Table 1 continued

Study	Peginterferon type and dose	Ribavirin	Duration, weeks[a]	Patients, *N*	Male, *N*	Age, years (mean)	BW, kg (mean)	Ethnic group, *N*				HCV genotype, *N*			
								Caucasian	African	Asian	Other	G1	G2	G3	G4–6
Mendez-Navarro [71]	2a 180 μg	1000–1200 mg	48	63	26	46.2	70.4	0	0	0	63	63	0	0	0
Meyer-Wyss [72]	2b 1.0 μg/kg	800 mg, fixed	24–48[a]	113	64	39[b]	72	NR	NR	NR	NR	49	14	41	9
	2b 1.5 μg/kg	800 mg, fixed	24–48[a]	106	76	42[b]	73	NR	NR	NR	NR	64	10	26	6
Napoli [73]	2b 1.5 μg/kg	800–1200 mg	48[a]	14	10	46.9	NR	NR	NR	NR	NR	14	0	0	0
	2b 1.5 μg/kg	800–1200 mg	48	17	11	47.3	NR	NR	NR	NR	NR	17	0	0	0
Pearlman [74]	2b 1.5 μg/kg	800–1400 mg	48	49	23	56[b]	NR	NR	23	NR	26	49	0	0	0
	2b 1.5 μg/kg	800–1400 mg	72	52	34	54[b]	NR	NR	25	NR	27	52	0	0	0
Roberts [75]	2a 180 μg	1000–1200 mg	48	438	285	43.3	78.7	365	55	0	1	436	0	0	0
	2a 360 μg	1000–1200 mg	48[a]	433	298	43.6	77.3	355	61	0	2	432	0	0	0
Roffi [76]	2b 1.0 μg/kg	1000–1200 mg	48	57	36	56[b]	75	NR	NR	NR	NR	33	15	9	0
Rossignol [77]	2a 180 μg	1000–1200 mg	48	40	36	39	NR	NR	NR	NR	NR	0	0	0	40
Rumi [16]	2a 180 μg	1000–1200 mg	24–48[a]	212	128	51.6	72.2	NR	NR	NR	NR	91	69	34	18
	2b 1.5 μg/kg	1000–1200 mg	24–48[a]	219	120	52.8	68.9	NR	NR	NR	NR	87	74	32	26
Rustgi [78]	2a 180 μg	1000–1200 mg	24–48[a]	117	81	50	89.7	79	26	0	12	117	0	0	0
Sanchez-Tapias [79]	2a 180 μg	800 mg, fixed	48	165	113	42.8	73.3	NR	NR	NR	NR	149	1	7	8
	2a 180 μg	800 mg, fixed	72	161	102	43.2	74.4	NR	NR	NR	NR	142	1	8	8
	2a 180 μg	800 mg, fixed	24	148	88	39.3	67.9	NR	NR	NR	NR	45	18	75	10
	2a 180 μg	800 mg, fixed	48	36	20	42.4	68.7	NR	NR	NR	NR	35	0	0	1
Scotto [17]	2a 180 μg	15 mg/kg	48	71	42	45.8	80.7	NR	NR	NR	NR	45	6	8	12
	2b 1.5 μg/kg	15 mg/kg	48	72	40	47.8	78.9	NR	NR	NR	NR	47	5	9	11
Shiffman [80]	2b 1.5 μg/kg	800–1400 mg	48	48	27	49[b]	82	NR	17	NR	31	48	0	0	0
Shiffman [81]	2a 180 μg	800 mg, fixed	16	732	448	46	81.5	635	22	21	54	NR	372	358	NR
	2a 180 μg	800 mg, fixed	24	731	461	45.6	81.6	638	21	18	54	NR	356	369	NR
Shiffman [82]	2a 180 μg	1000–1200 mg	48	936	673	50	NR	693	157	NR	NR	936	0	0	0
Sjogren [83]	2b 1.5 μg/kg	1000–1200 mg	48	29	19	46[b]	82	17	9	2	1	29	0	0	0
Sood [84]	2b 1.0 μg/kg	1000–1200 mg	24	76	67	43.1	NR	0	0	76	0	0	0	76	0
	2b 1.5 μg/kg	1000–1200 mg	24	27	21	37.3	NR	0	0	27	0	0	0	27	0
Tang [85]	2a 180 μg	1000–1200 mg	20[a]	11	4	42[b]	70	8	NR	NR	3	11	0	0	0
	2a 180 μg	1000–1200 mg	32[a]	10	5	38[b]	69	10	0	0	0	10	0	0	0
	2a 180 μg	1000–1200 mg	44[a]	11	8	41[b]	79	10	NR	NR	1	11	0	0	0
	2a 180 μg	1000–1200 mg	48[a]	13	9	41[b]	71	11	NR	NR	2	13	0	0	0
Toyoda [86]	2b 1.5 μg/kg	600–1000 mg	8[a]	15	5	53.6	NR	0	0	15	0	0	15	0	0
	2b 1.5 μg/kg	600–1000 mg	24[a]	28	16	57.8	62.2	0	0	28	0	0	28	0	0
	2b 1.5 μg/kg	600–1000 mg	24[a]	17	7	NR	NR	0	0	17	0	0	17	0	0

Table 1 continued

Study	Peginterferon type and dose	Ribavirin	Duration, weeks[a]	Patients, *N*	Male, *N*	Age, years (mean)	BW, kg (mean)	Ethnic group, *N*				HCV genotype, *N*			
								Caucasian	African	Asian	Other	G1	G2	G3	G4–6
Wagner [87]	2a 180 μg	800–1200 mg	16	71	52	38	75.3	NR	NR	NR	NR	0	19	51	0
	2a 180 μg	800–1200 mg	24	71	41	39	74.6	NR	NR	NR	NR	0	19	52	0
	2a 180 μg	800–1200 mg	24	11	4	42	80.1	NR	NR	NR	NR	0	1	10	0
Wagner [88]	2a 180 μg	1000–1200 mg	48	352	183	45.4	74	344	0	0	8	352	0	0	0
Yenice [18]	2a 180 μg	800–1200 mg	48	37	13	49.9	NR	NR	NR	NR	NR	37	0	0	0
	2b 1.5 μg/kg	800–1200 mg	48	37	10	50.8	NR	NR	NR	NR	NR	37	0	0	0
Yu [89]	2b 80–100 μg	1000–1200 mg	24[a]	45	28	45.4	68.3	0	0	45	0	45	0	0	0
	2b 80–100 μg	1000–1200 mg	48[a]	15	11	45.1	68.6	0	0	15	0	15	0	0	0
Yu [90]	2a 180 μg	1000–1200 mg	16	50	32	50.8	67.7	0	0	50	0	0	50	0	0
	2a 180 μg	1000–1200 mg	24	100	58	49.9	65.8	0	0	100	0	0	100	0	0
Yu [91]	2a 180 μg	1000–1200 mg	24	100	57	49.7	65.5	0	0	100	0	100	0	0	0
	2a 180 μg	1000–1200 mg	48	100	58	49.1	67.5	0	0	100	0	100	0	0	0
Zeuzem [92]	2a 180 μg	800 mg, fixed	24	212	90	43.8	73.9	183	17	5	7	144	38	20	10
	2a 180 μg	800 mg, fixed	48	210	82	43.9	73.7	180	20	4	6	141	41	18	10
Zeuzem [93]	2a 180 μg	1000–1200 mg	24[a]	43	33	39.1	74.7	NR	NR	NR	NR	23	NR	NR	1
	2a 180 μg	1000–1200 mg	48	134	83	43.2	73.8	NR	NR	NR	NR	90	NR	NR	6
	2a 360 μg	1000–1200 mg	48	11	6	42.6	79	NR	NR	NR	NR	9	NR	NR	2
Zeuzem [94]	2b 1.5 μg/kg	800–1200 mg	24	237	127	42.2	71.3	225	NR	NR	NR	237	0	0	0
Zeuzem [95]	2a 180 μg	1000–1200 mg	48	114	66	41.9	73.4	105	NR	NR	9	114	0	0	0

HCV hepatitis C virus, *BW* body weight, *NR* not reported

[a] Details of pegylated (Peg) interferon dose and duration of treatment are described in Supplementary Table 1

[b] Data values are expressed as medians

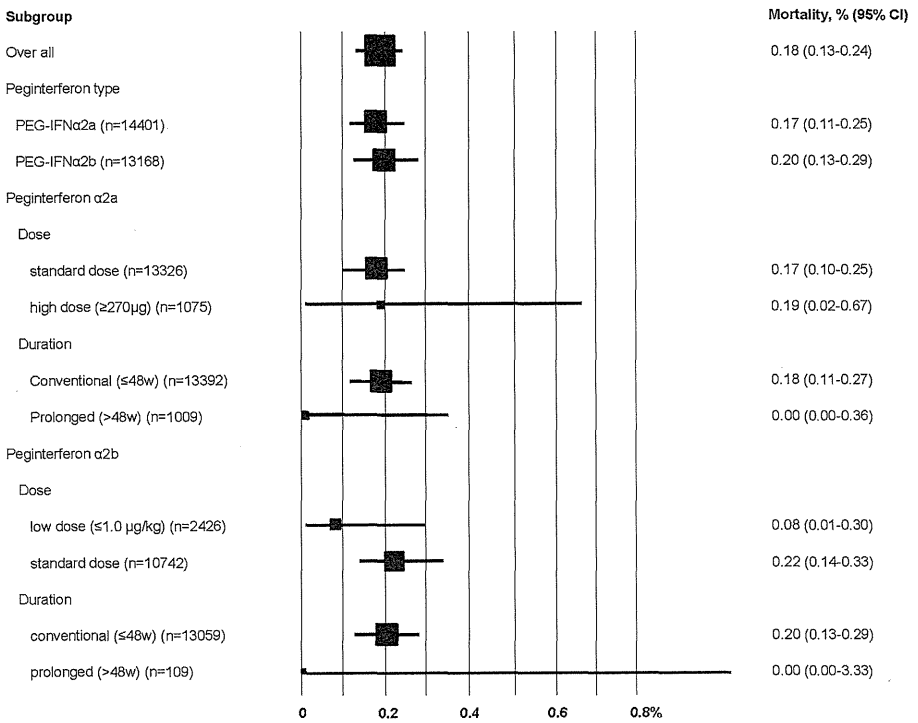

Fig. 2 Forest plot of mortality, comparing treatment regimens. Sizes of the *boxes* reflect sample sizes, with the *bars* showing the 95 % confidence interval (*CI*)

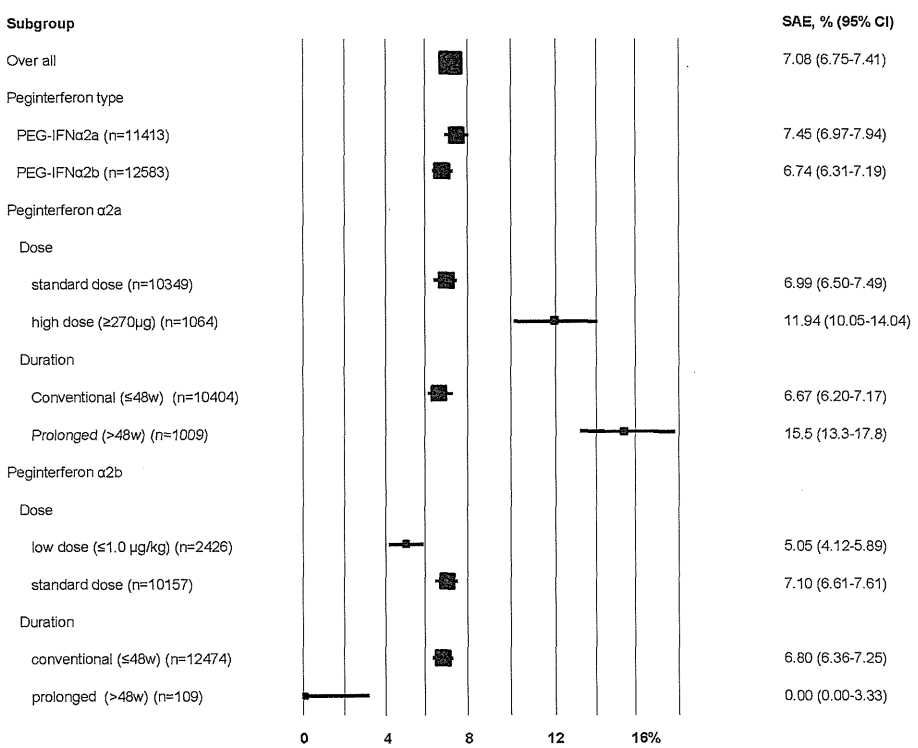

Fig. 3 Forest plot of SAEs, comparing treatment regimens. Sizes of the *boxes* reflect sample sizes, with the *bars* showing the 95 % confidence interval

Meta-regression analysis showed that greater body weight, an increased proportion of male patients, an increased proportion of HCV genotype 1, and an increased proportion of Caucasian patients and decreased proportion of Asian patients were significantly associated with increased SAE rates (Table 2). There was no significant

association between increased SAE rates and the mean patient age or the proportion of African patients.

Discussion

According to a report by the World Health Organization (WHO), age-specific annual death rates from all causes in individuals aged 45–49 years in the United States, Italy, and Japan (locations of the majority of our enrolled studies) were 409, 216, and 248 per 100000, respectively [11]. The crude mortality of 0.18 % (180 per 100000) found in the present study is low by comparison, even allowing for the biased population tolerable to PEG-IFN/RBV. Furthermore, the annual mortality rate could have been lower than the crude mortality rate, considering that the study period was longer than 1 year (including the follow-up period) in most enrolled studies. The annual treatment-related mortality rate could have been lower than our finding of a treatment-related mortality of 0.06 %. However, the treatment-related mortality rate may be an underestimate, as assessment of the causal relationship between treatment and mortality can be subjective and/or biased. Nonetheless, these PEG-IFN/RBV-related mortality rates would be acceptable considering the high SVR rates and considering that SVR drastically reduces adverse events related to chronic hepatitis C infection. In the present study, the most common cause of mortality was suicide, and all of the suicides were considered as treatment-related. This finding should alert treating physicians when they are treating patients with a history of psychiatric illness.

Two types of PEG-IFNs (i.e., PEG-IFN alpha-2a and 2b) are approved for the treatment of chronic hepatitis C. PEG-IFN alpha-2a has a molecular mass of 40 kDa and PEG-IFN alpha-2b a mass of 12 kDa. In comparison with PEG-IFN alpha-2b, PEG-IFN alpha-2a is less effectively

Table 2 Meta-regression analysis for continuous variables

Variables	Slope[a]	Standard error	*P* value
Mean age, per year increase			
All studies ($N = 100$)	−0.00244	0.00380	0.52
Alpha-2a ($N = 60$)	−0.00049	0.00513	0.93
Alpha-2b ($N = 40$)	−0.00203	0.00488	0.68
Mean body weight, per 1 kg increase			
All studies ($N = 95$)	0.00343	0.00147	0.02
Alpha-2a ($N = 64$)	0.00584	0.00242	0.02
Alpha-2b ($N = 31$)	0.00067	0.00178	0.71
Proportion of male patients, per 1 % increase			
All studies ($N = 125$)	0.00305	0.00130	0.02
Alpha-2a ($N = 73$)	0.00218	0.00182	0.23
Alpha-2b ($N = 52$)	0.00257	0.00166	0.13
Proportion of Caucasian patients, per 1 % increase			
All studies ($N = 75$)	0.00167	0.00043	<0.001
Alpha-2a ($N = 46$)	0.00102	0.00062	0.11
Alpha-2b ($N = 29$)	0.00201	0.00061	0.003
Proportion of African patients, per 1 % increase			
All studies ($N = 72$)	−0.00092	0.00113	0.42
Alpha-2a ($N = 41$)	0.00781	0.00394	0.55
Alpha-2b ($N = 31$)	−0.00030	0.00109	0.79
Proportion of Asian patients, per 1 % increase			
All studies ($N = 58$)	−0.00092	0.00042	0.03
Alpha-2a ($N = 32$)	−0.00042	0.00061	0.50
Alpha-2b ($N = 26$)	−0.00106	0.00053	0.06
Proportion of genotype 1 patients, per 1 % increase			
All studies ($N = 129$)	0.00143	0.00036	<0.001
Alpha-2a ($N = 73$)	0.00179	0.00048	<0.001
Alpha-2b ($N = 56$)	0.00075	0.00046	0.104

[a] Slope values indicate increases (decreases) in the rates of serious adverse events (SAEs) per unit. For example, a 1-year increase in mean age in a study results in 0.00464 (0.464 %) decrease in the SAE rate

cleared by the kidneys and therefore has a longer half-life. In fact, pharmacokinetic analysis in 22 patients showed that PEG-IFN alpha-2a was still detectable in 10 patients 168 h after the administration of 180 μg/week, whereas the administration of 1.0 μg/kg/week of PEG-IFN alpha-2b was undetectable in 11 of 12 patients at the same time point [12]. PEG-IFN alpha-2a is thought to be more effective than PEG-IFN alpha-2b because of its longer half-life. A recent meta-analysis showed a higher SVR rate after treatment with PEG-IFN alpha-2a than after treatment with PEG-IFN alpha-2b [13]. On the other hand, the half-life of each PEG-IFN may be related to its safety profile. However, among studies that have directly compared the safety of the two PEG-IFNs, only one reported a significant difference between SAE rates for PEG-IFN alpha-2a and PEG-IFN alpha-2b (11.7 vs. 8.6 %, $P = 0.02$) [14–18]. The inability of the other studies to detect such a difference may have been due to small sample sizes. In fact, a difference in SAE rates between the two PEG-IFNs was observed in pooled samples in our study.

Increasing the dose intensity of PEG-IFN and prolonging treatment duration have been attempted to achieve higher IFN levels in blood for longer periods, eventually resulting in a higher SVR rate. Treatment dose and duration are also expected to be related to the safety profile. The higher SAE rates in regimens with more intensive dosing observed for PEG-IFN alpha-2a and 2b and longer treatment duration observed for PEG-IFN alpha-2a support this hypothesis. The higher SAE rates in regimens with longer treatment duration were not observed for PEG-IFN alpha-2b, probably due to small sample sizes in regimens with longer treatment duration of PEG-IFN alpha-2b.

As mortality and SAE during PEG-IFN/RBV treatment are rare, most studies reported no such events. Therefore, the proportion calculated using the DerSimonian and Laird weight for the random-effect model showed considerable discrepancies between crude and pooled rates. In fact, pooled and treatment-related mortalities calculated using the random-effects (DerSimonian and Laird) model were 0.30 % (0.24–0.37 %) and 0.17 % (0.12–0.22 %), respectively, which were considerably different from the crude rates of each outcome (data not shown). Thus, we adopted crude instead of pooled rates for mortality and SAE.

Our meta-regression analysis showed a significant association between increased SAEs and HCV genotype 1. It is plausible that patients with genotype 1, which is difficult to treat, received a higher dose and longer duration of treatment. This is consistent with the results of the subgroup analysis.

A significant positive association between the SAE rate and the proportion of Caucasian patients, and an inverse relationship between SAEs and the proportion of Asian patients were also observed. This result may suggest a role of genetic diversity in the mechanisms underlying the adverse effects of PEG-IFN/RBV. Indeed, inosine triphosphate pyrophosphatase (*ITPA*) gene variants are associated with RBV-induced hemolytic anemia, and genetic polymorphisms near the interleukin-28B (*IL-28B*) gene were reported to be associated with response to HCV treatment with PEG-IFN and RBV, and the frequency of the variants differed between ethnic groups [19, 20].

We found that greater body weight was associated with a higher SAE rate. Of note, in the PEG-IFN alpha-2a-based regimen, the starting dose was fixed regardless of body weight; thus, with the PEG-IFN alpha-2a regimen, there might have been an overdose for patients of lower weight, leading to SAEs. However, whether such overdosing occurred was not clear in this study because there was a positive correlation between body weight and the SAE rate in patients receiving the PEG-IFN alpha-2a regimen. The reason for this positive relationship remains unclear; however, it may be because obesity is itself associated with various medical comorbidities.

We also found that an increased proportion of male patients in a study was associated with a higher SAE rate. It has been reported that female gender was an independent factor contributing to severe anemia [21], so the reason for the present finding of the increased proportion of male patients remains unclear; it may be correlated with increased body weight which caused a higher SAE rate. However, whether the proportions of individuals with obesity differed between male and female patients is not clear, because data on body mass index was often lacking.

In the present study increased mean age was not associated with a higher SAE rate, whereas discontinuation, dose reduction, and grade 3 adverse events were more frequent in older patients in previous studies [22, 23]. The lack of an association between mean age and the SAE rate in the present study could be due in part to the patients' mean age of 45.9 years, and the proportion of patients over 60 being small. Low-risk patients tend to be included in RCTs. This is one of the limitations of this study.

Recently, the use of HCV nonstructural 3/4A serine protease inhibitors combined with PEG-IFN and RBV were reported to achieve higher SVR rates in genotype 1 patients compared with conventional PEG-IFN/RBV. These triple therapies are considered to be the next standard of care for chronic hepatitis C [24, 25]. Adverse events during triple therapies could include those related to PEG-IFN/RBV, as these regimens include PEG-IFN/RBV.

We extracted only RCTs for our analysis in order to obtain highly reliable data and minimize the influence of recall bias because RCTs are prospectively designed, and SAEs should be defined a priori. However, several limitations are still worth noting. The latent limitation of this study is inter-study variability in the definition of SAE. The

precise meaning of 'serious' has not been determined, and some discrepancies between studies exist. These discrepancies may diminish the accuracy of the pooled SAE rate in this study. Second, even by choosing only RCTs, we could not completely exclude the influence of publication bias.

Overall, PEG-IFN/RBV treatment is relatively safe, with low mortality, considering the fact that chronic hepatitis C patients carry a high risk of cirrhosis and HCC. Nevertheless, the SAE rate with this treatment is not negligible and the development of safer regimens should be, and is, encouraged.

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References

1. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45(4):529–38.
2. Yvan H, Mary EK, Gregory JD, Joseph FP, Gregory LA, Geoffrey D, et al. Global burden of disease (GBD) for hepatitis C. J Clin Pharmacol. 2004;44(1):20–9.
3. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958–65.
4. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002; 347(13):975–82.
5. Bruno S, Camma C, Di Marco V, Rumi M, Vinci M, Camozzi M, et al. Peginterferon alpha-2b plus ribavirin for naive patients with genotype 1 chronic hepatitis C: a randomized controlled trial. J Hepatol. 2004;41(3):474–81.
6. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004;140(5): 346–55.
7. Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, et al. Peginterferon alpha-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2005;352(25):2609–17.
8. Brok J, Gluud LL, Gluud C. Meta-analysis: ribavirin plus interferon vs. interferon monotherapy for chronic hepatitic C—an updated Cochrane review. Aliment Pharmacol Ther. 2010;32(7): 840–50.
9. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med. 1999;131(3):174–81.
10. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
11. World Health Organization. Available at: http://apps.who.int/ghodata/?vid=720 (2011). Accessed 24 Oct 2011.
12. Bruno R, Sacchi P, Ciappina V, Zochetti C, Patruno S, Maiocchi L, et al. Viral dynamics and pharmacokinetics of peginterferon alpha-2a and peginterferon alpha-2b in naive patients with chronic hepatitis C: a randomized, controlled study. Antivir Ther. 2004;9(4):491–7.
13. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alpha-2b in chronic hepatitis C: systematic review of randomized trials. Hepatology. 2010;51(4):1176–84.
14. Ascione A, De Luca M, Tartaglione MT, Lampasi F, Di Costanzo GG, Lanza AG, et al. Peginterferon alpha-2a plus ribavirin is more effective than peginterferon alpha-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology. 2010;138(1):116–22.
15. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alpha-2b or alpha-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009;361(6):580–93.
16. Rumi MG, Aghemo A, Prati GM, D'Ambrosio R, Donato MF, Soffredini R, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology. 2010;138(1):108–15.
17. Scotto G, Fazio V, Fornabaio C, Tartaglia A, Di Tullio R, Saracino A, et al. Peg-interferon alpha-2a versus Peg-interferon alpha-2b in nonresponders with HCV active chronic hepatitis: a pilot study. J Interferon Cytokine Res. 2008;28(10):623–9.
18. Yenice N, Mehtap O, Gumrah M, Arican N. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol. 2006;17(2):94–8.
19. Fellay J, Thompson AJ, Ge D, Gumbs CE, Urban TJ, Shianna KV, et al. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. Nature. 2010;464(7287):405–8.
20. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399–401.
21. Hung CH, Lee CM, Lu SN, Wang JH, Chen CH, Hu TH, et al. Anemia associated with antiviral therapy in chronic hepatitis C: incidence, risk factors, and impact on treatment response. Liver Int. 2006;26(9):1079–86.
22. Iwasaki Y, Ikeda H, Araki Y, Osawa T, Kita K, Ando M, et al. Limitation of combination therapy of interferon and ribavirin for older patients with chronic hepatitis C. Hepatology. 2006;43(1): 54–63.
23. Oze T, Hiramatsu N, Yakushijin T, Mochizuki K, Oshita M, Hagiwara H, et al. Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alpha-2b plus ribavirin combination therapy. J Hepatol. 2011;54(4):604–11.
24. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009;360(18):1827–38.
25. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1195–206.
26. Abergel A, Hezode C, Leroy V, Barange K, Bronowicki JP, Tran A, et al. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. J Viral Hepat. 2006;13(12):811–20.
27. Alfaleh FZ, Hadad Q, Khuroo MS, Aljumah A, Algamedi A, Alashgar H, et al. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C in Saudi patients commonly infected with genotype 4. Liver Int. 2004;24(6):568–74.

28. Andriulli A, Cursaro C, Cozzolongo R, Iacobellis A, Valvano MR, Mangia A, et al. Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to Peg-interferon alpha-2a and ribavirin. J Viral Hepat. 2009;16(1):28–35.
29. Angelico M, Koehler-Horst B, Piccolo P, Angelico F, Gentile S, Francioso S, et al. Peginterferon alpha-2a and ribavirin versus peginterferon alpha-2a monotherapy in early virological responders and peginterferon alpha-2a and ribavirin versus peginterferon alpha-2a, ribavirin and amantadine triple therapy in early virological nonresponders: the SMIEC II trial in naive patients with chronic hepatitis C. Eur J Gastroenterol Hepatol. 2008;20(7):680–7.
30. Benhamou Y, Afdhal NH, Nelson DR, Shiffman ML, Halliman DG, Heise J, et al. A phase III study of the safety and efficacy of viramidine versus ribavirin in treatment-naive patients with chronic hepatitis C: ViSER1 results. Hepatology. 2009;50(3): 717–26.
31. Berg C, Goncales FL Jr, Bernstein DE, Sette H Jr, Rasenack J, Diago M, et al. Re-treatment of chronic hepatitis C patients after relapse: efficacy of peginterferon-alpha-2a (40 kDa) and ribavirin. J Viral Hepat. 2006;13(7):435–40.
32. Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alpha-2a plus ribavirin. Gastroenterology. 2006;130(4):1086–97.
33. Berg T, Weich V, Teuber G, Klinker H, Moller B, Rasenack J, et al. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. Hepatology. 2009;50(2):369–77.
34. Bosques-Padilla F, Trejo-Estrada R, Campollo-Rivas O, Cortez-Hernandez C, Dehesa-Violante M, Maldonado-Garza H, et al. Peginterferon alpha-2a plus ribavirin for treating chronic hepatitis C virus infection: analysis of Mexican patients included in a multicenter international clinical trial. Ann Hepatol. 2003;2(3): 135–9.
35. Brady DE, Torres DM, An JW, Ward JA, Lawitz E,Harrison SA. Induction pegylated interferon alpha-2b in combination with ribavirin in patients with genotypes 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study. Clin Gastroenterol Hepatol. 2010;8(1):66–71e1.
36. Brandao C, Barone A, Carrilho F, Silva A, Patelli M, Caramori C, et al. The results of a randomized trial looking at 24 weeks vs. 48 weeks of treatment with peginterferon alpha-2a (40 kDa) and ribavirin combination therapy in patients with chronic hepatitis C genotype 1. J Viral Hepat. 2006;13(8):552–9.
37. Bressler B, Wang K, Grippo JF, Heathcote EJ. Pharmacokinetics and response of obese patients with chronic hepatitis C treated with different doses of PEG-IFN alpha-2a (40 kD) (PEGASYS). Br J Clin Pharmacol. 2009;67(3):280–7.
38. Bronowicki JP, Ouzan D, Asselah T, Desmorat H, Zarski JP, Foucher J, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alpha-2a plus ribavirin. Gastroenterology. 2006;131(4):1040–8.
39. Carr C, Hollinger FB, Yoffe B, Wakil A, Phillips J, Bzowej N, et al. Efficacy of interferon alpha-2b induction therapy before retreatment for chronic hepatitis C. Liver Int. 2007;27(8): 1111–8.
40. Ciancio A, Picciotto A, Giordanino C, Smedile A, Tabone M, Manca A, et al. A randomized trial of pegylated-interferon-alpha2a plus ribavirin with or without amantadine in the re-treatment of patients with chronic hepatitis C not responding to standard interferon and ribavirin. Aliment Pharmacol Ther. 2006;24(7):1079–86.
41. Dalgard O, Bjoro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, et al. Pegylated interferon alpha and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology. 2008;47(1):35–42.
42. Diago M, Crespo J, Olveira A, Perez R, Barcena R, Sanchez-Tapias JM, et al. Clinical trial: pharmacodynamics and pharmacokinetics of re-treatment with fixed-dose induction of peginterferon alpha-2a in hepatitis C virus genotype 1 true non-responder patients. Aliment Pharmacol Ther. 2007;26(8):1131–8.
43. Ferenci P, Formann E, Laferl H, Gschwantler M, Hackl F, Brunner H, et al. Randomized, double-blind, placebo-controlled study of peginterferon alpha-2a (40 kD) plus ribavirin with or without amantadine in treatment-naive patients with chronic hepatitis C genotype 1 infection. J Hepatol. 2006;44(2):275–82.
44. Ferenci P, Brunner H, Laferl H, Scherzer TM, Maieron A, Strasser M, et al. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alpha-2a in hepatitis C virus genotypes 2 and 3. Hepatology. 2008;47(6):1816–23.
45. Ferenci P, Laferl H, Scherzer TM, Maieron A, Hofer H, Stauber R, et al. Peginterferon alpha-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. Gastroenterology. 2010;138(2):503–12e1.
46. Fried MW, Jensen DM, Rodriguez-Torres M, Nyberg LM, Di Bisceglie AM, Morgan TR, et al. Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon alpha-2a and ribavirin. Hepatology. 2008;48(4):1033–43.
47. Gish RG, Arora S, Rajender Reddy K, Nelson DR, O'Brien C, Xu Y, et al. Virological response and safety outcomes in therapy-naive patients treated for chronic hepatitis C with taribavirin or ribavirin in combination with pegylated interferon alpha-2a: a randomized, phase 2 study. J Hepatol. 2007;47(1):51–9.
48. Glue P, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, Salfi M, et al. A dose-ranging study of pegylated interferon alpha-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Therapy Group. Hepatology. 2000;32(3):647–53.
49. Hasan F, Al-Khaldi J, Asker H, Al-Ajmi M, Owayed S, Varghese R, et al. Peginterferon alpha-2b plus ribavirin with or without amantadine [correction of amantidine] for the treatment of non-responders to standard interferon and ribavirin. Antivir Ther. 2004;9(4):499–503.
50. Helbling B, Jochum W, Stamenic I, Knopfli M, Cerny A, Borovicka J, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. J Viral Hepat. 2006;13(11):762–9.
51. Herrine SK, Brown RS Jr, Bernstein DE, Ondovik MS, Lentz E, Te H. Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. Dig Dis Sci. 2005;50(4): 719–26.
52. Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009;360(18):1839–50.
53. Ide T, Hino T, Ogata K, Miyajima I, Kuwahara R, Kuhara K, et al. A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C. Am J Gastroenterol. 2009;104(1):70–5.
54. Jacobson IM, Gonzalez SA, Ahmed F, Lebovics E, Min AD, Bodenheimer HC Jr, et al. A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. Am J Gastroenterol. 2005;100(11):2453–62.
55. Jacobson IM, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, et al. Peginterferon alpha-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology. 2007;46(4):971–81.

56. Jensen DM, Marcellin P, Freilich B, Andreone P, Di Bisceglie A, Brandao-Mello CE, et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. Ann Intern Med. 2009;150(8):528–40.
57. Kamal SM, El Tawil AA, Nakano T, He Q, Rasenack J, Hakam SA, et al. Peginterferon {alpha}-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. Gut. 2005;54(6): 858–66.
58. Kamal SM, El Kamary SS, Shardell MD, Hashem M, Ahmed IN, Muhammadi M, et al. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: the role of rapid and early virologic response. Hepatology. 2007;46(6): 1732–40.
59. Kawaoka T, Kawakami Y, Tsuji K, Ito H, Kitamoto M, Aimitsu S, et al. Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial. J Gastroenterol Hepatol. 2009;24(3):366–71.
60. Khattab M, Emad M, Abdelaleem A, Eslam M, Atef R, Shaker Y, et al. Pioglitazone improves virological response to peginterferon alpha-2b/ribavirin combination therapy in hepatitis C genotype 4 patients with insulin resistance. Liver Int. 2010;30(3): 447–54.
61. Kuboki M, Iino S, Okuno T, Omata M, Kiyosawa K, Kumada H, et al. Peginterferon alpha-2a (40 kD) plus ribavirin for the treatment of chronic hepatitis C in Japanese patients. J Gastroenterol Hepatol. 2007;22(5):645–52.
62. Lagging M, Langeland N, Pedersen C, Farkkila M, Buhl MR, Morch K, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008;47(6):1837–45.
63. Langlet P, D'Heygere F, Henrion J, Adler M, Delwaide J, Van Vlierberghe H, et al. Clinical trial: a randomized trial of pegylated-interferon-alpha-2a plus ribavirin with or without amantadine in treatment-naive or relapsing chronic hepatitis C patients. Aliment Pharmacol Ther. 2009;30(4):352–63.
64. Lee SD, Yu ML, Cheng PN, Lai MY, Chao YC, Hwang SJ, et al. Comparison of a 6-month course peginterferon alpha-2b plus ribavirin and interferon alpha-2b plus ribavirin in treating Chinese patients with chronic hepatitis C in Taiwan. J Viral Hepat. 2005;12(3):283–91.
65. Liu CH, Liu CJ, Lin CL, Liang CC, Hsu SJ, Yang SS, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. Clin Infect Dis. 2008;47(10):1260–9.
66. Lodato F, Azzaroli F, Brillanti S, Colecchia A, Tame MR, Montagnani M, et al. Higher doses of peginterferon alpha-2b administered twice weekly improve sustained virological response in difficult-to-treat patients with chronic hepatitis C: results of a pilot randomized study. J Viral Hepat. 2005;12(5):536–42.
67. Marcellin P, Horsmans Y, Nevens F, Grange JD, Bronowicki JP, Vetter D, et al. Phase 2 study of the combination of merimepodib with peginterferon-alpha2b, and ribavirin in nonresponders to previous therapy for chronic hepatitis C. J Hepatol. 2007;47(4): 476–83.
68. Marcellin P, Gish RG, Gitlin N, Heise J, Halliman DG, Chun E, et al. Safety and efficacy of viramidine versus ribavirin in ViSER2: randomized, double-blind study in therapy-naive hepatitis C patients. J Hepatol. 2010;52(1):32–8.
69. McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010;362(14):1292–303.
70. Mecenate F, Pellicelli AM, Barbaro G, Romano M, Barlattani A, Mazzoni E, et al. Short versus standard treatment with pegylated interferon alpha-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. BMC Gastroenterol. 2010;10:21.
71. Mendez-Navarro J, Chirino RA, Corey KE, Gorospe EC, Zheng H, Moran S, et al. A randomized controlled trial of double versus triple therapy with amantadine for genotype 1 chronic hepatitis C in Latino patients. Dig Dis Sci. 2010;55(9):2629–35.
72. Meyer-Wyss B, Rich P, Egger H, Helbling B, Mullhaupt B, Rammert C, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 μg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. J Viral Hepat. 2006;13(7):457–65.
73. Napoli N, Giannelli G, Antonaci A, Antonaci S. The use of different peg-interferon alpha-2b regimens plus ribavirin in HCV-1b-infected patients after rapid virological response does not affect the achievement of sustained virological response. J Viral Hepat. 2008;15(4):300–4.
74. Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. Hepatology. 2007;46(6):1688–94.
75. Roberts SK, Weltman MD, Crawford DH, McCaughan GW, Sievert W, Cheng WS, et al. Impact of high-dose peginterferon alpha-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology. 2009;50(4):1045–55.
76. Roffi L, Colloredo G, Pioltelli P, Bellati G, Pozzpi M, Parravicini P, et al. Pegylated interferon-alpha2b plus ribavirin: an efficacious and well-tolerated treatment regimen for patients with hepatitis C virus related histologically proven cirrhosis. Antivir Ther. 2008;13(5):663–73.
77. Rossignol JF, Elfert A, El-Gohary Y, Keeffe EB. Improved virologic response in chronic hepatitis C genotype 4 treated with nitazoxanide, peginterferon, and ribavirin. Gastroenterology. 2009;136(3):856–62.
78. Rustgi VK, Lee WM, Lawitz E, Gordon SC, Afdhal N, Poordad F, et al. Merimepodib, pegylated interferon, and ribavirin in genotype 1 chronic hepatitis C pegylated interferon and ribavirin nonresponders. Hepatology. 2009;50(6):1719–26.
79. Sanchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R, et al. Peginterferon-alpha2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. Gastroenterology. 2006;131 (2):451–60.
80. Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. Hepatology. 2007;46(2):371–9.
81. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon alpha-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2007;357(2):124–34.
82. Shiffman ML, Ghany MG, Morgan TR, Wright EC, Everson GT, Lindsay KL, et al. Impact of reducing peginterferon alpha-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. Gastroenterology. 2007;132(1):103–12.
83. Sjogren MH, Sjogren R Jr, Lyons MF, Ryan M, Santoro J, Smith C, et al. Antiviral response of HCV genotype 1 to consensus interferon and ribavirin versus pegylated interferon and ribavirin. Dig Dis Sci. 2007;52(6):1540–7.
84. Sood A, Midha V, Hissar S, Kumar M, Suneetha PV, Bansal M, et al. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. J Gastroenterol Hepatol. 2008;23(2):203–7.

85. Tang KH, Herrmann E, Pachiadakis I, Paulon E, Tatman N, Zeuzem S, et al. Clinical trial: individualized treatment duration for hepatitis C virus genotype 1 with peginterferon-alpha 2a plus ribavirin. Aliment Pharmacol Ther. 2008;27(9):810–9.
86. Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, et al. Eight-week regimen of antiviral combination therapy with peginterferon and ribavirin for patients with chronic hepatitis C with hepatitis C virus genotype 2 and a rapid virological response. Liver Int. 2009;29(1):120–5.
87. von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, et al. Peginterferon-alpha-2a (40 kD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology. 2005;129(2):522–7.
88. von Wagner M, Hofmann WP, Teuber G, Berg T, Goeser T, Spengler U, et al. Placebo-controlled trial of 400 mg amantadine combined with peginterferon alpha-2a and ribavirin for 48 weeks in chronic hepatitis C virus-1 infection. Hepatology. 2008;48(5):1404–11.
89. Yu ML, Dai CY, Lin ZY, Lee LP, Hou NJ, Hsieh MY, et al. A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan. Liver Int. 2006;26(1):73–81.
90. Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut. 2007;56(4):553–9.
91. Yu ML, Dai CY, Huang JF, Chiu CF, Yang YH, Hou NJ, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. Hepatology. 2008;47(6):1884–93.
92. Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, et al. Peginterferon alpha-2a (40 kD) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology. 2004;127(6):1724–32.
93. Zeuzem S, Pawlotsky JM, Lukasiewicz E, von Wagner M, Goulis I, Lurie Y, et al. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. J Hepatol. 2005;43(2):250–7.
94. Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alpha-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. J Hepatol. 2006;44(1):97–103.
95. Zeuzem S, Yoshida EM, Benhamou Y, Pianko S, Bain VG, Shouval D, et al. Albinterferon alpha-2b dosed every two or four weeks in interferon-naive patients with genotype 1 chronic hepatitis C. Hepatology. 2008;48(2):407–17.

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IGF-II Producing Hepatocellular Carcinoma Treated with Sorafenib: Metabolic Complications and a Foresight to Molecular Targeting Therapy to the IGF Signal

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Key Words
IGF-II · Hepatocellular carcinoma · Sorafenib · Metabolic complications · Molecular targeting therapy · IGF signal · Hypoglycemia

Abstract
Hypoglycemia is a rare paraneoplastic manifestation of patients with neoplasms. Hypoglycemia can be induced by several causes, including an aberrant increase of hypoglycemic agents and adrenal insufficiency. Sorafenib is the first agent to demonstrate a survival benefit in the treatment of advanced hepatocellular carcinoma (HCC). This small molecule inhibits serine/threonine kinase RAF in tumor cells and tyrosine kinases VEGFR/PDGFR in tumor vasculature and decreases tumor growth and angiogenesis. In this paper, we report a case of HCC who was treated with sorafenib and showed severe hypoglycemia. This hypoglycemia might be induced by two causes, both adrenal insufficiency as an adverse effect of sorafenib and activation of the insulin-like growth factor (IGF) signal by excessive secretion of incompletely processed precursors of IGF-II. Although the IGF signal is suggested to be involved in aberrant growth of HCC in some cases, there is no other report showing the influence of sorafenib on HCC with active IGF signal. Unfortunately, the effect of sorafenib was limited in the present case. However, emerging drugs that directly inhibit the IGF signal can be expected to be highly effective in the treatment of HCC with hypoglycemia.

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Introduction

Hypoglycemia is a rare but well-known paraneoplastic manifestation of patients with neoplasms, including hepatocellular carcinoma (HCC), which is referred to as non-islet cell tumor-induced hypoglycemia (NICTH) [1]. Excessive secretion of incompletely processed precursors of insulin-like growth factor-II (termed the 'big' IGF-II) has been suggested to cause NICTH. The IGF signal is involved in both glucose metabolism and cellular proliferation [2]. The 'big' IGF-II excessively stimulates both IGF-I and the insulin receptor, inducing hypoglycemia and tumor growth. In the era of molecular-targeted therapy, agents targeting the IGF signal are being developed to treat lung and pancreatic cancers [3]. Although this signal is suggested to be involved in aberrant growth of HCC [4], clinical trials using these agents against HCC have been initiated only recently.

Sorafenib is the first agent to demonstrate a survival benefit in the treatment of advanced HCC [5]. This small molecule inhibits serine/threonine kinase RAF in tumor cells and tyrosine kinases vascular endothelial growth factor receptor (VEGFR)/platelet-derived growth factor receptor (PDGFR) in the tumor vasculature, decreasing tumor growth and angiogenesis.

In this paper, we report a case of HCC that showed severe hypoglycemia and was treated with sorafenib. Since RAF is one of the downstream components of the IGF signal, sorafenib may be effective against tumors with an activated IGF signal. Although the effect was limited in the present case, emerging drugs that directly inhibit the IGF signal can be expected to be highly effective in the treatment of HCC with NICTH.

Case Report

A 77-year-old male patient with HCC was referred to the authors' hospital. As he had no previous episodes of liver disorders, no imaging procedures had been performed. In February 2010, he was first admitted to another hospital due to bleeding gastric ulcers induced by non-steroidal anti-inflammatory drugs. During hospitalization, an abdominal CT scan showed multiple liver tumors and multiple lung nodules (fig. 1a, b). Based on elevated serum AFP (897 ng/ml) and typical CT scan images as HCC, he was diagnosed as advanced HCC and referred to our hospital in March 2010.

Administration of sorafenib was initiated at a dosage of 800 mg b.i.d. On day 7, pleural effusion was detected and his serum potassium concentration was elevated to 5.5 mEq/l. His general condition declined and he was unable to stand by day 11. On day 14, he was hospitalized because of hyperpotassemia (6.7 mEq/l) and hypoglycemia (27 mg/dl). Hyperpotassemia improved by the administration of an intravenous drip infusion of glucose and furosemide, but hypoglycemia continued at a level of 40 mg/dl. Although the basal levels of adrenal hormones were normal, ACTH and cortisol did not increase at the time of hypoglycemia. This suggested that the relative adrenal insufficiency exerted some influence on the hypoglycemia. We started to administer a short-acting corticosteroid (hydrocortone), and the blood glucose level increased rapidly to around 150 mg/dl.

However, several days later, the patient's morning fasting blood glucose level decreased to around 20 mg/dl. We administrated a longer-acting corticosteroid and the patient also began to have late evening snacks. Although a sufficient amount of cortisol (prednisolone 10 mg/day) was administered, his hypoglycemia continued. We suspected that other factors were involved in the hypoglycemia, but the serum levels of insulin and IGF-I were lower than the normal limits. We assayed the patient's serum using immunoblotting with an anti-IGF-II antibody. The 'big' IGF-II was detected in the serum (fig. 2, lane 2) similarly to the serum of a patient with NICTH (lane 4). Only mature IGF-II was detected in the serum of the normal control (lane 3). Lane 1 was recombinant IGF-II.

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By day 14 of sorafenib administration, though the number of lung metastases had increased (fig. 1d), the size of the liver tumors had not changed (fig. 1c) and the tumor marker levels had decreased (AFP from 4,112 to 2,381 ng/ml and PIVKA-II from 4,645 to 952 mAU/ml) (fig. 3). We concluded that sorafenib was effective. The dose of sorafenib was decreased to half (400 mg b.i.d.), and the patient was discharged. Ten days later, he was hospitalized because of unconsciousness caused by hypoglycemia. Though the hypoglycemia improved with treatments, sadly the patient died 6 days later of respiratory failure due to advanced lung metastases.

Discussion

We treated a case of IGF-II producing HCC with sorafenib. Several previous reports have shown NICTH as a rare paraneoplastic manifestation of advanced HCC with a poor prognosis [6]. As far as we are aware, there are no reports describing HCC with NICTH treated with this novel molecular targeted agent, sorafenib. The present case showed interesting endocrine abnormalities such as hypoglycemia and hyperpotassemia due to relative adrenal insufficiency. The possibility that sorafenib suppressed adrenal function must be considered, since there were no other factors known to affect adrenal function such as metastasis to the adrenal glands. No reports have been identified that describe adrenal insufficiency due to sorafenib, while the drug is reported to affect thyroid functions. The possibility that sorafenib played a role in adrenal insufficiency is also supported by the fact that there are some reports of adrenal dysfunction caused by a similar molecular agent, sunitinib, targeting VEGFR/PDGFR [7].

The IGF signal is related to cell proliferation and tumor growth of HCC through the IGF-I receptor [4]. Kaseb et al. [8] reported that lower plasma IGF-I levels are correlated with advanced HCC and poor overall survival. Reactivation of IGF-II, including the 'big' IGF-II, is one of the most frequent mechanisms of IGF signal activation in HCC. Expression of IGF-I may be suppressed by a negative feedback of IGF-II overexpression, resulting in lower plasma IGF-I levels.

The 'big' IGF-II is suggested to induce hypoglycemia through IGF-I and the insulin receptor. Usually, hypoglycemia due to the 'big' IGF-II is not controllable with continuous infusion of glucose. Reduction of tumor volume by surgical operation [9], transarterial chemoembolization or systemic chemotherapy [1] is sometimes effective. Palliative treatments, including administration of hyperglycemic hormones such as corticosteroids and growth hormones, are performed, but the effects are transient and limited.

When the IGF-I receptor is stimulated, the downstream signaling pathways, including PI3K-AKT-TOR and RAF-MEK-ERK, are activated [2]. Sorafenib inhibits the activation of RAF. However, the efficacy of sorafenib was limited in the present case (fig. 3). Several drugs that target the IGF signal are under development [3]. Such drugs directly inhibit intracellular kinase activities or block the binding of IGF to the receptors. We suggest that these agents will likely be effective in NICTH cases. In particular, use of antibodies against IGF-II will probably be selective and safe in such cases.

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Disclosure Statement

The authors have no competing interests to disclose.

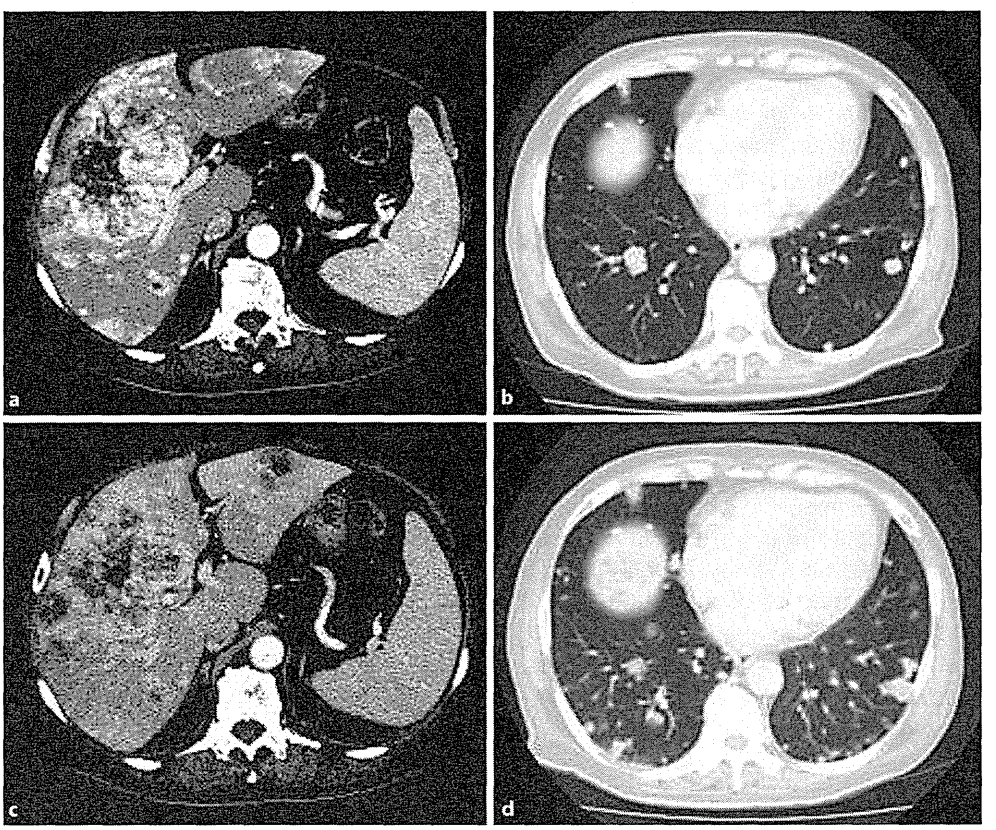

Fig. 1. CT scan images before and after the administration of sorafenib. **a**, **b** Images before therapy. **c**, **d** Images after therapy. By the administration of sorafenib, the size of the liver tumors had not changed (**a** to **c**), but the number of lung metastases had increased (**b** to **d**).

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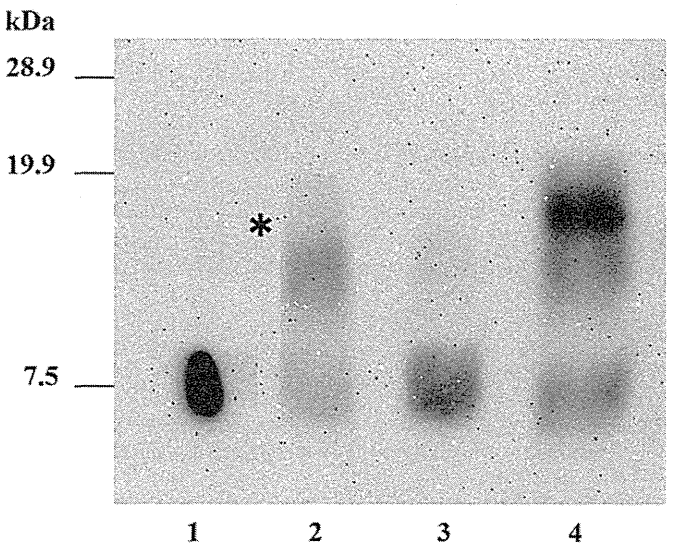

Fig. 2. Immunoblotting images of the patient's serum with an anti-IGF-II antibody. The 'big' IGF-II was detected in the patient's serum (lane 2, asterisk) similarly to the serum of a patient with NICTH (lane 4). Only mature IGF-II was detected in the serum of the normal control (lane 3). Lane 1 is recombinant IGF-II.

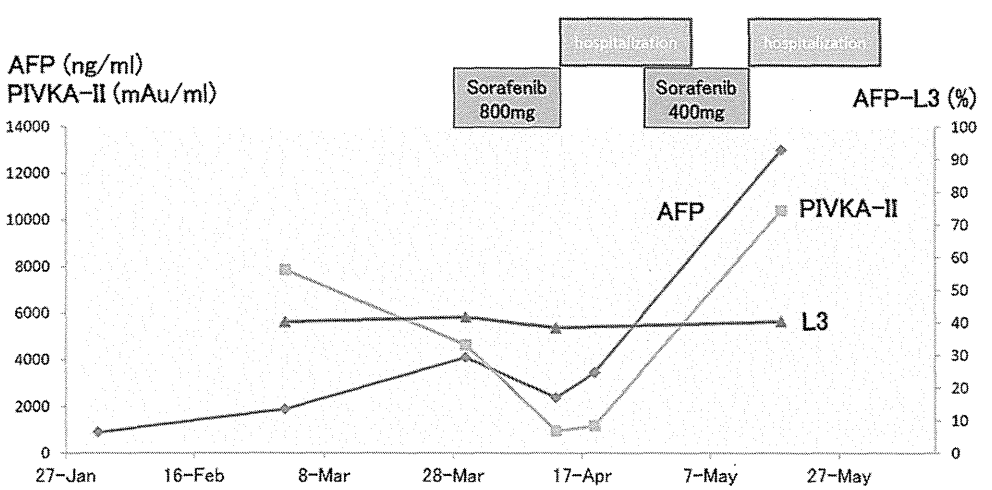

Fig. 3. Changes in the tumor marker levels before and after the administration of sorafenib. By day 14 of sorafenib administration, the tumor marker levels had decreased (AFP from 4,112 to 2,381 ng/ml and PIVKA-II from 4,645 to 952 mAU/ml). However, the effects were transient and the tumor marker levels increased again in spite of the administration of sorafenib.

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References

1 de Groot JW, Rikhof B, Van Doorn J, Bilo HJ, Alleman MA, Honkoop AH, Van Der Graaf WT: Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. Endocr Relat Cancer 2007;14:979–993.

2 Pollak M: Insulin, insulin-like growth factors and neoplasia. Best Pract Res Clin Endocrinol Metab 2008;22:625–638.

3 Gualberto A, Pollak M: Emerging role of insulin-like growth factor receptor inhibitors in oncology: early clinical trial results and future directions. Oncogene 2009;28:3009–3021.

4 Scharf JG, Dombrowski F, Ramadori G: The IGF axis and hepatocarcinogenesis. Mol Pathol 2001;54: 138–144.

5 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.

6 Fukuda I, Hizuka N, Ishikawa Y, Yasumoto K, Murakami Y, Sata A, Morita J, Kurimoto M, Okubo Y, Takano K: Clinical features of insulin-like growth factor-II producing non-islet-cell tumor hypoglycemia. Growth Horm IGF Res 2006;16:211–216.

7 Rock EP, Goodman V, Jiang JX, Mahjoob K, Verbois SL, Morse D, Dagher R, Justice R, Pazdur R: Food and Drug Administration drug approval summary: Sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. Oncologist 2007;12:107–113.

8 Kaseb AO, Morris JS, Hassan MM, Siddiqui AM, Lin E, Xiao L, Abdalla EK, Vauthey JN, Aloia TA, Krishnan S, Abbruzzese JL: Clinical and prognostic implications of plasma insulin-like growth factor-1 and vascular endothelial growth factor in patients with hepatocellular carcinoma. J Clin Oncol 2011;29: 3892–3899.

9 Renard E, Langbour-Remy C, Klein M, Le Bouc Y, Weryha G, Cuny T: Severe hypoglycemia with 'Big'-IGF-2 oversecretion by a giant phyllode tumor of the breast: a rare case of non-islet cell tumor-induced hypoglycemia (NICTH). Ann Endocrinol 2012;73:488–491.

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ORIGINAL ARTICLE

Chronic hepatitis B in patients coinfected with human immunodeficiency virus in Japan: a retrospective multicenter analysis

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Abstract A nationwide survey in Japan revealed that about 6 % of human immunodeficiency virus (HIV)-positive patients are coinfected with hepatitis B virus (HBV). To further analyze the features of liver disease in HIV/HBV-coinfected patients, we analyzed 252 patients from six hospitals in the HIV/AIDS (acquired immunodeficiency syndrome) Network of Japan. The mean age was 39.5 years, and the proportion of male patients was very high (243 of 252; 96 %). The main transmission route was male homosexual contact (186 of 252; 74 %), followed by heterosexual contact. The HBV genotype was determined in 77 patients. Among them, genotype A HBV was the most frequent (58 of 77; 75 %) and was detected almost exclusively in homosexual patients. Acute hepatitis B was documented in 21 patients (8 %). Three of the 252 HIV/HBV-coinfected patients developed advanced liver disease with the complication of ascites, hepatic encephalopathy, or hepatocellular carcinoma. A comparison between patients not treated and those treated with antiretroviral drugs including anti-HBV drugs revealed that the baseline liver function was worse in treated patients. However, the serum albumin levels and platelet counts in both groups increased after treatment and were similar. Liver disease-associated death was not observed. Here, we characterize the clinical features of liver disease in HIV/HBV-coinfected patients in Japan for the first time. The findings suggest that antiretroviral therapy with anti-HBV drugs may retard the progression of a liver disease and prevent liver disease-associated death in such patients.

Keywords Acquired immunodeficiency syndrome · Chronic liver disease · HBV DNA · Genotype

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Introduction

The number of human immunodeficiency virus (HIV)-positive patients is growing in Japan [1]. Although combination therapy with antiretroviral agents has made HIV infection itself somewhat controllable in many cases since its introduction in 1996, and mortality from opportunistic infection has decreased, existing comorbidities are the focus of current patient care. In fact, more than 50 % of deaths in HIV-1-infected patients are not related to acquired immunodeficiency syndrome (AIDS); the mortality from liver disease is second only to AIDS-related mortality [2]. Risk factors related to significant liver

diseases among HIV-positive patients include a diagnosis of viral hepatitis [3], nonalcoholic fatty liver disease [4], and excessive alcohol consumption [5]. Among these factors, hepatitis B and hepatitis C are of particular importance because they can often lead to life-threatening diseases such as cirrhosis and hepatocellular carcinoma by themselves.

The estimated prevalence of chronic hepatitis B virus (HBV) infection in Japan is less than 1 %, or 0.9 million carriers [6]. However, about 6 % of HIV-positive patients are coinfected with HBV [7]; this coinfection rate is more than six times higher than that in the non-HIV population. In the United States, the HIV/HBV coinfection rate is reported to be in the range of 6–14 % [8–10].

Several issues make the management of HIV/HBV coinfection complicated. HBV infection tends to be persistent in HIV-positive patients [9, 11, 12]. Chronic HBV infection may lead to hepatitis, cirrhosis, or hepatocellular carcinoma. The progression of a liver disease associated with chronic HBV infection is more rapid in HIV/HBV-coinfected patients than in HBV-monoinfected patients [13].

Combination regimens of antiretroviral therapy (ART) for coinfected patients should be carefully determined. Initial combination regimens of ART for HIV/hepatitis C virus (HCV)-coinfected patients are basically the same as those for HIV patients without HCV infection. However, because some nucleoside reverse transcriptase inhibitors (NRTIs) used in HIV treatment have activity against HBV, and some NRTIs mainly used in HBV treatment have partial activity against HIV [14], careful choice of treatment agents is necessary in HIV/HBV coinfection. Abrupt discontinuation of NRTIs that are active against HBV may aggravate viral hepatitis. Administration of entecavir, which has a weak activity against HIV, to HIV/HBV-coinfected patients without simultaneous effective HIV treatment may cause the accumulation of drug-resistant HIV strains [15–17]. In such cases, drug resistance of HBV may occur as well [18].

Drug-induced liver injury following ART is another concern. HIV/HBV-coinfected patients show an increase in transaminase level at a higher rate [19, 20]. However, it is often unclear whether this increase is caused by drug hepatotoxicity because the treatment of HIV infection causes immune reconstruction in patients, which alone could contribute to the transaminase level increase in viral hepatitis.

The objective of this study is to clarify the clinical features of HIV/HBV coinfection in Japan and to clarify the impact of ART on liver function among HIV/HBV-coinfected patients. The estimated prevalence of chronic HBV infection among the general population in Japan is decreasing yearly, but it remains much higher than that in the United States [21], where universal hepatitis B vaccination is introduced. Thus, the detailed analysis of HIV/HBV coinfection in Japan is of particular importance.

Patients and methods

We have conducted a multicenter retrospective study based on the data from a nationwide survey in 2006 conducted by sending questionnaires to 372 member hospitals of the HIV/AIDS network of Japan as of January 2006, and part of the results was reported earlier [7]. Following the survey, 6 of the 207 hospitals that responded to the survey—Hokkaido University Hospital (Hokkaido, Japan), University of Tokyo Hospital (Tokyo, Japan), Nagoya University Hospital (Aichi, Japan), International Medical Center of Japan (currently, National Center for Global Health and Medicine, Tokyo, Japan), Osaka National Hospital (Osaka, Japan), and Hiroshima University Hospital (Hiroshima, Japan)—were chosen for further studies because more than two-thirds of the HIV/HBV-coinfected patients identified in the survey went to these hospitals, and because both HIV experts and hepatologists were following up those patients there.

The questionnaire sent to the hospitals included items regarding the number of patients who visited the hospitals at least once between January and December in 2006 as follows: (1) the number of HIV-positive patients; (2) the number of hepatitis B surface antigen (HBsAg)-positive patients among (1); (3) the number of patients among (2) who were determined at least once to have a serum alanine aminotransferase (ALT) level higher than 100 IU/l; (4) the number of HIV-positive patients who contracted HIV from blood products; (5) the number of HBsAg-positive patients among (4); (6) the number of patients among (5) who were determined at least once to have a serum ALT level higher than 100 IU/l; (7) the number of HIV-positive patients whose presumed transmission route is through homosexual contact; (8) the number of HBsAg-positive patients among (7); (9) the number of patients among (8) who were determined at least once to have a serum ALT level higher than 100 IU/l; (10) the number of HIV-positive patients who presumably contracted HIV through injection drug use; (11) the number of HBsAg-positive patients among (10); (12) the number of patients among (11) who were determined at least once to have a serum ALT level higher than 100 IU/l; (13) the number of HIV-positive patients whose transmission routes were classified as "others"; (14) the number of HBsAg-positive patients among (13); and (15) the number of patients among (15) who were determined at least once to have a serum ALT level higher than 100 IU/l.

We defined confirmed HIV infection with positivity for serum HBsAg as the criterion for HIV/HBV coinfection.

After identifying HIV/HBV-coinfected patients, medical records including laboratory data of these patients were reviewed between the date of the oldest available record for these patients and the final date of the record acquired by the end of the study. The laboratory data at the diagnosis or first recognition of HBV infection and the latest data in the study period were compared for analysis unless otherwise noted. HBV genotypes (A through D) were determined serologically by enzyme immunoassay (EIA) using commercial kits (HBV GENOTYPE EIA; Institute of Immunology, Tokyo, Japan) on the basis of the pattern of detection using monoclonal antibodies of a combination of epitopes on preS2-region products, each of which was specific for each genotype [22, 23].

Ethical issues

The respective ethics committees of the six hospitals approved the study. Informed consent was obtained from each study participant.

Statistical analyses

For the comparison of means of collected data, Student's *t* test (paired *t* test) was performed unless otherwise specified. The chi-square test was performed to determine the independence of clinical parameters.

Results

Two hundred and fifty-two patients were identified to have HIV/HBV coinfection. The mean age was 39.5 years, and the proportion of male patients was very high (243 of 252; 96.4 %). The main presumed transmission route of HIV was male homosexual contact (186 of 252; 73.8 %), followed by heterosexual contact. Among those HIV/HBV-coinfected patients, 21 of the 252 (8.3 %) acquired acute hepatitis during the study period (Table 1).

Table 1 Clinical background of HIV/HBV-coinfected patients

Number (male:female)	243:9
Age (year)	39.5 ± 9.6[a]
Presumed Transmission Route	
Transfusion	14
Homosexual contact	186
Heterosexual contact	24
Injection drug use	2
Others	4
Onset as acute hepatitis	21

[a] Mean ± standard deviation

The HBV genotype was determined in 77 patients. Among them, genotype A HBV was the most frequent (58 of 77; 75.3 %), followed far behind by genotype C (7 of 77; 9.1 %), which is the predominant genotype in the entire chronic hepatitis B population in Japan. Genotype B, which is also common in Japan, was found only in three patients (3.9 %). Genotype A was detected almost exclusively in homosexual patients (57 of 58; 98.3 %) (Fig. 1).

At the end of the study period, 113 patients (44.8 %) received some type of anti-HBV drug such as interferon, lamivudine, adefovir, or entecavir, not as part of anti-HIV treatment. Ninety-seven (38.5 %) patients were still taking anti-HBV drugs by the end of the study period. The median ALT level was 30.0 IU/l (5th percentile, 11.1; 95th percentile, 128.9), suggesting the existence of some liver injury. Liver function was normal in most HIV/HBV-coinfected patients. The mean serum albumin level was 4.1 ± 0.6 g/dl, and the median serum total bilirubin level was 0.8 mg/dl (5th percentile, 0.3; 95th percentile, 3.8). The mean platelet count was 21.0 ± 6.1 × 10^4/ml. The hepatitis B e antigen (HBeAg) was detected in 84 patients, and the HBV DNA level was high (higher than 100,000 IU/l) in 55 patients (Table 2). Three of the 252 (1.1 %) HIV/HBV-coinfected patients developed advanced chronic liver diseases, such as cirrhosis with the complication of ascites and/or hepatic encephalopathy, or hepatocellular carcinoma. Although we tried to retrieve information on alcohol consumption of the patients, it was available for only a limited number of patients (26 of 252); among the 26, only 2 patients had a habit of taking more than 60 g alcohol per day. The remaining 24 patients took alcohol only on social occasions. The antiretroviral agents used for these study patients are listed in detail in Table 3. Among those who had a known history of ART, 158 of 252 (62.7 %) received regimens that include anti-HBV drugs at least once previously, whereas 42 (16.7 %) did not, and no information is available for the remaining 52. The most common drug combination for HIV/HBV-coinfected patients was ATV/r + FTC/TDF (22 of 172; 12.8 %) (Table 4). FTC/TDF, composed of two drugs active against HBV, is recommended for HIV/HBV-coinfected patients

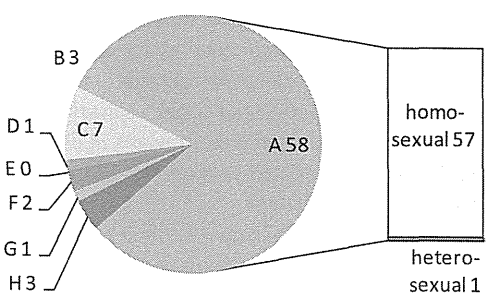

Fig. 1 Hepatitis B virus (HBV) genotype

Table 2 Liver function and related parameters of HIV/HBV-coinfected patients

Albumin (g/dl)	4.1 ± 0.6
Bilirubin[a] (mg/dl)	0.8 (5th percentile, 0.3; 95th percentile, 3.8)
ALT[a] (IU/l)	30.0 (5th percentile, 11.1; 95th percentile, 128.9)
WBC ($\times 10^3/\mu l$)	5.2 ± 1.6
Platelet ($\times 10^4/\mu l$)	21.0 ± 6.1
HBeAg (positive:negative)	84:68
HBV DNA (high:low)[b]	55:127

[a] Median and percentiles are provided instead of mean and standard deviation because of the nonnormality of the distribution

[b] HBV DNA level of 100,000 IU/l or higher is categorized as "high"

as one of the preferred NRTI backbones of the ART regimen [24].

We compared the clinical characteristics between patients who received the full ART and those who did not. Regarding the baseline statistical data, the observation period was longer for patients on ART, and there were more patients with AIDS in the ART group (10 of 64 vs. 52 of 162) (Table 5a). No significant difference was observed between the non-ART and ART groups in male/female ratio, age, transmission route, HBV markers, or advanced liver disease. Liver-related death was not observed, but hepatic failure with ascites and/or hepatic encephalopathy developed in 2 patients on ART and hepatocellular carcinoma developed in another patient.

Comparison between the ART group and the non-ART group revealed that the baseline liver function was worse in the ART group. At the beginning of the study period, the ART group showed a significantly lower CD4+ T-cell count than the non-ART group. The total white blood cell count and platelet count were also lower in the ART group. Although it is not statistically significant, the serum albumin level and prothrombin time (PT) index were lower in the ART group. However, at the end of the observation period, these parameters improved significantly in the ART group. The difference in CD4+ T-cell count between the ART and non-ART groups became marginal and became statistically insignificant (Table 5b).

Changes in the liver function of HIV/HBV-coinfected patients may not be fully explained by the changes in HBV activity because some parameters relevant to the estimation of liver function showed paradoxical changes. To clarify this observation, we compared the changes in liver function among HIV/HBV-coinfected patients on ART with respect to protease inhibitor (PI) use.

The mean serum total bilirubin level in patients on ART with PI use (PI group) at the beginning of the observation period was 1.1 mg/dl, whereas that in patients without PI use (non-PI group) was 0.8 mg/dl. The means at the end of the study period were 1.6 mg/dl in the PI group and 0.7 mg/dl in the non-PI group. Because the sample distribution of serum total bilirubin level did not follow the normal distribution by logarithmic transformation, we compared the means statistically. At the beginning, the difference in the mean between the PI group and the non-PI group was not significant ($p = 0.257$). At the end of the observation period, a statistically significant difference ($p = 0.001$) was observed. We then calculated the

Table 3 Antiretroviral treatment of HIV/HBV-coinfected patients

Antiretroviral drugs	Number of patients
NRTIs	
Zidovudine (AZT)	34
Didanosine (ddI)	9
Ddl / enteric coated	7
Zalcitabine (ddC)	1
Stavudine (d4T)	4
Lamivudine[a] (3TC)	84
Abacavir[3] (ABC)	38
Tenofovir[3] (TDF)	27
Emtricitabine (FTC) / TDF[a]	57
NNRTIs	
Nevirapine (NVP)	10
Efavirenz (EFV)	34
Delavirdine (DLV)	1
PIs	
Indinavir (IDV)	4
Ritonavir (RTV)	50
Nelfinavir (NFV)	8
Lopinavir (LPV)	3
Ritonavir-boosted LPV (LPV/r)	40
Atazanavir (ATV)	39
ATV/r	6
Fosamprenavir (FPV)	13

NRTI nucleoside reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor

[a] Agents with anti-HBV activity

Table 4 Antiretroviral regimens used for HIV/HBV-coinfected patients

Antiretroviral regimen	Number of patients
ATV/r + FTC/TDF	22
LPV/r + 3TC + TDF	8
LPV/r + FTC/TDF	7
EFV + FTC/TDF	6
ATV/r + 3TC + TDF	5

Table 5 Comparison of changes in clinical parameters of HIV/HBV-coinfected patients with or without antiretroviral therapy (ART)

a. Baseline statistical data	Natural course[a] (without ART)	With ART	*p* value (with vs. without ART)
Number (male:female)	84:6	159:3	0.105†
Age (year)	37.0 ± 10.3	39.0 ± 9.1	0.362
Observation period (month)	34.5 ± 55.5	50.9 ± 43.9	0.022*
Presumed transmission route	Blood products:homosexual contact:heterosexual contact:injection drug use:other		
	5:60:12:2:3	9:126:12:0:1	0.052†
Recognized acute hepatitis	10	11	0.243†
HBeAg (positive:negative)	42:18	100:40	0.394†
HBV DNA (high:low)	29:18	83:37	0.356†
HBV genotype	A:B:C:D:F:G:H		
	17:0:1:1:1:0:1	31:3:6:0:1:1:2	0.372†
Ascites	1/56	2/144	1.000†
Hepatocellular carcinoma	0/62	1/159	1.000†
Acquired immunodeficiency syndrome (AIDS)	10/64	52/162	0.012*,†

b. Comparison of clinical parameters between pre- and post-ART among patients with and without ART	Natural course (without ART)	With ART	*p* value (with vs. without ART)
CD4 count (per μl)			
Start[b]	402.9 ± 180.1	242.5 ± 187.6	0.000*
End[c]	406.4 ± 212.4	398.1 ± 195.9	0.883
p value (start vs. end)	0.893	0.000*	
Albumin (g/dl)			
Start	4.1 ± 0.4	3.8 ± 0.8	0.292
End	3.9 ± 0.8	4.2 ± 0.4	0.025*
p value	0.473	0.001*	
Bilirubin[d] (mg/dl)			
Start	0.7 (0.30, 4.26)	0.5 (0.30, 2.62)	0.138
End	0.5 (0.25, 1.30)	0.9 (0.36, 4.32)	0.000*
p value	0.046*	0.000*	
ALT[d] (IU/l)			
Start	46.0 (15.0, 1418.2)	34.0 (12.8, 1,068.8)	0.120
End	27.0 (9.9, 229.9)	31.5 (12.73, 89.3)	0.713
p value	0.003*	0.000*	
Prothrombin time index (%)			
Start	89.4 ± 13.1	78.8 ± 23.0	0.650
End	78.8 ± 27.3	84.2 ± 16.3	0.531
p value	0.377	0.218	
WBC ($\times 10^3/\mu l$)			
Start	6.1 ± 2.4	4.8 ± 2.1	0.000*
End	5.4 ± 1.4	5.1 ± 1.6	0.404
p value	0.044*	0.247	
Platelet ($\times 10^4$ /μl)			
Start	22.2 ± 6.5	19.3 ± 6.3	0.010*
End	21.2 ± 6.5	20.8 ± 6.1	0.649
p value	0.204	0.001*	

* $p < 0.05$

† Chi-square test was performed

[a] Two patients with habitual alcohol intake were included in this group

[b] Start of observation period

[c] End of observation period

[d] Means were compared by log transformation because of the nonnormality of the distribution; median and percentiles (5th percentile, 95th percentile) are provided