion	25 days of completion	36 days of completion	46 days of completion
T-Bil (mg/dL)	1.5	1.6	2.9	37.8	16.7	22.0	25.2.
D-Bil (mg/dL)	－	－	－	－	12.7	18.7	20.0
AST (IU/L)	41	66	36	47	23	37	607
ALT (IU/L)	38	91	37	27	13	21	210
ALP (IU/L)	153	－	－	－	188	282	554
γ-GTP (IU/L)	44	85	70	83	59	84	76
BUN (mg/dL)	16	15	11	89	12	24	94
Creatinine (mg/dL)	1.02	1.06	0.91	6.75	2.00	2.06	9.15

－: not available