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Saquinavir Therapy in Patients with the Advanced HIV Infection and Liver Cirrhosis

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Most Japanese adult hemophiliacs infected with HIV are also infected with HCV. As HIV infection accelerates the progression of HCV infection (1), such patients often develop liver cirrhosis (LC) before 40 years of age. Co-infection is very high (75-90%) (2) in injecting drug users due to the high prevalence of HCV infection among them. Liver dysfunction particularly in HCV-positive patients hinders treatment of HIV infection with protease inhibitor (PI) (3). However, patients with LC also require highly active antiretroviral therapy (HAART) which dramatically improves the prognosis of HIV infection (4). In patients undergoing combination treatment with ritonavir (RTV) and saquinavir (SQV), serum concentration of SQV has been reported to elevate to as much as 20 to 40-times higher than when SQV was used alone (5). Despite such high concentrations of SQV, this dual protease therapy was well-tolerated (6). In light of these background data, we

administered SQV to Japanese hemophiliacs with advanced stages of HIV infection and LC and evaluated its clinical benefits and side effects. We also measured the trough concentration of SQV. The trial was performed on four patients who gave us their informed consents.

All four patients had LC which had been diagnosed clinically (liver biopsy was not performed). All the patients had esophageal varices and three patients had experienced the varices' rupture. Two patients had an episode of ascites and one patient experienced hepatic coma. Two patients had AIDS with esophageal candidiasis and non-Hodgkin's lymphoma. All the patients had received antiviral therapies with nucleoside reverse-transcriptase inhibitors and two were treated with PIs for only a short period. SQV treatment (1200 mg-1800 mg/day) was started in all the four patients. Two patients received lamivudine (3TC) and stavudine and another patient received

Table 1. Patients' characteristics (hemophiliacs with HIV, HCV, and liver cirrhosis)

case	1	2	3	4
age	36	39	25	39
AIDS	esophageal candidiasis	(-)	non-Hodgkin's lymphoma	(-)
prior antiretroviral therapy				
NRTI	ZDV,ddI	ZDV	ZDV	ZDV,ddI
PI	(-)	RTV 800mg (4 weeks)	SQV 1200mg (2 weeks)*	(-)
SQV therapy				
SQV (/day)	1800mg	1200mg	1200mg	1200mg
NRTIs (/day)	3TC 300mg and d4T 60mg	3TC 300mg	(-)	3TC 150mg and d4T 40mg
before/after SQV therapy				
CD4 (/mm ³)	130/95	104/115	0.5/25	103/60
HIV RNA (log ₁₀ copies/ml)	3.65/BQL	3.18/BQL	4.51/4.63	3.18/BQL
HCV RNA (×10 ³ copies/ml)	330/790	BQL/13	BQL/1300	92/BQL
duration of SQV therapy	66 weeks	77 weeks	9 weeks	45 weeks
trough concentration of SQV	258.8 ng/ml	555 ng/ml	181.5 ng/ml	185.6 ng/ml
adverse events with SQV therapy	T-bil 5.0mg/dl ascites,general fatigue	(-)	T-bil 21mg/dl	repeated GI bleeding
adverse events with previous PI		liver dysfunction ALT 412 IU/ml T-bil 3.9mg/dl	GI bleeding (gastric ulcer)	

ZDV: zidovudine ddI: didanosine 3TC: lamivudine d4T: stavudine SQV: saquinavir RTV: ritonavir
NRTI: nucleoside reverse-transcriptase inhibitor, PI: protease inhibitor, GI: gastro-intestinal,
BQL: below quantifiable level (HIV < 2.6 log₁₀ copies/ml and HCV <1×10³copies/ml)

*duration of the therapy

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3TC in addition to SQV. Their CD4 counts did not increase significantly during the therapy, although these patients' HIV RNA decreased to below quantifiable levels (BQL) (BQL; <400 copies/ml). Two patients had to discontinue SQV administration after 9 to 66 weeks of the trial because of advanced liver dysfunction (elevation of total bilirubin with 5.0 mg/dl and 21 mg/dl, normal range: 0.2-1.0 mg/dl) and one due to repeated gastrointestinal bleeding. Only one patient was able to continue SQV/3TC therapy for more than 77 weeks though he had a history of liver dysfunction caused by RTV. Plasma HCV RNA increased in three patients after starting SQV therapy. The trough concentration of SQV was 182 to 555 ng/ml, which was several times higher than that in patients with normal liver function (46 ng/ml) (7).

The aim of HAART is to decrease HIV RNA and to increase CD4 counts. Without HAART, the CD4 count is bound to decrease. As patients experience more and more opportunistic infections (OIs), they usually have to take drugs to control these infections over a long period, which often aggravates liver damage. It is considered that only HAART can avoid this vicious circle. However, our data did not confirm any potential clinical benefits of the inclusion of SQV in HAART in these patients. Indeed in three patients, concentrations of SQV elevated to a level higher than those with normal liver function, and HIV RNA decreased to BQL. However, the decreased levels of HIV RNA for more than 45 weeks (patients 1,2,4) were not associated with recovery of CD4 counts. In addition, the regimen containing SQV caused the elevation of the total bilirubin level in two patients (patients 1,3) and gastrointestinal bleeding in two patients (patients 3,4). In patients 1 and 3, HCV RNA even increased. However, the correlation between adverse events and elevation of SQV-concentration was not clear.

Zylberberg reported an unusual case of rapidly evolving HCV-related cirrhosis which paralleled the restoration of immune status in an HIV-infected patient (8). This and our observations demonstrate the difficulty of managing patients with advanced HIV infections combined with LC. In conclusion, SQV therapy in patients with advanced HIV infections and LC experienced side effects with few clinical benefits. We should pay much attention to HCV infection so as not to cause its progression to LC. Use of interferon and/or ribavirin have to be considered in dually infected patients.

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