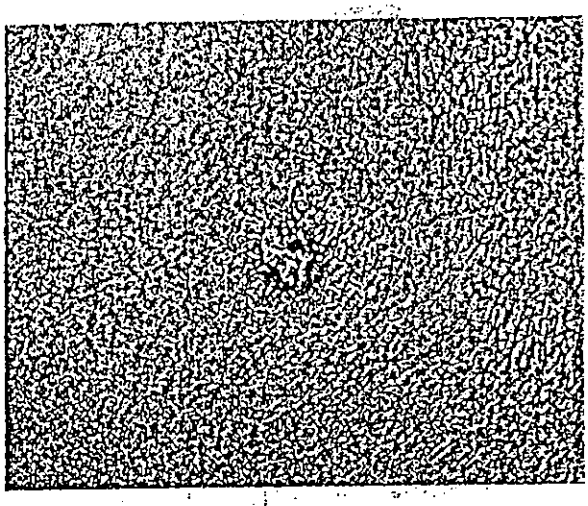

Figure 3. Cutaneous lichen planus of the legs and arms 6 months after stopping administration of interferon and ribavirin as shown in Fig. 5D.

treatment, but aggravation began at the beginning of the 8th week of administration. Hence, after 18 weeks and 4 days (on August 25), IFN and ribavirin were stopped completely because of aggravation of the OLP (Fig. 2). His oral pain and hemorrhagic crusts on the lower lip became severe and impaired his intake of food. A steroid for external use (Salcoat®) and gargles with an enzyme drug (Elase®) were used to treat the site showing severe inflammation. We also instructed him in tooth brushing. Elevated aminotransferase levels returned to normal during IFN and ribavirin therapy, then and serum HCV RNA disappeared. But during the 7th week after the discontinuation, aminotransferase levels increased to 10 times the normal range and the level of serum HCV RNA rose to 354 kIU/ml (on January 13, 2004). The patient then received the medication for his liver disease other than IFN treatment, such as glycyrrhizin (Stronger Neo-Minophagen C®) and ursodeoxycholic acid (Urso®) as conservative (anti-inflammatory) therapy, and his elevated aminotransferase levels decreased, but serum HCV RNA became positive. Papules of CLP with pruritic violaceous papules developed on the skin of his arms, legs, and trunk at the beginning of February 2004, and treatment of CLP was started (Fig. 3). At this writing, eight months have passed since IFN and ribavirin therapy were discontinued, and the erosion of OLP has reduced gradually. The pain has relieved, but the erosion of the lower lip remains (Fig. 4). The leukoplakia of the vocal cord was resected under general anesthesia on May 6, 2004. Fig. 5 illustrates the results of liver function tests and the clinical course of the patient.

Discussion

Many studies have shown that IFN results in biochemical improvement, viral suppression, histologic improvement, regression of fibrosis and reduced incidence of HCC (24,25). Moreover, therapy with IFN and ribavirin for patients with chronic hepatitis C is more effective than IFN alone in inducing virologic and histologic improvement (26).

On the other hand, it is well known that HCV induces not only chronic liver diseases but also extrahepatic manifestations (5,6). Subsequently, it has been reported that therapeutic effects of IFN alone or IFN plus ribavirin have also been confirmed in the treatment of extrahepatic lesions such as membranoproliferative glomerulonephritis (27), cryoglobulinemia (28), and porphyria cutanea tarda (29). With regard to the effects of IFN therapy on the LP lesion, one of the extrahepatic manifestations, there are reports of improvement in LP lesions (8,9), reports of LP manifestations triggered by IFN (10-18), and reports of aggravation of LP (19,20). Recently, Harden *et al* reported 5 cases (4 with CLP, 1 with CLP and OLP) that were treated with IFNα and ribavirin for chronic hepatitis C (22). The authors reported that 3 patients who became HCV negative as a result of therapy of with IFNα and ribavirin after 4 weeks showed improvement in their LP. In the remaining two patients the eruption worsened initially, but improved later, near the end of therapy, and one of these patients was a non-responder. However, the clinical course of CLP or OLP and the details about the inflammation of chronic hepatitis are unknown because long follow-up on the 5 patients was not carried out. We observed long-term histologic changes in Japanese patients with OLP and chronic hepatitis C (21). Over 3 years or longer, some OLP lesions (all reticular types) were improved, not only macroscopically, but also on histo-

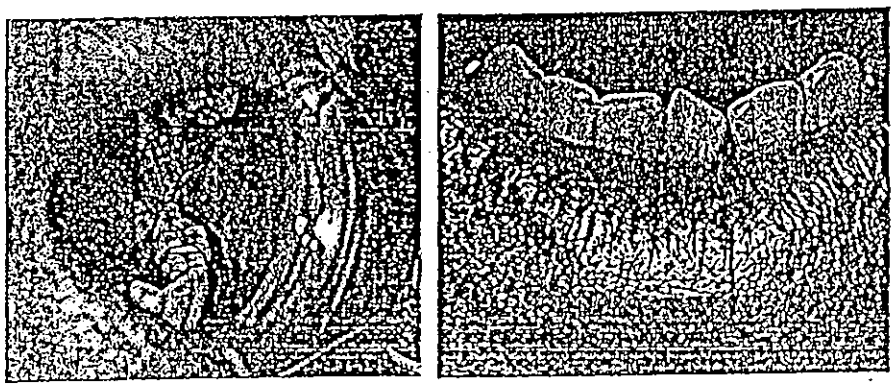

Figure 4. Lichen planus of the buccal mucosa and lip at the 7 months after stopping the administration of interferon and ribavirin as shown in Fig. 5C. Exacerbation of the oral erosion was reduced gradually.

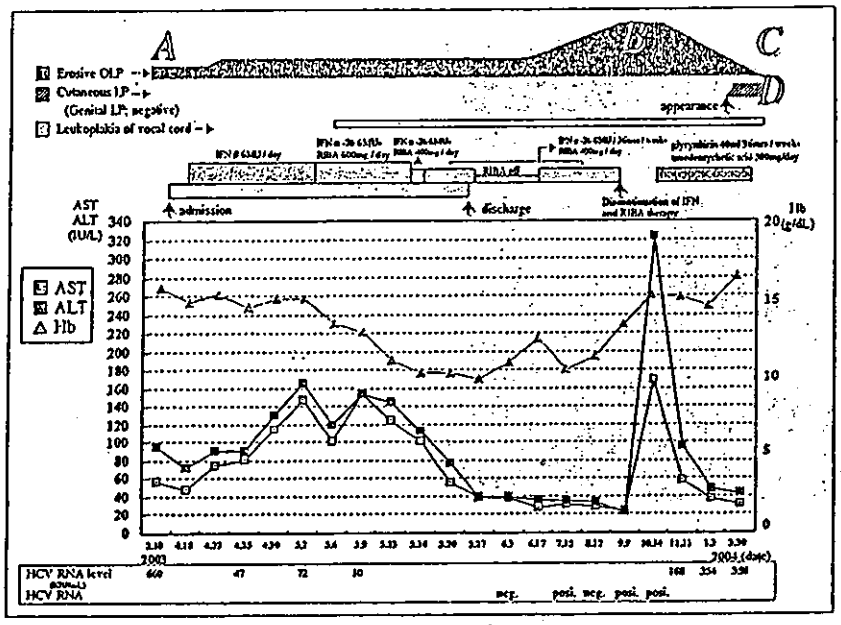

Figure 5. Clinical course of the patient. The photograph at point A shows oral lichen planus (OLP) before administration of interferon and ribavirin therapy (Fig. 1). The photograph at point B shows exacerbation of OLP during the therapy (Fig. 2). The photograph at point C shows reduced OLP after discontinuation of the therapy (Fig. 4). The photograph at point D shows the appearance of cutaneous lichen planus after discontinuation of therapy (Fig. 3).

pathologic examination. This finding resembles a histologic cure that has been confirmed in cases of chronic hepatitis C for which IFN treatment is markedly effective. The ability of IFN to eradicate HCV and improve liver damage may contribute to the improvement of OLP because histologic improvement of OLP was observed in our cases of OLP with chronic hepatitis C (21).

Dalekos *et al* prospectively evaluated dermatological side-effects during IFN therapy for chronic hepatitis B or C (15). Their study, which was done in northwestern Greece, demonstrated that IFNα only rarely (3.3%) induces immune-mediated dermatological disorders, especially LP in patients with chronic viral hepatitis. The authors reported that the development of these disorders may reflect a subclinical or covert autoimmune background of the patients. In our observations of oral lesions made before, during and after IFN treatment, OLP occurred in 16.7% (4/24 patients) of Japanese subjects (13). Some OLP lesions that appeared during IFN treatment and were aggravated temporarily were improved by symptomatic therapy, so that IFN treatment was continued. Two had OLP before treatment, 1 during treatment and 1 after treatment. Oral leukoplakia was seen in 4 patients before treatment and oral cancer in one patient 6 months after completing treatment (30).

In general, it is has been reported that caution should be exercised when IFN therapy is applied to chronic hepatitis C patients with prior OLP manifestations (5). It is difficult to predict which HCV cases will show IFN/ribavirin-induced OLP or cutaneous LP. However, caution is required in administering IFN or ribavirin to the HCV carriers who already suffer from LP, especially severe OLP of the erosive type. A close inspection of LP is essential before administering antiviral drugs to HCV carrier patients. When oral or cutaneous symptoms are exacerbated during IFN or ribavirin therapy, even if an oral surgeon or a dermatologist treats OLP or CLP, IFN or ribavirin should be reduced or discontinued immediately.

IFN may induce the expression of previously hidden surface antigens on keratinocytes, similar to the probable mechanism for achieving virus elimination from hepatocytes (19). Prolonged courses of IFN were reported to induce autoantibodies as well as autoimmune disorders (31). Garcia-Buey *et al* reported that 7 female patients developed features of autoimmunity during IFN therapy for chronic hepatitis C, suggesting a triggering by immune-stimulating effects of IFN (31). IFN contributes to the exacerbation of autoimmune phenomenon. HCV infection can be a trigger to an underlying immunologic abnormality that can worsen with IFN immunomodulation.

In conclusion, we report a case of chronic hepatitis C patient with exacerbation of prior erosive OLP, appearance of CLP and leukoplakia by treatment with IFN and ribavirin. The aggressive OLP has gradually diminished after discontinuation of the therapy, aminotransferase levels decreased, but serum HCV RNA levels remained elevated. Aggressive treatment with IFN or with a combination of IFN plus ribavirin for eradication of HCC may increase the chance of complications with various extrahepatic manifestations such as lichen planus. It is therefore important to examine oral membranes and skin before administering IFN or IFN plus ribavirin for patients with HCV infections. Accumulation of a larger study cohort and long-term follow-up is now needed to elucidate the therapeutic effects of IFN therapy on extrahepatic lesions.

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Types of human leukocyte antigen and decrease in HCV core antigen in serum for predicting efficacy of interferon-α in patients with chronic hepatitis C: analysis by a prospective study

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Background. A prospective study was conducted to evaluate the influence of host factors, including human leukocyte antigen (HLA), and viral factors, including hepatitis C virus (HCV) core antigen, on the response to interferon (IFN)-α. ***Methods.*** Natural IFN-α was given to 66 patients with chronic hepatitis C at a dose of 9 million units per day for 2 weeks, followed by 9 million units three times a week for 22 weeks. ***Results.*** Sustained virological response without detectable HCV RNA in serum 24 weeks after the end of IFN therapy was achieved in 21 patients, while it was not in 32 patients; the remaining 13 patients were not evaluated. HCV core antigen and HCV RNA started to decrease 1 and 4 weeks, respectively, after the commencement of IFN in responders ($P = 0.02$ and $P = 0.05$, respectively). On univariate analysis, age of 50 years or less ($P < 0.001$); lack of HLA DR6 ($P = 0.018$) or DR52 ($P < 0.041$); platelets more than $14 \times 10^4/mm^3$ ($P = 0.031$); HCV core antigen 500 fmol/l or less ($P = 0.001$); and HCV RNA 100 KIU/ml or less were predictive of response. On multivariate analysis, age 50 years or less (odds ratio [OR], 4.009; $P = 0.039$); lack of HLA DR6 (OR, 8.130; $P = 0.027$); IFN-naive (OR, 11.63; $P = 0.016$); HCV core antigen 500 fmol/l or less (OR, 10.61; $P = 0.007$); and genotypes other than 1b (OR, 8.929; $P = 0.010$) were predictive of response. ***Conclusions.*** Lack of HLA DR6 determined the response to IFN. HCV core antigen was useful in predicting and monitoring the response to IFN.

Key words: hepatitis C virus, interferon, core antigen, human leukocyte antigen

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Introduction

There are 190 million people estimated to be infected with hepatitis C virus (HCV) in the world,[1] and in Japan alone, 1.5 million are infected with HCV. Persistent HCV infection can induce a spectrum of chronic liver disease, ranging from chronic hepatitis through liver cirrhosis to eventual hepatocellular carcinoma (HCC) during the lifetime.[2] Liver cancers, including HCC and cholangioma, rank as the fourth most frequent malignancy in Japan and cause more than 30 000 deaths annually, and by far the greatest majority of liver cancers (>95%) are HCC.[3] In the individuals infected with HCV, it is necessary to diagnose chronic hepatitis and treat them without delay, in order to prevent the development of HCC.

Interferon (IFN) is the only drug that can clear HCV infection. Not all patients with chronic hepatitis C, however, respond virologically, with the loss of HCV RNA from serum, and/or biochemically, with the normalization of alanine aminotransferase (ALT) levels in serum. A number of factors have been reported to influence the response to IFN. They include virological factors, such as HCV genotypes[4–8] and viral load;[4,6,7,9] as well as host factors, such as age,[4,8] sex,[9] pretreatment ALT levels,[8] and fibrosis of the liver.[4,5] Some of these factors are not unanimously agreed upon, while others have not yet been studied enough to be conclusive.

Human leukocyte antigen (HLA) has attracted attention for its possible influence on the response to IFN-α therapy.[10–17] Insofar as HLA is associated with the immune responses of the host, it may modify the pathogenesis of chronic hepatitis C that is mediated by the immunity of the host to HCV.[16,18–20] As such, HLA may influence the response to IFN-α for treatment of chronic hepatitis C. Because previous studies along this line are retrospective and controversial, we conducted a prospective study to evaluate HLA and other host factors to find their influence on response to IFN-α.

Table 1. Comparison of demographic, clinical, and virological characteristics between patients with and without sustained virological response to IFN-α

Features	Responders (n = 21)	Nonresponders (n = 32)	P value
Male	11 (52%)	18 (56%)	0.784
Median age (years)[a]	46 (30–72)	57 (31–66)	0.015
History of blood transfusion	8 (38%)	19 (59%)	0.133
History of IFN treatment	2 (10%)	7 (22%)	0.246
ALT (IU/l)[a]	94 (22–272)	83 (40–355)	0.877
Platelet count ($\times 10^4$/ml)[a]	167 (84–315)	144 (62–320)	0.047
Fibrosis (F1/F2/F3/ND)	11/5/3/0/2	13/11/4/3/1	0.472
HCV genotype (1b/2a or 2b/UC)	6/15/0	22/8/2	0.013
HCV RNA (KIU/ml)[a]	30 (0.5–330)	150 (0.5–850)	0.004
HCV core antigen (fmol/l)[a]	221 (3.0–14426)	3794 (112–19383)	0.001

IFN, interferon; KIU, kilo international units; ND, not determined: UC, unclassifiable
[a]Median value is shown, with the range in parentheses

correction for qualitative data. Fisher's exact test was used for comparison of small numbers. Multivariate analysis was performed using a logistic regression model, with a stepwise method, employing the statistical computer program known as SPSS 6.1J (SPSS, Chicago, IL, USA). Differences were evaluated by two-tailed analysis and considered significant for P values of less than 0.05.

Results

Sustained virological response to IFN-α therapy in patients with chronic hepatitis C

Of the 66 patients with chronic hepatitis C who were eligible for INF-α therapy, 4 dropped out and 9 were withdrawn from treatment. The 4 dropouts included 1 who did not comply with the treatment protocol and 3 who failed to visit hospitals by their own judgments. IFN-α was withdrawn because of a psychiatric condition (depression) in 4 patients, severe general malaise in 2, continuous fever in 1, pain in the neck and upper left arm in 1, and ophthalmagra in 1. Of the 9 patients in whom IFN-α was withdrawn, 3 were sustained virological responders and had completed more than 65% of the total regimen of 720MU. Their HCV genotypes were 1b, 2a, and unclassifiable, respectively.

A reduction of IFN-α dose was necessary in 2 of the 53 patients who completed the 24-week therapy, because of anorexia and fever, respectively. The dose was reduced from 9 to 6MU in the former patient, while 9MU was given twice a week instead of three times a week in the latter. Because these 2 patients had received more than 80% of the total dose of IFN-α, they were included in the study. The 53 patients eligible for the evaluation of virological response had a median age of 56.1 years (range, 30–72 years) and included 29 (55%) men, and 9 of them had been treated with IFN before. Liver biopsies performed before treatment revealed fibrosis of stage F1 in 24 (45%), F2 in 16 (30%), F3 in 7 (13%), and F4 in 3 (6%); liver biopsy was not performed in the remaining 3 (6%) patients.

The HCV genotype was 1 in 28 patients and 2 in 23; genotype was unclassifiable in 2 patients by the EIA genotype method.[25] Genotype 1 in all the 28 patients was found to be 1b by PCR with type-specific primers.[26] Of the 23 patients with genotype 2 determined by EIA, 13 had genotype 2a and 5 had 2b; subtypes of genotype 2 were not distinguishable in the remaining 5 patients. Genotypes in the 2 patients unclassifiable by EIA were not determined by PCR, either. Based on these results, genotypes of HCV were judged to be 1b in 28 (53%) patients, 2a or 2b in 23 (43%) patients, and unclassifiable in the remaining 2 (4%) patients.

Sustained virological response to IFN-α was achieved by 21 (40%) of the 53 patients. Table 1 compares demographic, clinical, and virological characteristics between the 21 responders and 32 nonresponders to IFN-α. Responders were significantly younger and had higher platelet counts than non-responders. Virologically, responders were significantly less frequently infected with HCV genotype 1b and had significantly lower levels of both HCV RNA and HCV core antigen.

HLA types were determined for loci with more than five patients testing positive for them (Table 2). Significant differences were observed only for DR6 and DR52, both of which were more frequency in nonresponders than responders.

Factors influencing the response to IFN-α therapy

The results of univariate analysis for evaluating factors predictive of sustained virological response to IFN-α

Table 4. Multivariate analysis of factors for the association with sustained virological response to IFN-α in 53 patients with chronic hepatitis C

	n	OR	95% CI	*P* value
HCV core antigen				
>500 fmol/l	37	1.000		
≤500 fmol/l	16	10.610	1.924–58.53	0.007
HCV genotype				
1b	28	1.000		
Non-1b	25	8.929	1.681–47.62	0.010
History of IFN treatment				
Present	9	1.000		
Absent	44	11.630	1.570–83.33	0.016
HLA DR6				
Present	19	1.000		
Absent	34	8.130	1.269–52.63	0.027
Age				
>50 Years	35	1.000		
≤50 Years	18	4.009	1.073–15.66	0.039

OR, odds ratio; CI, confidence interval

IFN-α treatment. At the end of follow-up, both HCV core antigen and HCV RNA were negative in all the responders, while they were positive in all the nonresponders.

There were no significant differences in the frequency of elevated ALT levels (>45 IU/l) between responders and nonresponders during IFN-α treatment (Fig. 1c). Elevated ALT levels were observed less frequently in responders than in nonresponders 12 and 24 weeks after the completion of IFN-α treatment. The difference, however, was not clear-cut. There were sustained virological responders who kept elevated ALT levels, while some nonresponders did not possess them.

Discussion

Although IFN clears HCV infection in patients with chronic hepatitis C, sustained virological response is achieved in only 50% of these patients even with the most sophisticated combination therapy with pegylated IFN and ribavirin.[29] It remains difficult to treat patients who are infected with HCV genotype 1b with a high viral load. Because IFN can induce grave side effects, such as autoimmune thyroiditis and severe depression, patients who would be likely to respond need to be identified beforehand, to spare nonresponders unfruitful side effects. Many host and viral factors have been proposed to be predictive of the response to IFN.[4-9] Only a few of them, however, were evaluated in prospective studies.

In the present prospective study, various host and viral factors were evaluated as predictors of sustained virological response, focusing on HLA types and HCV core antigen. These factors were chosen because no agreement has been reached on the association of HLA types with the response to IFN,[10-17] and the determination of HCV core antigen by EIA is very handy and less expensive than PCR for testing HCV RNA.[21,22] In previous studies, there were many patients with low pretreatment viral loads, disproportional to the number of patients with chronic hepatitis C who receive IFN therapy. Patients with low baseline viral loads might have tended to be registered more frequently in studies than those with higher loads, because of a better response to IFN.

HLA DR6 and DR52 were predictive of the virological response by univariate analyses performed in 21 responders and 32 nonresponders to natural IFN-α who had a total dose of 720 MU. By multivariate analysis, only HLA DR6 was significantly predictive of the response, and this has not attracted attention in previous studies. Thus far, association with response has been reported for DRB1*0404 in Canda,[14] DRB1*07− in France,[15] DR2+ and DR3− in an Egyptian population living in Qatar,[12] and the DRB1*0701-DQA1*0202-DQB1*02 haplotype in Poland.[17] There are, however, reports showing no influence of HLA types on the response to IFN.[16] Inasmuch as HLA types represent anthropological markers and show distinct differences with different ethnicities, the HLA types have cohort effects in studies in which it is attempted to correlate therapeutic efficacy with HLA types. It would not be easy, therefore, to reconcile the results obtained in different countries.

In Japan, Kikuchi et al.[13] reported detecting B54 and A24-B54-DR4 more frequently in nonresponders. Miyaguchi et al.[11] found B55, B62, Cw3, and Cw4 more

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Ribavirin-Induced Pure Red-Cell Aplasia during Treatment of Chronic Hepatitis C

TO THE EDITOR: Interferon and ribavirin in combination are the standard treatment for chronic hepatitis C. Hematologic abnormalities, including thrombocytopenia and anemia, are major side effects.[1] Ribavirin is closely associated with hemolytic anemia.[2] We report a case of severe anemia due to acute pure red-cell aplasia during combination therapy, which rapidly improved after the discontinuation of ribavirin.

A 61-year-old man was admitted for treatment of chronic hepatitis C. He had received a blood transfusion after hemorrhoidectomy at the age of 30 years. Abnormal results on liver-function tests and antibody to hepatitis C virus (HCV) had been detected at a health checkup when the man was 55 years of age. His body weight was 75 kg, and physical examination showed only mild hepatomegaly. Laboratory tests demonstrated elevated alanine aminotransferase levels. The hemoglobin level and reticulocyte count were normal. A test for HCV RNA by the polymerase chain reaction was positive at a level above 850,000 IU per milliliter; the genotype was 1b. A liver biopsy showed chronic inflammation with portal fibrosis.

Treatment with interferon alfa-2b (Intron A, 6 million units) and ribavirin (Rebetol, 800 mg) was started. Eight weeks after the initiation of the treatment, the ribavirin dose was reduced to 600 mg per day because the hemoglobin level had decreased from 15.5 g per deciliter to 8.0 g per deciliter. Three weeks later, however, the hemoglobin level dropped to 6.0 g per deciliter even after the reduction in the dose of ribavirin. The reticulocyte count dropped from 7.8×10^4 per microliter to 0.2×10^4 per microliter. During the treatment, no changes in the indirect bilirubin, lactate dehydrogenase, or haptoglobin level were observed.

Bone marrow examination at week 12 showed mild hypocellularity without any morphologic abnormalities and a selective depletion of erythroid precursor cells (Fig. 1). On the basis of these findings, a diagnosis of acute pure red-cell aplasia was made, and ribavirin was discontinued. Thereafter, the anemia and reticulocytopenia improved and had normalized by week 24. Administration of interferon was continued for 24 weeks and resulted in a sustained virologic response.

Acute pure red-cell aplasia is characterized by rapidly progressive anemia with reticulocytopenia and is caused by viral infection, certain drugs, and nutritional disorders.[3] Ribavirin induced dose-related anemia, erythroid hypoplasia, and vacuolization of erythroid precursors in rhesus monkeys, which disappeared after the discontinuation of ribavirin.[4,5] We believe that our patient had acute pure red-cell aplasia caused by ribavirin used in the treatment of chronic hepatitis C. When anemia develops during treatment with interferon and ribavirin, the possibility of ribavirin-induced pure red-cell aplasia should be considered, and careful monitoring of the reticulocyte count is needed.

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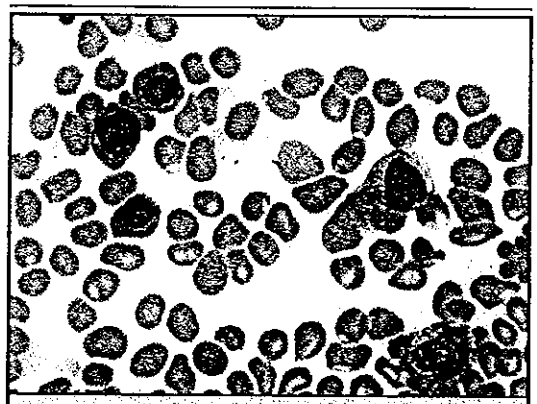

Figure 1. Findings on Microscopical Examination of Bone Marrow 12 Weeks after the Initiation of Combination Treatment with Interferon and Ribavirin (Wright–Giemsa Stain, ×1000).

The nuclear cell count was 8.6×10^4 per microliter (normal range, 10×10^4 to 25×10^4 per microliter), and the ratio of myeloid to erythroid precursors was 5.8 (normal range, 2 to 4). No morphologic abnormalities were found in precursor cells.

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Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response

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Editorial on page 1123

Background. In Japan, generally, patients with chronic hepatitis C are aged. The aim of this study was to investigate the effect of interferon (IFN) therapy on the mortality of chronic hepatitis C patients over age 60. ***Methods.*** Seven-hundred and seven patients with histologically proven chronic hepatitis C were enrolled in this study; 649 received IFN therapy (IFN group) and 58 did not (control group). The standardized mortality ratio (SMR) and Cox proportional hazard regression analysis were used to evaluate the effect of IFN on the survival of the patients. ***Results.*** Mean follow-up periods in the IFN and control groups were 5.7 and 6.7 years, respectively. During follow-up, 13 patients in the control group died (7 of liver-related diseases) and 42 in the IFN group died (29 of liver-related diseases). The SMRs of the control and IFN groups were 1.40 (95% confidence interval [CI], 0.76–2.45) and 0.73 (95% CI, 0.52–0.98) for overall death, and 10.70 (95% CI, 4.29–22.05) and 5.05 (95% CI, 3.38–7.26) for liver-related death, respectively. Sustained and transient biochemical responders in the IFN group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively) showed lower liver-related mortality compared with the control group. In patients with sustained virological response, liver-related mortality was also very low (SMR, 0.65; 95% CI, 0.01–3.61). The risk for liver-related death of sustained and transient biochemical responders was also low compared with that of the control group (adjusted risk ratios 0.10 [95% CI, 0.01–0.95] and 0.50 [95% CI, 0.11–2.21], respectively). ***Conclusions.*** These results suggest that IFN treatment could reduce liver-related mortality in chronic hepatitis C patients over age 60, notably in patients showing a biochemical response and in those showing a sustained virological response.

Key words: interferon, chronic hepatitis C, aged, liver-related mortality, standardized mortality ratio

Introduction

A high prevalence of hepatitis C virus (HCV) infection is observed in patients with hepatocellular carcinoma (HCC) in Japan.[1–4] In the early 1990s, interferon (IFN) was introduced, and it is now widely used worldwide, as well as in Japan, for the treatment of patients with chronic hepatitis C. Hitherto, many studies, including our own reports, have shown that IFN therapy reduced the incidence of HCC in patients with chronic hepatitis C.[5–10]

Recently, several groups have studied the effect of IFN therapy on survival in patients with chronic hepatitis C. Most of these studies reported that IFN therapy improved the survival of HCV-related chronic hepatitis and cirrhosis, although some studies did not find any efficacy of IFN therapy on survival.[10–19] We also reported the beneficial effect of IFN therapy on survival in chronic hepatitis C patients. In that report, we also

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showed that the effect of IFN therapy on survival was notable in the patients exhibiting sustained and transient biochemical responses, as well as in those showing sustained virological response.[20]

Many clinical trials showed that IFN therapy resulted in normalization of serum aminotransferase levels and eradication of serum HCV RNA, although a sustained virological response was achieved in a limited number of patients.[21-25] Recently, a combination therapy of ribavirin and IFN, or pegylated IFN, has been shown to have efficacy superior to IFN monotherapy for chronic hepatitis C.[26-28]

Patients in Japan with chronic hepatitis C are, generally, aged.[29,30] Also, patients with HCV-related HCC have been shown to be old, with a peak around age 70.[31] Despite the beneficial effects of IFN therapy or combination therapy of IFN and ribavirin for chronic hepatitis C patients, these treatments have several adverse effects which are not tolerable, especially for aged patients who have illnesses other than liver disease.[32] If IFN therapy does not prolong life expectancy in aged patients with chronic hepatitis C, the indications for IFN therapy in these patients may be very limited. Therefore, it is very important to investigate whether IFN therapy could improve survival in aged patients with chronic hepatitis C.

The aim of this study was to evaluate the effect of IFN therapy on mortality in aged patients with chronic hepatitis C. We conducted a multicenter, large-scale, retrospective cohort study of chronic hepatitis C patients over 60 years of age.

Patients and methods

Patients

We found previously that IFN therapy improved the survival in patients with chronic hepatitis C.[20] Of the 2954 patients with chronic hepatitis C in that study, we enrolled 707 patients over age 60 in the present study, to investigate the effect of IFN therapy on mortality in aged patients. Accordingly, the inclusion criteria were the same as those of the previous study: (1) histological diagnosis of chronic hepatitis or cirrhosis; (2) no history of clinical signs, at entry into the study, of complications of cirrhosis, i.e., ascites, jaundice, encephalopathy, or variceal bleeding; (3) no evidence of HCC at entry into the study, as assessed by ultrasonography and/or computed tomography; (4) absence of serum hepatitis B surface antigen; (5) absence of coexisting liver diseases, such as autoimmune hepatitis or primary biliary cirrhosis; (6) absence of excessive alcohol consumption (>80 g/day); and (7) absence of human immunodeficiency virus antibodies.[20]

The IFN group comprised 649 patients who had started IFN therapy between 1992 and 1997 and had received a 4- to 12-month course of IFN, which was initiated within 1 month after liver biopsy. None of the patients had received IFN therapy before entry into this study. The control group consisted of 58 patients who had received liver biopsies between 1986 and 1997, but who did not undergo IFN therapy.

Biochemical responses to IFN therapy were categorized as follows. Patients whose alanine aminotransferase (ALT) levels decreased to the normal range during therapy and remained normal for up to 24 weeks after the end of the therapy were considered to have a sustained biochemical response. Patients whose ALT levels decreased to the normal range by the end of therapy, remained normal during therapy, but returned to abnormal levels during the 24 weeks following the end of the IFN therapy were considered to have a transient biochemical response. All other ALT patterns were classified as showing biochemical non-response. A sustained virological response was defined as persistent HCV RNA negativity during IFN therapy and follow-up. Patients showing positive HCV RNA after IFN therapy were classified as virological non-responders.

Follow-up

Abdominal ultrasonography or computed tomography and biochemical examinations, including α-fetoprotein, were carried out before a liver biopsy and every 3 to 6 months during follow-up, equally in the IFN and control groups. The starting date of follow-up for patients in the control and IFN groups was defined as the date of liver biopsy. Follow-up data that were not available were collected from the resident registry of the local municipal office. In the patients residing in Osaka whose follow-up data were not obtained, the Osaka Cancer Registry was used, and the data were available until the end of 1999.[6] Therefore, it was decided to use the date of death or the end of 1999 as the end of follow-up. Because the longest observation period of the patients in the IFN group was 96 months, only the follow-up data for the first 96 months were considered in the control group. Causes of death were divided into liver-related and liver-unrelated deaths. Causes of liver-related death included HCC, liver failure, and esophageal variceal bleeding.

Informed consent was obtained from each patient included in the study. The study protocol was in accordance with the Helsinki Declaration of 1975 (revised in 1983) and was approved by the Ethics Committee of the Osaka University Graduate School of Medicine.

Table 1. Baseline characteristics of the interferon and control groups

	Interferon group						
	Virological response		Biochemical response				
	Sustained response (n = 161)	Non-response (n = 484)	Sustained response (n = 206)	Transient response (n = 144)	Non-response (n = 299)	Total (n = 649)	Control group (n = 58)	P value
Age (years; mean ± SD)	63.6 ± 3.0	63.3 ± 2.9	63.8 ± 3.1	63.0 ± 2.8	63.1 ± 2.8	63.3 ± 2.9	64.1 ± 3.1	0.06
Age distribution (years; %)								
60–64	67.7	71.1	63.6	75.0	72.9	70.4	56.9	0.03
≥65	32.3	28.9	36.4	25.0	27.1	29.6	43.1	
Male/Female	110/51	272/212	134/72	80/64	171/128	385/264	31/27	0.38
Histologic staging score (%)								
0	0.6	0.2	0.5	0.0	0.3	0.3	5.2	0.06
1	24.8	18.2	27.7	25.0	12.4	20.0	31.0	
2	29.2	27.7	26.7	28.5	28.8	28.0	20.7	
3	39.8	46.9	40.3	39.6	50.5	44.8	31.0	
4	5.6	7.0	4.9	6.9	8.0	6.8	12.1	
ALT (IU/l; mean ± SD)	113 ± 82	107 ± 68	110 ± 86	87 ± 45	117 ± 69	108 ± 71	105 ± 80	0.75

Histological evaluation

In all patients, liver biopsy was undertaken before IFN therapy. Sections were stained with hematoxylin-eosin and Azan-Mallory and analyzed by two pathologists in a blinded manner. For the assessment of liver histology, the classification of Desmet et al.[33] was used.

Statistical analysis

To compare the distribution of age at liver biopsy and histological staging between the IFN and control groups, the Wilcoxon rank-sum test was used. Differences in age at liver biopsy and ALT between the two groups was assessed for significance by Student's t-test. The χ^2 test was used to compare sex differences. The Kaplan-Meier method was used to compare the cumulative survival rates in the IFN and control groups.

We compared the observed number of deaths with the expected number of deaths, which was calculated by applying sex-, 5-year age, 5-year calendar time, and cause-specific mortality rates for the general population in Japan, as prepared by the Statistics and Information Department, Japan Ministry of Health and Welfare.[34] The standardized mortality ratio (SMR) was expressed by dividing the observed number of deaths by the expected number of deaths. Survival was also analyzed by Cox proportional hazards regression. For analysis, age, sex, stage of liver fibrosis (stages 0,1/2/3/4), time of liver biopsy (until 1992/after 1993), and IFN therapy were used as variables. SMRs and hazard risk ratios were expressed with 95% confidence intervals (CIs).

Data analysis was performed with the SAS/PC statistical package (SAS Institute, Cary, NC, USA). All reported P values were two-sided, and a P value of less than 0.05 was considered to be significant.

Results

Baseline characteristics

In the IFN group, 206 patients (31.7%) had a sustained biochemical response, 144 (22.2%) had a transient biochemical response, and 299 patients (46.1%) were biochemical non-responders. Four sustained biochemical responders whose serum HCV RNA was not examined during follow-up were excluded from the analysis. Accordingly, 161 patients (25.0%) of the 645 IFN-treated patients were classified as sustained virological responders. Table 1 shows the baseline characteristics of the IFN and control groups. Age at entry, sex, histologic staging score, and serum ALT level did not differ between the two groups. The proportion of patients more than 65 years of age in the control group was higher than that in the IFN group (P = 0.03).

Table 2. Cumulative survival rate calculated from overall deaths

	Interferon group					
	Virological response		Biochemical response			
	Sustained response	Non-response	Sustained response	Transient response	Non-response	Total	Control group
Mean follow-up period (years; mean ± SD)	5.7 ± 1.6	5.7 ± 1.7	5.6 ± 1.7	5.7 ± 1.8	5.8 ± 1.6	5.7 ± 1.7	6.7 ± 1.7
4-Year survival rate	99.3%	96.2%	98.4%	99.2%	95.0%	97.0%	93.0%
8-Year survival rate	94.6%	86.8%	94.3%	93.0%	83.4%	88.7%	73.9%
P Value[a]	<0.001	0.0197	<0.001	0.0036	0.1212	0.0031	

[a] The log rank test was used to determine the difference against the control group

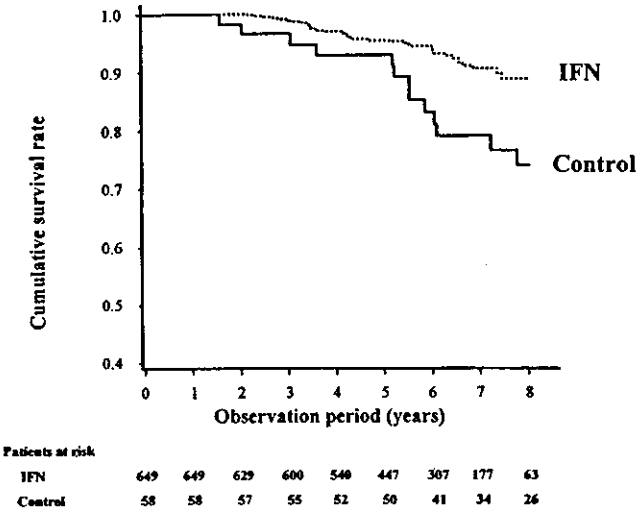

Fig. 1. Cumulative survival rates in the interferon (*IFN; dotted line*) and control (*solid line*) groups. Log-rank test of the two curves showed a significant difference between the two groups ($P = 0.003$)

Cumulative survival and cause of death

The mean follow-up periods of the IFN and control groups were 5.7 and 6.7 years, respectively. The mean follow-up periods of the patients with each response in the IFN group are shown in Table 2. Figure 1 shows the cumulative survival rates of the IFN and control groups, estimated by the Kaplan-Meier method. The 8-year survival rates of the IFN and control groups were 88.7% and 73.9%, respectively (log-rank test; $P = 0.003$; Table 2). The cumulative survival rates of sustained virological responders were significantly higher than those for virological non-responders (log-rank test; $P = 0.02$). The 8-year survival rates of sustained virological responders and virological non-responders were 94.6% and 86.8%, respectively (Table 2). The cumulative survival rates of both the sustained and transient biochemical responders were significantly higher than that of the biochemical non-responders (log-rank test; $P = 0.007$ and $P = 0.049$; Fig. 2). The 8-year survival rates of sustained and transient biochemical respon-ders and biochemical non-responders were calculated to be 94.3%, 93.0% and 83.4%, respectively (Table 2).

During follow-up, 42 of the 649 IFN-treated patients and 13 of the 58 control patients died. The numbers of liver-related and liver-unrelated deaths in the IFN and control groups are shown in Table 3. Liver-related deaths corresponded to 69% of all deaths (29/42) in the IFN group and 54% of all deaths (7/13) in the control group. HCC was the major cause of liver-related deaths in both groups. Only one liver-related death (17%) was found in the deaths of sustained biochemical respond-

Table 3. Causes of death in the interferon and control groups

	Interferon group					
	Virological response		Biochemical response			
	Sustained response (n = 161)	Non-response (n = 484)	Sustained response (n = 206)	Transient response (n = 144)	Non-response (n = 299)	Total (n = 649)	Control group (n = 58)
All deaths (n)	4	38	6	6	30	42	13
Liver-related deaths (n)	1	28	1	4	24	29	7
Hepatocellular carcinoma	1	25	1	3	22	26	5
Other causes	0	3	0	1	2	3	2
Liver-unrelated deaths (n)	3	10	5	2	6	13	6

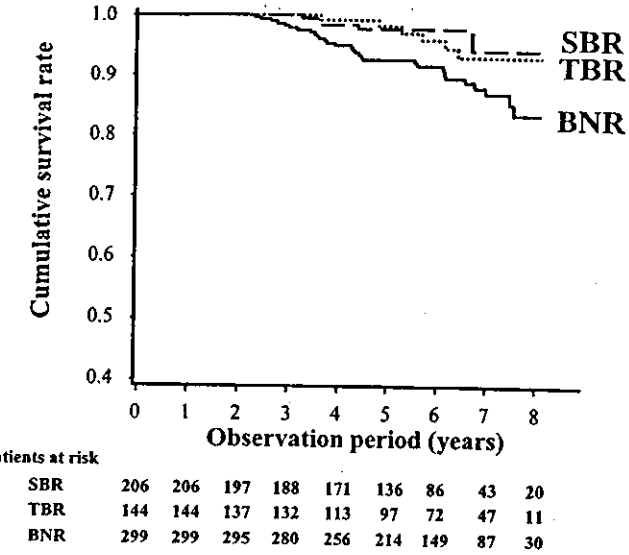

Fig. 2. Cumulative survival rates in the IFN-treated patients, categorized by sustained biochemical response (*SBR*; *dashed line*), transient biochemical response (*TBR*; *dotted line*), and biochemical non-response (*BNR*; *solid line*). Log-rank test showed significant differences between SBR and BNR (P = 0.007) and between TBR and BNR (P = 0.049)

ers. In the control group, 6 patients died of causes other than liver disease; 2 patients died of stomach cancer; 1 patient each died of lung cancer, colon cancer, and cerebral infarction; and in 1 patient, the cause of death was a traffic accident. In the IFN group, we identified 13 liver-unrelated deaths; 4 patients died of stomach cancer; 3 died of lung cancer; and 1 each died of breast cancer, colon cancer, esophageal cancer, pneumonia, chronic renal failure, and multiple myeloma.

Cox proportional hazard regression analysis

Cox proportional hazard regression analysis revealed that the risk of overall death in the IFN group was lower than that in the control group, with a marginally significant difference (risk ratio, 0.37; 95% CI, 0.13–1.05; Table 4). The patients with a sustained virological response had a low risk of overall death (risk ratio, 0.15; 95% CI, 0.04–0.59) compared with the control group. Sustained and transient biochemical responders also showed low risks of overall death (risk ratio, 0.18; 95% CI, 0.05–0.65; and risk ratio, 0.24; 95% CI, 0.07–0.87). The risk of liver-related death in the IFN group was similar to that in the control group (Table 4). However, the patients with sustained virological and biochemical response had a low risk of liver-related death compared to the control group (risk ratio, 0.12; 95% CI 0.01–1.16 and risk ratio, 0.10; 95% CI, 0.01–0.95, respectively). In transient biochemical responders, the risk ratio for liver-related deaths was 0.50 (95% CI, 0.11–2.21).

Table 4. Risk ratios for death in interferon and control groups

	All deaths			Liver-related deaths		
	Risk ratio	95% CI	*P* value	Risk ratio	95% CI	*P* value
Control group	1.00			1.00		
IFN group	0.37	0.13–1.05	0.06	0.80	0.25–2.53	0.71
Sustained virological response	0.15	0.04–0.59	0.01	0.12	0.01–1.16	0.07
Virological non-response	0.44	0.16–1.23	0.12	0.97	0.31–3.05	0.96
Sustained biochemical response	0.18	0.05–0.65	0.01	0.10	0.01–0.95	0.05
Transient biochemical response	0.24	0.07–0.87	0.03	0.50	0.11–2.21	0.36
Biochemical non-response	0.54	0.19–1.53	0.24	1.26	0.40–4.03	0.69

Age, sex, time of liver biopsy (until 1992/after 1993) and histologic staging score were adjusted in the Cox proportional hazard analysis

SMR

The SMRs in the IFN and control groups are shown in Table 5 and Fig. 3. In the control group, overall mortality was slightly higher than that in the sex- and age-matched general population (SMR, 1.40; 95% CI, 0.76–2.45). On the other hand, overall mortality in the IFN group was significantly lower compared with that of the general population (SMR, 0.73; 95% CI, 0.52–0.98). Liver-related mortality was high in the control group (SMR, 10.70; 95% CI, 4.29–22.05), and it was also high in the IFN group (SMR, 5.05; 95% CI, 3.38–7.26), although it was half of that in the control group. In the patients with sustained virological response, liver-related mortality (SMR, 0.65; 95% CI, 0.01–3.61) was very low compared with that in the control group, and it was similar to that for the general population. On the contrary, liver-related mortality was high in virological non-responders (SMR, 6.71; 95% CI, 4.46–9.70).

In terms of biochemical response, the SMRs for liver-related death of sustained and transient biochemical responders in the IFN groups were low compared with that in the control group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively). In the patients with biochemical non-response, liver-related mortality was high, and was equal to that in the control group (SMR, 9.12; 95% CI, 5.84–13.57).

The IFN group showed lower liver-unrelated mortality than the general population (SMR, 0.25; 95% CI, 0.13–0.43), whereas the control group had liver-unrelated mortality similar to the general population (SMR, 0.71; 95% CI, 0.26–1.55).

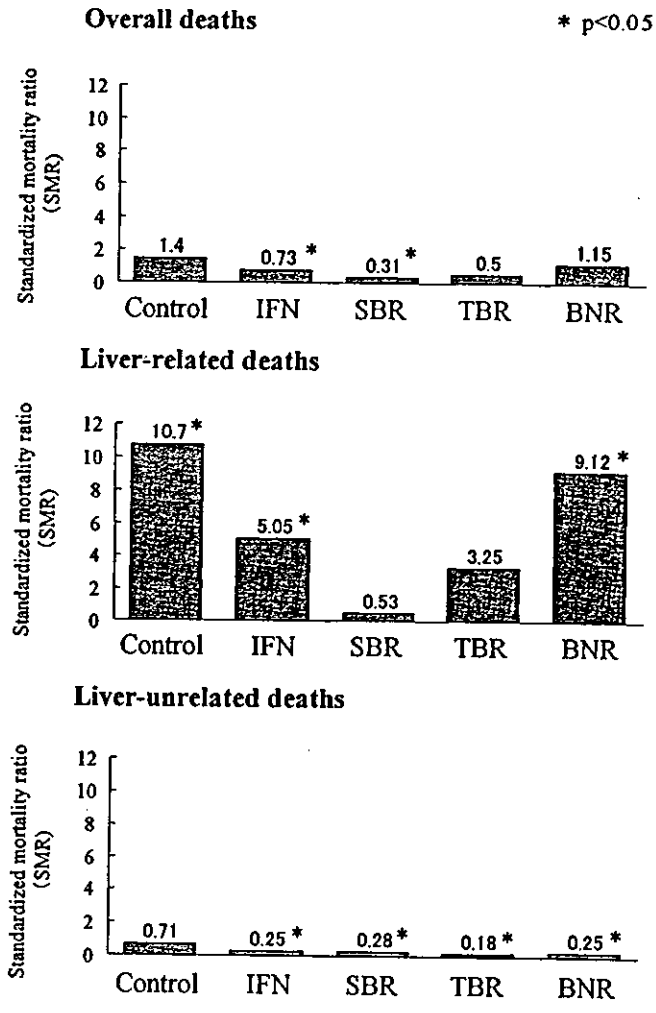

Fig. 3. Standardized mortality ratios (*SMRs*) for overall, liver-related, and liver-unrelated deaths. *SBR*, sustained biochemical response; *TBR*, transient biochemical response; *BNR*, biochemical non-response. When the SMR did not include unity, we considered the difference from the expected number of deaths to be significant

Discussion

There have been a few reports regarding the effect of IFN therapy on survival in chronic hepatitis C patients.[10,16–19] Yoshida et al.[17] reported that IFN therapy had a preventive effect on liver-related death, bringing

Table 5. Standardized mortality ratios (SMRs) in interferon and control groups

	All deaths			Liver-related deaths			Liver-unrelated deaths		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Control group	13	9.1	1.40 (0.76–2.45)	7	0.7	10.70 (4.29–22.05)	6	8.4	0.71 (0.26–1.55)
Interferon group	42	57.8	0.73 (0.52–0.98)	29	5.7	5.05 (3.38–7.26)	13	52.0	0.25 (0.13–0.43)
Sustained virological response	4	15.8	0.25 (0.07–0.65)	1	1.5	0.65 (0.01–3.61)	3	14.3	0.21 (0.04–0.61)
Virological non-response	38	41.7	0.91 (0.64–1.25)	28	4.2	6.71 (4.46–9.70)	10	37.6	0.27 (0.13–0.49)
Sustained biochemical response	6	19.5	0.31 (0.11–0.67)	1	1.9	0.53 (0.01–2.97)	5	17.6	0.28 (0.09–0.66)
Transient biochemical response	6	12.1	0.50 (0.18–1.08)	4	1.2	3.25 (0.87–8.32)	2	10.9	0.18 (0.02–0.66)
Biochemical non-response	30	26.2	1.15 (0.77–1.64)	24	2.6	9.12 (5.84–13.57)	6	23.5	0.25 (0.09–0.55)

A difference from the expected number of deaths was considered significant when the 95% confidence interval (CI) of SMR did not include unity

about improved survival of chronic hepatitis C patients, as assessed by multivariate analysis and SMR. Recently, we also reported that IFN therapy improved survival by preventing liver-related deaths in patients with chronic hepatitis C, in a multicenter, large-scale, retrospective cohort study.[20] In that study, we showed that liver-related mortality, as well as overall mortality, was much higher in untreated patients than in IFN-treated patients, as assessed by SMR. Furthermore, we found that patients showing sustained and transient biochemical responses to IFN therapy had a very low risk of death compared with untreated patients.

In this study, we evaluated the effect of IFN therapy on survival in patients over 60 years of age with histologically proven chronic hepatitis C, by SMR and by risk ratio calculated by Cox proportional hazard regression analysis. Compared with the general population, liver-related mortality was high in the IFN-treated patients (SMR, 5.05), but it was much lower than that in the control group (SMR, 10.70). Yoshida et al.[17] also examined the effect of IFN therapy on liver-related mortality in chronic hepatitis C patients over 60 years of age in their large-scale retrospective cohort study, and reported that the SMR for liver-related death in IFN-treated patients was much lower than that in the untreated patients, which was consistent with our result. In our IFN group, sustained virological responders and sustained biochemical responders had very low liver-related mortality (SMR, 0.65 and 0.53, respectively), which was equal to that in the sex- and age-matched general population. Multivariate regression analysis also showed that IFN therapy reduced the risk of liver-related death in sustained virological responders by 88% and in sustained biochemical responders by 90%. The overall mortality in the control group was not high (SMR, 1.40), whereas that in the IFN group was significantly lower in comparison with the sex- and age-matched general population (SMR, 0.73). These results may reflect a selection bias due to the nature of the liver biopsy procedure, which was undergone by all of the patients in our study. This kind of selection bias may occur, as aged patients sometimes have illnesses other than liver disease, which make a liver biopsy difficult. Furthermore, IFN-treated patients had a significantly lower risk of liver-unrelated mortality compared with the untreated patients. It seems likely that this may be attributed not to the beneficial effect of IFN therapy on liver-unrelated mortality but to a selection bias in using IFN; only the patients who had no serious diseases, such as cardiovascular disease, received IFN therapy. However, our study indicated that IFN therapy could reduce liver-related mortality, particularly in patients with sustained virological or biochemical response.

In the patients with a transient biochemical response, liver-related mortality was low when compared with the

control group, as assessed by SMR. The SMR of the transient biochemical responders (3.25; 95% CI, 0.87–8.32), which included unity, was lower than that in the control patients (10.70; 95% CI, 4.29–22.05). Similarly, the risk ratio for liver-related death in transient biochemical responders was 0.50, although this was not significant. On the other hand, SMR, as well as the risk of liver-related death estimated by multivariate analysis in the biochemical non-responders (SMR, 9.12; adjusted risk ratio, 1.26), was similar to that in the control patients. These data suggest that a reduction in liver-related mortality by IFN therapy can be expected in patients showing a transient biochemical response. Retreatment or long-term treatment with IFN might lead to an improved survival rate in transient biochemical responders, although such treatment may not be easy with some aged patients.

There was no difference between the baseline characteristics of the IFN and control groups, except for the age distribution. However, because our study was a retrospective cohort study, it had some limitations. Because the time at liver biopsy in the control group was earlier than that in the IFN group, lead-time bias may have existed. The survival of the IFN group could be higher than that of the control group. To minimize this bias, 5-year time-specific mortality rates for the general population were prepared in the SMR analysis. Furthermore, the time at liver biopsy was included as a variable for the multivariate analysis. Another limitation of our study is the small number of patients in the control group compared with the IFN group. This limitation may also be overcome by calculating the SMRs of the IFN and control groups, representing the ratio of the observed number of deaths to the expected number of deaths, calculated after taking sex-, calendar time-, and cause-specific mortality rates for the general population into consideration. The beneficial effect of IFN therapy on survival in the aged patients with chronic hepatitis C resulting from the SMR analysis was consistent with that of the Cox proportional hazard regression analysis.

In conclusion, we showed in this study that IFN therapy reduced liver-related mortality in aged patients with chronic hepatitis C, especially in those exhibiting a biochemical response and in those showing a sustained virological response. IFN therapy is recommended for aged patients with chronic hepatitis C in whom a biochemical response or a sustained virological response can be expected, after screening for diseases other than chronic hepatitis C.

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Efficacy of lamivudine treatment in Japanese patients with hepatitis B virus-related cirrhosis

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Background. Several clinical trials have suggested that lamivudine therapy is effective in patients with hepatitis B virus (HBV)-related cirrhosis. However, there are few studies of lamivudine therapy in Japanese patients with HBV cirrhosis. The aim of this study was to evaluate the efficacy of lamivudine therapy in Japanese patients with cirrhosis, and to evaluate the clinical course after the emergence of YMDD mutants. ***Methods.*** Fifty-four consecutive adult Japanese patients with HBV-related cirrhosis were enrolled and continuously treated with lamivudine, daily for 6–35 months (median, 25 months). Twelve of the 54 patients were hepatitis B envelope antigen (HBeAg)-positive. The clinical courses of 21 of the patients were evaluated using the Child-Pugh-Turcott (CPT) score. ***Results.*** Lamivudine suppressed serum HBV-DNA to undetectable levels (<3.7 LGE/ml) in 77.8% of patients at 12 months and in 61.3% at 24 months. Before the emergence of YMDD mutants, clinical improvement, defined as a decrease in the CPT score of 2 points or more, was apparent in 6 of 21 (29%) patients. No change in CPT score was evident in 14 of 21 patients (67%). YMDD mutants emerged in 19 of 54 (35%) patients. The cumulative emergence rates increased each year. The emergence rate of YMDD mutants in patients with HBV cirrhosis was higher than that in patients with chronic hepatitis. After the emergence of YMDD mutants, 3 of 12 (25%) patients with YMDD mutants showed CPT score increases of 2 points or more. ***Conclusions.*** Lamivudine therapy improved the clinical course in some cirrhotic patients. However, in patients with Child's B and C cirrhosis, the emergence of YMDD mutants sometimes led to deterioration of liver function.

Key words: HBV, cirrhosis, lamivudine, Child-Pugh-Turcott score

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Introduction

Lamivudine, an oral cytosine nucleoside analogue, potently inhibits hepatitis B virus (HBV) replication by interfering with HBV reverse transcriptase activity.[1–4] Several studies have reported the effectiveness of lamivudine in the suppression of HBV replication, improvement of transaminase levels and liver histology, and enhancement of the rate of loss of hepatitis B envelope antigen (HBeAg).[3–7]

Recently, several studies have suggested the effectiveness of lamivudine therapy for patients with HBV-related cirrhosis, especially those with decompensated cirrhosis.[8–15] Lamivudine therapy for cirrhotic patients may also be recognized as a bridge to more definitive therapy, such as liver transplantation. However, in several countries, including Japan, liver transplantation is not available because of the insufficiency of donors, and even in other countries, many patients have to wait long periods for liver transplantation. Therefore, lamivudine has been used for patients with HBV-related cirrhosis for long durations. Although several studies showed the efficacy of lamivudine therapy for patients with HBV cirrhosis in the United States and European countries,[9–15] there are few studies of lamivudine therapy in which all patients were Japanese, with HBV of genotype C, with liver cirrhosis. In this regard, a major problem with the long-term use of lamivudine is the development of viral resistance, associated with increases in HBV-DNA and serum transaminase levels.[16–18] There are few studies that have addressed this issue in Japanese patients with cirrhosis.

The aims of the present study were: (1) to assess the benefits of long-term lamivudine therapy for Japanese patients with HBV-related cirrhosis, (2) to evaluate the progress after the appearance of YMDD mutants, and (3) to determine differences in the emergence rate of YMDD mutants between patients with chronic hepatitis and those with liver cirrhosis.

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Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death

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SUMMARY. Interferon therapy for chronic hepatitis C reduces the risk of hepatocellular carcinoma, especially among virological and biochemical responders. However, little is known about the effect of interferon therapy on mortality. We studied the long-term effect of interferon therapy on mortality in patients with chronic hepatitis C. For this retrospective cohort study, 2954 patients with chronic hepatitis C were recruited, of whom 2698 received interferon therapy and 256 did not. The effect of interferon therapy on survival was assessed by standardized mortality ratio (SMR) based on published mortality data for the general Japanese population and by risk ratio calculated by proportional hazard regression. Over 6.0 ± 2.2 years follow-up, death from liver-related diseases was observed in 69 (68%) of 101 deaths among interferon-treated patients and in 42 (81%) of 52 deaths among untreated patients. Compared with the general population, overall mortality was high among untreated patients (SMR: 2.7; 95% CI: 2.0–3.6) but not among interferon-treated patients (SMR: 0.9; 95% CI: 0.7–1.1). Liver-related mortality was extremely high among untreated patients (SMR: 22.2; 95% CI: 16.0–30.0) and less among interferon-treated patients (SMR: 5.5; 95% CI: 4.3–6.9). The risk of death from all causes was lower for interferon-treated than untreated patients (risk ratio: 0.47; 95% CI: 0.261–0.836; $P = 0.01$). The risk of death from liver-related diseases was significantly lower for sustained virological responders (risk ratio: 0.04; 95% CI: 0.005–0.301; $P = 0.002$) compared with untreated patients, but not for nonsustained virological responders. Sustained biochemical responders (risk ratio: 0.03; 95% CI: 0.004–0.230; $P < 0.001$) and transient biochemical responders (risk ratio: 0.18; 95% CI: 0.063–0.532; $P = 0.002$) showed a significantly reduced risk of death from liver-related death, whereas biochemical nonresponders did not. Hence interferon treatment improved survival in chronic hepatitis C patients showing a biochemical as well as a virological response by preventing liver-related deaths.

Keywords: chronic hepatitis C, interferon, liver-related mortality, multivariate analysis, standardized mortality ratio.

Abbreviations: HCC, hepatocellular carcinoma; SMR, standardized mortality ratio.

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