with typical histology; however +1 point is assigned to patients without rosetting of liver cells even if interface hepatitis and lymphocytic/lymphoplasmocytic infiltration into portal tracts exist. In this study, approximately 70% of patients did not show rosetting of liver cells although all liver biopsy specimens were 1.5 cm or more in length. Rosetting of liver cells is a form of liver cell regeneration developing in isolated surviving hepatocytes or small groups of hepatocytes within areas of collapse and is found in chronic active hepatitis due to various causes [25]. We consider that the necessity of rosetting of liver cells for the diagnostic criteria for AIH should be re-estimated.

In conclusion, the simplified criteria are generally useful for the diagnosis of AIH, and patients diagnosed with AIH according to the simplified criteria have more typical AIH features than those diagnosed according to the original criteria. However, approximately 20% of patients with atypical features diagnosed with AIH according to the original criteria are not diagnosed with AIH according to the simplified criteria. The simplified criteria may be useless for the diagnosis of patients with atypical features, especially patients with histological acute hepatitis who require a prompt introduction of immunosuppressive treatment. To improve the diagnostic ability of these criteria in patients with atypical features, a new specific marker for AIH may be required.

Conflict of interest statement

None.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Mortality rate of patients with asymptomatic primary biliary cirrhosis diagnosed at age 55 years or older is similar to that of the general population

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Abstract
Purpose Recent routine testing for liver function and anti-mitochondrial antibodies has increased the number of newly diagnosed patients with primary biliary cirrhosis (PBC). This study investigated the prognosis of asymptomatic PBC patients, focusing on age difference, to clarify its effect on the prognosis of PBC patients.
Methods The study was a systematic cohort analysis of 308 consecutive patients diagnosed with asymptomatic PBC. We compared prognosis between the elderly (55 years or older at the time of diagnosis) and the young patients (<55 years). The mortality rate of the patients was also compared with that of an age- and gender-matched general population.
Results The elderly patients showed a higher aspartate aminotransferase-to-platelet ratio, and lower alanine aminotransferase level than the young patients ($P < 0.01$ and $P = 0.03$, respectively). The two groups showed similar values for alkaline phosphatase and immunoglobulin M. Death in the young patients was more likely to be due to liver failure (71%), while the elderly were likely to die from other causes before the occurrence of liver failure (88%; $P < 0.01$), especially from malignancies (35%). The mortality rate of the elderly patients was not different from that of the age- and gender-matched general population (standardized mortality ratio, 1.1; 95% confidence interval, 0.6–1.7), although this rate was significantly higher than that of the young patients ($P = 0.044$).

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Conclusions PBC often presents as more advanced disease in elderly patients than in the young. However, the mortality rate of the elderly patients is not different from that of an age- and gender-matched general population.

Keywords Primary biliary cirrhosis · Age difference · Mortality rate

Abbreviations

PBC	Primary biliary cirrhosis
AMA	Anti-mitochondrial antibody
AIH	Autoimmune hepatitis
HCV	Hepatitis C virus
SMR	Standardized mortality ratio
CI	Confidence interval
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
HCC	Hepatocellular carcinoma
UDCA	Ursodeoxycholic acid

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease characterized by progressive destruction of the small septal and interlobular bile ducts [1–3]. Chronic cholestasis may result in hepatic fibrosis and portal hypertension, which may eventually progress to hepatic failure or gastrointestinal bleeding. Thirty years ago, most patients diagnosed with PBC showed liver cirrhosis and disease-related symptoms [4–6]. The overall survival of PBC patients was 10–15 years, which was significantly less than that of age- and gender-matched controls from the general population [7–10].

Recent routine testing for liver function and anti-mitochondrial antibodies (AMAs) has increased the number of newly diagnosed cases of asymptomatic PBC [11]. There are several prognostic studies of these asymptomatic patients, suggesting that a significant proportion are in the early stage of PBC and might respond favorably to medication without further disease progression for several years [2, 11, 12]. Studies of the clinical significance of antinuclear antibodies (ANAs) in PBC have indicated that PBC-specific ANAs, such as Sp100, promyelocytic leukemia proteins, gp210, and p62 correlate with disease activity and may be markers of poor prognosis [13]. The only accepted index to estimate patient survival is the Mayo risk score, which is very useful in advanced cases; however, it is of limited use in patients with early disease [14].

Recent studies on age differences in patients with autoimmune hepatitis (AIH) showed more frequent presentation of elderly patients with severe disease [15, 16]. However, the relationship between age at diagnosis and the prognosis of PBC patients remains unclear. The present study investigated the proposal that young and elderly asymptomatic PBC patients have different prognoses. To test this hypothesis, we compared clinical features, including prognosis, between the two age groups of patients. We also compared the mortality rates for PBC patients with those of an age- and gender-matched general population.

Patients and methods

Patients

This study was a systematic cohort analysis of 308 consecutive patients (271 females and 37 males) diagnosed with asymptomatic PBC at Okayama University and affiliated hospitals from 1980 to 2004. A diagnosis of PBC was made based on any two of the following criteria: [1] positive test for AMA, [2] biochemical evidence of cholestasis, and [3] liver biopsy compatible with the diagnosis [12]. The presence of AMA was determined by indirect immunofluorescence on murine tissue sections (cutoff value; 1:40) or enzyme-linked immunosorbent assay against beef pyruvate dehydrogenase. Pruritus, jaundice (bilirubin > 2 mg/dl), bleeding varices, severe general fatigue, and ascites were defined as symptoms associated with disease progression. Patients showing serum positivity for hepatitis B surface antigen or anti-hepatitis C virus (HCV) antibodies, those with a daily ethanol intake of more than 60 g, and those with other signs of liver injury were excluded from this study. The study was carried out in accordance with the Helsinki Declaration, and was approved by the ethics committees of the relevant institutes. All patients provided informed consent.

Histological evaluation

Histological stages were evaluated according to the criteria of Ludwig et al. [1]. Briefly, stage I was defined as portal inflammation confined to the portal triads; stage II as portal and periportal inflammation without septal fibrosis or bridging necrosis; stage III as lobular fibrosis and/or bridging necrosis; and stage IV corresponded to cirrhosis.

Survival statistics

All patients were examined for physical status and the development of disease-related symptoms. Patients who had not visited our hospitals in the previous 6 months were contacted by letter or telephone and asked to provide details of recent medications and any disease-related

symptoms, by using questionnaires. If they had visited other hospitals, we also asked them about the results of any endoscopy or imaging studies. For patients who had died, the date and cause of death were recorded. Only those patients followed for at least 1 year were included in the prognostic analysis. Survival statistics were compared between PBC patients and the general population (age- and gender-matched), using a standardized mortality ratio (SMR). The SMR was calculated by dividing the observed number of deaths by the expected number of deaths, as calculated from gender- and age (5-year)-ranked mortality in the Japanese general population in 2003, in *Vital statistics in Japan* published by the Statistics and Information Department of the Japan Ministry of Health and Welfare [17]. The 95% confidence intervals (CIs) for the SMR values were assumed to follow Poisson's distribution.

Statistical analysis

Data values are expressed as means ± SD or medians (ranges). Patient characteristics were compared among the groups by using the χ^2 test, Mann-Whitney-*U* test, and Kruskal-Wallis test. The proportional hazards model was utilized to estimate the effects of patients' characteristics on survival. The survival rates and disease progression to symptomatic PBC were estimated by the Kaplan–Meier method, and compared using the log rank test. A *P* value of less than 0.05 was considered significant.

Results

Patient characteristics

Table 1 lists the clinical characteristics of the patients recruited in this study. The age of patients in this study showed a single peak in the fifties, with a median age at diagnosis of 56 years, which is in agreement with several previous studies [11, 18, 19]. Based on these results, the patients were divided into two groups: the young group (age < 55 years) and the elderly group (≥55 years). Most patients were female (88.3%). Interestingly, the male patients had a peak age distribution in the sixties (63 ± 11 years), which was significantly higher than that of the female patients (55 ± 11 years; $P < 0.01$; Mann–Whitney *U* test). The frequencies of positive AMA and ANA showed no significant difference between the groups. The two groups showed similar values for alkaline phosphatase (ALP), but the young group had higher alanine aminotransferase (ALT) levels than the elderly ($P = 0.03$; Mann–Whitney *U* test). The elderly group had a significantly higher aspartate aminotransferase (AST)-to-platelet

Table 1 Clinical characteristics of the patients at the time of diagnosis

	All patients ($n = 308$)	Young group ($n = 133$)	Elderly group ($n = 175$)	*P*
Age (years)	56 (24–83)[c]	48 (24–54)[c]	63 (55–83)[c]	
Gender (female/male)	272/36	123/10	149/26	0.04
Liver histology (I/II/III/IV)[a]	120/67/19/3	59/33/5/1	61/34/14/2	0.28
Treatment (UDCA/other/none)	273/10/25	119/5/10	154/5/15	0.86
Laboratory data at diagnosis				
AMA (% positive)	78.9	80.5	77.7	0.65
ANA (% positive)	58.1	57.9	58.3	1
AST (IU/L)	58 ± 70[d]	57 ± 60[d]	59 ± 78[d]	0.73
ALT (IU/L)	62 ± 71[d]	72 ± 92[d]	54 ± 49[d]	0.034
ALP (ratio)[b]	1.9 ± 1.3[d]	1.8 ± 1.3[d]	2.0 ± 1.3[d]	0.39
Total bilirubin (mg/dl)	0.7 ± 0.3[d]	0.7 ± 0.4[d]	0.8 ± 0.3[d]	0.02
Platelet count ($\times 10^4/mm^3$)	21.1 ± 6.7[d]	23.3 ± 6.6[d]	19.5 ± 6.3[d]	<0.01
Total cholesterol (mg/dl)	209 ± 46[d]	207 ± 44[d]	211 ± 47[d]	0.099
Immunoglobulin G (mg/dl)	1852 ± 560[d]	1817 ± 500[d]	1878 ± 602[d]	0.68
Immunoglobulin M (mg/dl)	473 ± 332[d]	449 ± 263[d]	492 ± 376[d]	0.71
AST-to-platelet ratio	3.3 ± 5.6[d]	2.5 ± 2.2[d]	4.0 ± 7.0[d]	<0.01

[a] Histological stage classified by Ludwig et al. [1]

[b] Expressed relative to the upper limit of normal

[c] Median (range)

[d] Mean ± SD

UDCA ursodeoxycholic acid; *AMA* anti-mitochondrial antibody; *ANA* anti-nuclear antibody; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase; *ALP* alkaline phosphatase

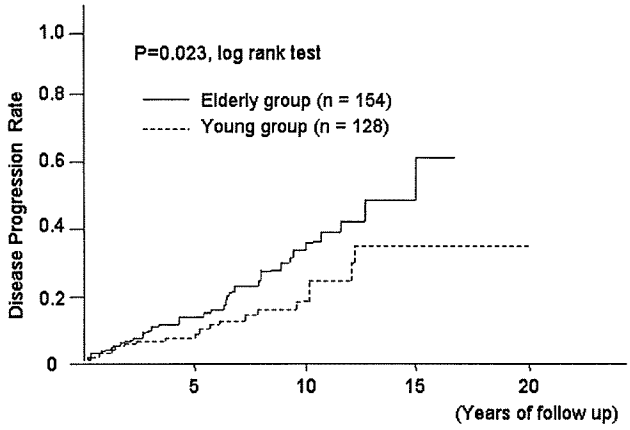

Fig. 1 Disease progression rate to symptomatic primary biliary cirrhosis (PBC), stratified by age at diagnosis. The rates of disease progression to symptomatic PBC were estimated for both the young and elderly groups by the Kaplan–Meier method. The log rank test was used to compare the two rates. The rate of disease progression to a symptomatic state was significantly higher in the elderly group than the young group ($P = 0.023$; log rank test). At 10 years' follow up, 19% of the young and 35% of the elderly patients would have progressed to a symptomatic state

ratio and lower platelet count than the young group ($P < 0.01$; Mann–Whitney U test).

Survival of PBC patients

The survival of the PBC patients was evaluated with the data from 282 patients who were followed for at least 1 year. The mean period of follow up was 81 ± 50 months (86 ± 53 months in the young group and 77 ± 47 months in the elderly group). This period was defined as the time between diagnosis and either death or the latest confirmation of survival. The accumulated observation was 1904 person-years, accounting for 92.6% of the total potential follow up. The rate of disease progression to symptomatic PBC was significantly higher in the elderly group than in the young group ($P = 0.023$, log rank test; Fig. 1). At 10 years' follow up, 19% of the young and 35% of the elderly patients would have progressed to symptomatic PBC. Causes of death are summarized in Table 2. Liver transplantation was considered a liver-related death when calculating the SMR. Twenty-four patients died or had a liver transplant. Liver failure and malignancies were the leading causes of death in both groups. Death in the young patients was most likely to have been due to liver failure (71%), while the elderly patients were more likely to have died from other causes before the occurrence of liver failure (88%; $P < 0.01$; Fisher's exact probability test), especially from malignancies other than hepatocellular carcinoma (HCC; 35%). Two of the three patients who died of HCC were likely to have had advanced liver diseases,

Table 2 Causes of death

Cause of death	All patients	Young group	Elderly group
Liver-related	10	5	5
Liver transplantation	1	1	0
Hepatocellular carcinoma	3	0	3
Liver failure	6	4	2
Liver-unrelated	14	2	12
Malignancies[a]	8	2	6
Heart failure	1	0	1
Cerebrovascular disease	2	0	2
Pneumonia	3	0	3
Total deaths or liver transplantation	24	7	17

[a] Malignancies other than hepatocellular carcinoma

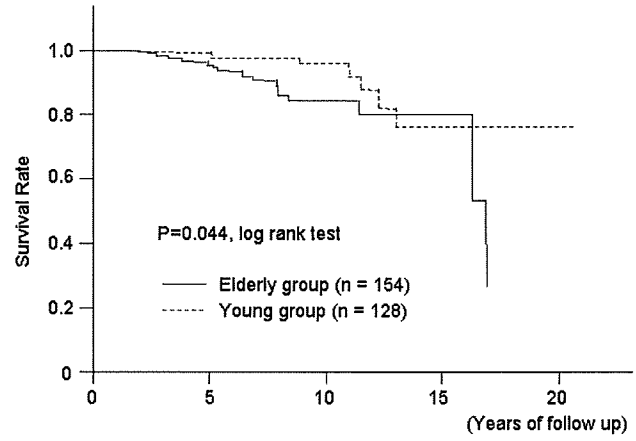

Fig. 2 Overall survival rate of PBC patients, stratified by age at diagnosis. The survival rates of the young and elderly groups were compared by using the Kaplan–Meier method. The *survival curves* showed a significantly lower survival rate in the elderly group than in the young group ($P = 0.044$; log rank test). At 10 years' follow up, 4.3% of the young and 16% of the elderly patients would be dead

because they were in histological stage 3 at the time of diagnosis and the tumors were detected during an observation period of more than than 10 years. The annual incidence rate of HCC was 0.13%. Figure 2 shows that the overall survival rate was significantly lower in the elderly group than in the young group ($P = 0.044$; log rank test). At 10 years' follow up, 4.3% of the young and 16% of the elderly patients would have died. The results indicated that the elderly patients died from other causes before the occurrence of liver failure, and their survival rate was significantly lower than that of the young patients. We evaluated the effects of patients' characteristics on prognosis with the proportional hazards model (Table 3). In the univariate analysis, old age, male gender, high

Table 3 Analysis of factors predictive of survival; proportional hazards model

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio (Range)[a]	*P*	Odds ratio (Range)[a]	*P*
Age (55 years or older)	2.35 (0.96–5.73)	0.061	2.90 (0.78–10.7)	0.11
Gender (male)	2.94 (1.15–7.53)	0.025	1.71 (0.57–5.17)	0.34
Liver histology (II/III/IV)	0.748 (0.29–1.90)	0.54		
ALT (higher than twofold ULN)	1.58 (0.66–3.80)	0.30		
ALP (higher than twofold ULN)	2.59 (1.12–6.02)	0.027	1.25 (0.42–3.69)	0.69
Platelet count (<ULN)	1.43 (0.55–3.73)	0.46		
Total cholesterol (>ULN)	1.00 (0.42-2.39)	0.99		
Immunoglobulin G (>ULN)	1.76 (0.65-4.77)	0.27		
Immunoglobulin M (>ULN)	1.23 (0.51–2.98)	0.64		
AST-to-platelet ratio (>3.0)	4.89 (1.72–13.9)	<0.01	3.42 (1.04–11.2)	0.042

[a] 95% confidence interval

ULN upper limit of normal; *ALT* alanine aminotransferase; *ALP* alkaline phosphatase; *AST* aspartate aminotransferase

Table 4 Standardized mortality ratio (SMR) of the patients

	All patients ($n = 282$)	Young group ($n = 128$)	Elderly group ($n = 154$)
Overall deaths			
Observed/expected	24/15	7/1	17/16
SMR (range)[a]	1.6 (1.0–2.4)	7.4 (3.0–15.2)	1.1 (0.6–1.7)
Liver-related deaths			
Observed/expected	10/0.2	5/0.0	5/0.2
SMR (range)[a]	47 (23–86)	218 (71–509)	23 (7.3–53)
Liver-unrelated deaths			
Observed/expected	14/14	2/0.9	12/16
SMR (range)[a]	1.0 (0.5–1.6)	2.2 (0.3–7.8)	0.8 (0.4–1.3)
Malignancies			
Observed/expected	11/4.7	2/0.6	9/6.1
SMR (range)[a]	2.3 (1.2–4.2)	3.3 (0.4–12)	1.5 (0.7–2.8)

[a] 95% confidence interval

AST-to-platelet ratio, and high ALP predicted short survival. The multivariate analysis, adjusted with the logistic likelihood ratio test, indicated that a high AST-to-platelet ratio, but not older age, was a significant predictive factor for short survival.

Comparison of PBC patients' mortality rate with that of age- and gender-matched general population

Table 4 shows the overall mortality rate and the mortality rates for liver-related deaths, liver-unrelated deaths, and malignancies. The overall mortality rate of PBC patients was slightly higher than that of the matched general population (SMR, 1.6; 95% CI, 1.0–2.4). Importantly, the overall mortality rate of the elderly group was not different from that of the matched general population (SMR, 1.1; 95% CI, 0.6–1.7). Liver-related mortality was significantly higher among PBC patients (SMR, 47; 95% CI, 23–86), especially the young patients (SMR, 218; 95% CI, 71–509) than in the matched general population, while liver-unrelated mortality among PBC patients was not different from that in the matched general population (SMR, 1.0; 95% CI, 0.5–1.6). The mortality for malignancies among PBC patients was twice as high as expected (SMR, 2.3; 95% CI, 1.2–4.2), as shown in previous reports [20, 21]. These results indicated that the young patients were more likely to die from liver-related causes during the course of PBC, and that the elderly patients were just as likely to die from liver-unrelated causes, with survival expectancy similar to that of the age- and gender-matched general population.

Discussion

Routine testing for liver function and AMA has increased the number of newly diagnosed cases of asymptomatic PBC, and several recent studies have attempted to clarify the prognosis of these asymptomatic patients, which has not been fully understood. The relationship between age at diagnosis and prognosis in PBC patients remains unclear. We hypothesized that age difference might have an important role in the prognosis of PBC patients, because age difference in disease progression has been reported in other chronic liver diseases such as chronic hepatitis C [22] and AIH [15]. The present study was a systematic cohort analysis of a large group of asymptomatic PBC patients, and the first to investigate the prognosis of PBC patients more precisely by dividing the patients according to their age at diagnosis.

Considering the possibility of lead time bias, in that some of the elderly patients may have had delayed diagnosis of advanced stage PBC, we analyzed the correlation between age at diagnosis and the AST-to-platelet ratio, in order to estimate the effect of age difference on liver damage, and the correlation was not significant ($R = 0.11$; $P = 0.065$, canonical correlation analysis). There was no significant difference between the two groups in histological stage of liver biopsy specimens obtained at the time of diagnosis, with approximately half of them defined as stage 1. The age distribution of patients in the present study was similar to that in other multicenter studies [11, 18, 19]. These findings do not indicate that the elderly group may have involved patients who had a delayed diagnosis of PBC.

In regard to the mortality of asymptomatic PBC patients, there have been several conflicting reports. Prince and James [12] suggested that asymptomatic PBC patients have reduced survival compared with the general population, with an SMR more than 2.5-fold higher than expected deaths. Springer et al. [11] reported that asymptomatic PBC patients had shortened survival compared with a matched control population, and only the patients who remained asymptomatic survived as well as a matched control population. Uddenfeldt and Danielsson [23] showed that survival in asymptomatic patients was similar to that in the general population. In the present study, the mortality of PBC patients was slightly higher than that of the general population (SMR, 1.6; 95% CI, 1.0–2.4). Our analysis, by dividing the patients in the two groups according to their age at diagnosis, clarified that the elderly patients had an SMR similar to that of the general population (SMR, 1.1; 95% CI, 0.6–1.7), while the mortality rate of the young patients was seven times as high as expected. The influence of the age difference on mortality occurred partly because the mortality rate of the young general population was as low as 0.15% annually, which was one-twelfth of that of the elderly general population. The mortality rate of the young patients was much higher than that of the young general population, although it was significantly lower than that of the elderly patients or the elderly general population.

In the young patients in our study, deaths were likely to be from liver failure, or the patients were likely to receive a liver transplant, while the deaths of the elderly patients were more likely to be due to liver-unrelated causes such as malignancies. The elderly patients would be likely to develop disease-related symptoms if they lived long enough, but their survival might not be affected by the subsequent development of disease-related symptoms, because a considerable number of them died of liver-unrelated causes before the occurrence of liver failure. These results indicated that death in the young patients would likely be due to liver-related causes during the course of PBC, and that the elderly patients were just as likely as the age- and gender-matched general population to die from liver-unrelated causes, with survival expectancies similar to those in the age- and gender-matched general population. Reports on cancer risk in PBC patients have suggested that there is a small increase in overall cancer incidence and mortality in these patients [20, 21]. Our results are consistent with these reports, showing that overall mortality for malignancies was higher than that in the general population (SMR, 2.3; 95% CI, 1.2–4.2). The mortality for malignancies was slightly higher that in the general population in both the young and the elderly groups, although this increase was not statistically significant. Except for HCC, it is unlikely that there is a high excess incidence of death for PBC patients from any cancer at a particular site. Periodical check-up for malignancies is necessary for the good management of PBC patients.

Many different drugs have been used to slow disease progression in PBC patients, with variable results. Ursodeoxycholic acid (UDCA) was reported to delay histological progression [24–29], and prolong survival without liver transplantation [30, 31]. However, these findings were challenged in two independent metaanalyses [32, 33], showing that UDCA did not affect survival. Most patients in the present study (276 patients; 89%) were treated with UDCA over the course of the disease. There was no significant difference in use of drugs between the young and elderly groups (Table 1). UDCA may be adequate as the initial treatment for elderly patients, because at least this agent does not reduce survival. On the other hand, young patients need active management to prevent liver failure, because our results indicated that they may develop disease-related symptoms at a relatively young age, and may not survive as well as the general population. Bezafibrate and immunosuppressants were additionally prescribed for 43 and 51 patients, respectively, in the present study. Our

data were not sufficient to assess the survival benefits of these drugs.

In conclusion, age difference could be one of the important factors for predicting the prognosis of PBC patients, because our findings showed that the mortality rate of PBC patients aged 55 years or more diagnosed at the asymptomatic stage was not different from the mortality rate of the general population. The elderly patients may have more advanced disease than the young patients. Death in the young patients was more likely to be due to liver failure, while the elderly patients died from liver-unrelated causes such as malignancies. Active management of liver disease may lead to a better prognosis in young PBC patients.

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Original Article

Clinical features of type 1 autoimmune hepatitis in adolescence and early adulthood

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Aim: The peak age of the presentation of autoimmune hepatitis (AIH) is between 40 years and 50 years. Elderly patients have been reported to have higher frequencies of concurrent thyroid or rheumatic diseases and histological cirrhosis and a lower occurrence of treatment failure. In this study, we assessed the clinical features of Japanese type 1 AIH in adolescence and early adulthood.

Methods: Fifteen patients aged ≤ 30 years (group 1) were compared with 79 patients aged between 40 years and 50 years (group 2).

Results: At presentation, patients aged ≤ 30 years accounted for 9% of the study population. Although frequencies of extrahepatic concurrent autoimmune diseases were similar between groups 1 and 2, a tendency toward a lower frequency of concurrent autoimmune thyroiditis was shown in group 1 (0 vs. 18%, $P = 0.08$). Group 1 had a lower frequency of human leukocyte antigen DR4 (27 vs. 78%, $P = 0.002$), and histological acute hepatitis was shown more frequently in group 1 (27 vs. 4%, $P = 0.002$). However, there were no differences in frequencies of the normalization of serum transaminase levels after the introduction of corticosteroid treatment or relapse after the normalization of serum transaminase levels between the two groups.

Conclusions: Japanese type 1 AIH patients in adolescence and early adulthood respond well to corticosteroid treatment. However, they may frequently show atypical features, and the diagnosis of type 1 AIH in adolescence and early adulthood may be difficult and should be made carefully.

Key words: acute hepatitis, autoimmune hepatitis, autoimmune thyroiditis, human leukocyte antigen

INTRODUCTION

CLASSICALLY, AUTOIMMUNE HEPATITIS (AIH) is a chronic hepatitis of unknown origin characterized by hypergammaglobulinemia, circulating autoantibodies and the presence of interface hepatitis and portal lymphoplasmacytic infiltration on histological examination.[1,2] Type 1 AIH is characterized by the presence of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA), and human leukocyte antigen (HLA) DR3 and DR4 are recognized as risk factors for type 1 AIH. Extrahepatic concurrent autoimmune disease is shown in 30–40% of AIH patients, and autoimmune thyroiditis is the most common finding.[3,4]

Generally, the peak age of AIH presentation is between 40 years and 50 years, although AIH affects adults of all ages.[5,6] Recently, the clinical features of elderly patients (≥ 60 years) with AIH have been reported from several groups.[5–7] At presentation, elderly patients account for 20–30% of all patients, have higher frequencies of concurrent thyroid or rheumatic diseases and histological cirrhosis and a lower occurrence of treatment failure.

The frequency of adolescent and early adulthood patients aged ≤ 30 years has been reported as 8–25%, but the clinical features in this population have not been fully elucidated.[5–7] The authors of one early study reported that in white North American patients, patients aged ≤ 30 years had a lower frequency of HLA DR4 and a higher frequency of DR3.[5] HLA affects the clinical expression and behavior of the disease.[8] Patients with

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HLA DR3 are younger and they have a higher frequency of treatment failure than those with DR4. In white North American patients, DR3 is the principal susceptibility allele, and DR4 is a secondary one.[3] In Japan, the disease is strongly associated with DR4, and almost no patients have DR3.[6] Thus, the clinical features of adolescent and early adulthood AIH patients in Japan may be different from features noted in previous reports. In this study, we compared Japanese AIH patients aged ≤ 30 years with those aged between 40 years and 50 years.

METHODS

OUR STUDY INCLUDED 176 patients with type 1 AIH (153 females, 23 males, median age 55 years) admitted to the Okayama University Hospital or six affiliated hospitals between March 1989 and April 2008. All patients were seronegative for hepatitis B surface antigen, anti-hepatitis C virus antibody, hepatitis C virus RNA and anti-mitochondrial antibody, and each underwent a liver biopsy. A diagnosis of AIH was made according to the revised scoring system proposed by the International Autoimmune Hepatitis Group.[9] A definite diagnosis of AIH based on this revised scoring system required a pretreatment score exceeding 15, while a probable diagnosis required a score between 10 and 15. Patients with an overlapping syndrome or a coexistent disease (for example primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic fatty liver disease and alcohol-induced liver injury) were excluded from this analysis.

In this study, patients were categorized according to age at presentation. Fifteen patients aged ≤ 30 years (9%) were classified into group 1, and 79 patients aged between 40 years and 50 years (45%) were classified into group 2.

An acute presentation was defined by the presence of acute onset of symptoms (for example, jaundice and/or fatigue and/or anorexia) in conjunction with bilirubin ≥ 5 mg/dL and/or serum alanine aminotransferase (ALT) levels higher than 10-fold the upper limit of normal.

The main extrahepatic concurrent autoimmune diseases, autoimmune thyroiditis and Graves' disease, were diagnosed according to the Japan Thyroid Association's diagnosis guidelines (http://thyroid.umin.ac.jp/flame.html1). Sjögren's syndrome was diagnosed according to the American–European Consensus Group Criteria,[10] and systemic lupus erythematosus according to the American College of Rheumatology criteria.[11]

Liver biopsy was performed with a Vim–Silverman needle (14-G) under laparoscopy or with a 17-G needle under ultrasonography guidance, before or just after commencing treatment. Liver biopsy specimens were evaluated by two pathologists and diagnosed as showing acute or chronic hepatitis. A diagnosis of acute hepatitis was made based on the presence of histologically predominant zone 3 necrosis with minimal lymphoplasmacytic cell infiltration into portal tracts, in the absence of interface hepatitis or portal fibrosis. Liver biopsy specimens diagnosed as showing chronic hepatitis underwent histological staging based on the classification of Desmet *et al.*[12]

The standard initial treatment was prednisolone monotherapy (30–40 mg/day) or a combination of prednisolone (20–40 mg/day) and azathioprine (50–100 mg/day). In patients with histological low-grade inflammatory activity, the initial treatment was low-dose prednisolone (20 mg/day). Elderly patients with histological low-grade inflammatory activity and comorbidities such as osteoporosis and/or diabetes were treated with ursodeoxycholic acid (300–600 mg/day) or a combination of lower doses of prednisolone (< 20 mg/day) and ursodeoxycholic acid. An initial treatment was defined as any therapy that was started within 3 months after the diagnosis of AIH.

To compare the clinicopathological characteristics at presentation between the two groups, we analyzed gender, pretreatment score based on the revised scoring system,[9] frequency of acute presentation, concurrent autoimmune disease, laboratory data (albumin, bilirubin, aspartate aminotransferase [AST], ALT, immunoglobulin G [IgG], ANA, SMA, HLA DR4, DR2) and histological features (staging of fibrosis, rosetting of liver cells, zone 3 necrosis).

Statistics

Statistical analysis was performed using the SPSS statistical program (release 11.0.1 J; SPSS Inc, Chicago, IL, USA).

Continuous variables were expressed as medians and ranges. The Mann–Whitney *U*-test was used to evaluate differences in the continuous variables. Dichotomous variables were compared by the χ^2-test. Cumulative incidental rates were estimated using the log–rank test. *P*-values of less than 0.05 were considered significant.

RESULTS

Clinical and HLA distinctions (Tables 1,2)

STUDY GROUPS 1 and 2 were similar in gender distribution, frequencies of acute presentation and

Table 1 Clinical features of 15 patients aged ≤ 30 years

Case	Age (years)	Gender	Score	ANA titer	SMA titer	HLA DR4	Staging
1	16	Female	17	Negative	1:160	NT	Acute
2	16	Female	17	1:320	Negative	Negative	Acute
3	18	Female	19	1:2560	1:40	Positive	F4
4	18	Female	20	1:80	1:320	NT	F2
5	19	Female	21	1:2560	1:640	Negative	F3
6	19	Male	15	Negative	1:40	Positive	F2
7	20	Female	15	1:320	1:640	NT	F1
8	20	Female	17	Negative	1:80	Negative	F4
9	22	Female	20	1:320	Negative	Negative	F2
10	24	Female	20	1:320	1:320	Negative	F3
11	24	Female	18	1:160	NT	Negative	F1
12	25	Female	18	1:2560	1:40	Negative	F3
13	26	Male	10	1:40	Negative	Negative	Acute
14	29	Female	20	1:160	1:160	NT	F1
15	30	Male	12	1:40	Negative	Positive	Acute

ANA, anti-nuclear antibody; HLA, human leukocyte antigen; NT, not tested; score, pretreatment score according to the revised scoring system proposed by the International Autoimmune Hepatitis Group; SMA, smooth muscle antibody; staging, histological staging of fibrosis.

pretreatment scores according to the revised scoring system proposed by the International Autoimmune Hepatitis Group.[9]

The frequency of extrahepatic concurrent autoimmune diseases was similar between the two groups. In group 1, one patient each had autoimmune hemolytic anemia, systemic lupus erythematosus, ulcerative colitis and Sjögren's syndrome. In group 2, 13 patients had autoimmune thyroiditis, two each had systemic lupus erythematosus and progressive systemic sclerosis and one each had both autoimmune thyroiditis and autoimmune hemolytic anemia, both systemic lupus erythematosus and Sjögren's syndrome, and Graves' disease. A tendency towards a low frequency of concurrent autoimmune thyroiditis was shown in group 1 (0 vs. 18%, $P = 0.08$).

Group 1 patients had slightly higher serum transaminase levels than those of group 2 patients; there were no differences in serum levels of albumin, bilirubin or IgG between the two groups.

Thirteen patients of group 1 and 72 patients of group 2 were positive for ANA titers of 1:40 or greater. Of the patients screened for SMA, 10 of 14 patients (71%) in group 1 and 34 of 50 patients (68%) in group 2 were positive for SMA titer of 1:40 or greater. There was no difference in positive proportions of ANA and/or SMA between the two groups.

Eleven patients of group 1 and 39 patients of group 2 were screened for HLA DR status by the polymerase chain reaction sequence-specific oligonucleotide hybridization method. Group 1 patients had a lower frequency of DR4 than group 2 patients (27 vs. 77%, $P = 0.002$).

Histologically, acute hepatitis was present more frequently in group 1 than in group 2 (27 vs. 4%, $P = 0.002$), and the frequency of zone 3 necrosis was slightly higher in group 1 patients (47 vs. 24%, $P = 0.07$).

Corticosteroid treatment

Fifteen patients of group 1 (100%) and 73 patients of group 2 (92%) were followed up for one year or more. Of the 73 patients in group 2, eleven were treated with ursodeoxycholic acid monotherapy. Thus, all group 1 patients and 62 group 2 patients treated with prednisolone ≥ 20 mg/day as the initial treatment were included in this analysis of corticosteroid treatment outcome. The follow-up duration was 55.5 (22.2–161) months in group 1 and 74.7 (12.2–204) months in group 2 ($P = 0.85$). There was no difference in the frequency of the normalization of serum ALT levels within 6 months after the introduction of prednisolone treatment between the two groups (87 vs. 87%, $P = 0.37$). Ultimately, 14 patients (93%) in group 1 and 60 patients (97%) in group 2 achieved the normalization of serum ALT levels during 0.5 (0.03–10.8) months and 0.9 (0.03–24.4) months, respectively. After the normalization of serum ALT levels, 6 of the 14 patients (43%) in group 1 and 33 of the 60 patients (55%) in group 2

Table 2 Comparison of clinical features between group 1 and group 2

	Group 1	Group 2	*P*-value
Patients, *n*	15	79	
Gender, female (%)	12 (80)	73 (92)	0.13
Criteria of the International Autoimmune Hepatitis Group			
Pretreatment score	18 (10–20)	18 (10–21)	0.86
Definite diagnosis (%)	11 (73)	67 (85)	0.28
Form of clinical onset, acute presentation (%)	7 (47)	21 (27)	0.12
Concurrent autoimmune disease, *n* (%)	4 (27)	20 (25)	0.91
Autoimmune thyroiditis, *n* (%)	0 (0)	14 (18)	0.08
Laboratory data			
Albumin (g/dL)†	3.9 (3.0–4.6)	3.9 (2.1–5.1)	0.64
Bilirubin (mg/dL)†	1.8 (0.5–17.1)	1.0 (0.3–24.3)	0.22
AST (IU/L)†	218 (74–2330)	157 (33–1716)	0.09
ALT (IU/L)†	335 (101–1805)	166 (23–2161)	0.09
IgG (mg/dL)†	2722 (1445–6562)	2528 (1170–5014)	0.68
ANA or SMA ≥ 1:40, *n* (%)	15 (100)	75 (95)	0.37
HLA DR4, *n* (%)	3/11 (27)	30/39 (77)	0.002
HLA DR2, *n* (%)	3/11 (27)	8/39 (21)	0.63
Fibrosis staging, *n* (%)			
Acute hepatitis	4 (27)	3 (4)	0.002
Chronic hepatitis	11 (73)	76 (96)	
F1	3 (20)	26 (33)	
F2	3 (20)	23 (29)	
F3	3 (20)	20 (25)	
F4	2 (13)	7 (9)	
Rosetting of liver cells, *n* (%)	6 (40)	20 (25)	0.24
Zone 3 necrosis, *n* (%)	7 (47)	19 (24)	0.07

†Median (range).
ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; HLA, human leukocyte antigen; IgG, immunoglobulin G; SMA, smooth muscle antibody.

relapsed ($P = 0.41$). The durations from the initial normalization of serum ALT levels to the initial relapse were similar between the two groups (19.8 [11.6–40.2] months vs. 8.0 [1.5–99.5] months; $P = 0.23$). During the follow-up, no patients in group 1 reached a fatal outcome; however two patients in group 2 developed hepatocellular carcinoma and died.

DISCUSSION

IN PATIENTS IN childhood, 25–38% had liver kidney microsomal type 1 antibodies (LKM-1),[13,14] and type 2 AIH is common. In Japanese patients in adolescence and early adulthood, type 2 AIH is rare.[6] This may be a difference between patients in childhood and those in adolescence and early adulthood. However, patients in childhood had DR4 less frequently. In this study, patients in adolescence and early adulthood also showed a lower frequency of DR4. Thus, patients in adolescence and early adulthood may have clinical characteristics that fall between patients in childhood and adult patients.

In this study, type 1 AIH patients aged ≤ 30 years showed a higher frequency of histological acute hepatitis. Of four patients with histological acute hepatitis who were aged ≤ 30 years, one was negative for ANA and two had ANA titer of 1:40. ANA titers of at least 1:80 are useful for the diagnosis of AIH. Furthermore, in two of the four patients, serum IgG levels at presentation were under the upper limit of normal. ANA titers and serum IgG levels are important and useful factors for the diagnosis of AIH according to the revised scoring system proposed by the International Autoimmune Hepatitis Group.[9] Thus, a diagnosis of type 1 AIH in

adolescence or early adulthood, especially in those showing atypical features, may be difficult and should be made carefully. In contrast, one ANA-negative patient with histological acute hepatitis relapsed after the normalization of serum ALT levels. The response to immunosuppressive treatment, especially relapse after an initial response, is affirmed to be a characteristic of AIH.[9] The response to immunosuppressive treatment during the follow-up may be useful for the diagnosis in ANA-negative patients.

Recently, autoimmune thyroiditis was reported to be strongly associated with HLA DR4.[15] Furthermore, in Japanese patients with autoimmune thyroiditis, a significant positive association of the disease with HLA DRw53, which is in positive linkage disequilibria with DR4, has been demonstrated.[16] Thus, in this study, the fact that none of the patients aged ≤ 30 years had autoimmune thyroiditis might be associated with a lower frequency of DR4.

In Caucasian patients with type 1 AIH, those aged ≤ 30 years show high frequencies of corticosteroid treatment failure (24%) and death from hepatic failure, or the need for liver transplantation (21%).[5] Furthermore, they have a high frequency of HLA DR3 (59%) and a low frequency of DR4 (14%). However, in this study, Japanese patients aged ≤ 30 years showed good response and the frequency of DR4 was low (27%), although none had HLA DR3. There was no difference in the frequency of HLA DR4 between study patients in the previous report on Caucasian patients[5] and those in this study ($P = 0.32$). Thus, we speculate that the good response to corticosteroid treatment in Japanese patients in adolescence and early adulthood may be due to other factors besides HLA DR status, or that HLA DR phenotypes except DR3 may be associated with good response to corticosteroid treatment.

In this study, two adolescent patients with histological cirrhosis at presentation were able to achieve the normalization of serum transaminase levels within 3 months after the introduction of corticosteroid treatment. However, one of them relapsed 11.6 months after the normalization of serum transaminase levels. Although AIH patients respond well to immunosuppressive treatment and appropriate treatment improves histological fibrosis,[17] patients with cirrhosis at presentation, even if they are adolescent patients, tend to reach liver failure and require liver transplantation more frequently than do those without cirrhosis.[18,19] Long-term corticosteroid treatment may be required to improve the prognosis of the two adolescent patients with cirrhosis in the present study.

In the previous reports,[20,21] patients showing histological acute hepatitis had higher serum levels of bilirubin and transaminase and lower serum IgG levels than those showing chronic hepatitis. Furthermore, patients showing histological acute hepatitis were younger, although the statistically significant differences were not accepted. In this study, seven patients with acute hepatitis were younger (30 [16–52] years vs. 50 [18–59] years; $P = 0.003$) and had higher frequencies of serum IgG levels under the upper limit of normal (43 vs. 11%; $P = 0.02$) than those with chronic hepatitis. These findings may be clinical features of patients with acute hepatitis, although a further study with a large number of patients is required.

A low frequency of HLA DR4 in adolescent and early adulthood patients with type 1 AIH may indicate participation of other factors besides HLA DR status in the pathogenesis. Recently, cytotoxic T-lymphocyte antigen-4 and programmed cell death-1, which are co-stimulatory molecules, were reported to be associated with the pathogenesis of AIH.[22–24] Impairment of these co-stimulatory molecules results in downregulation of regulatory T cells and breakdown of self-tolerance. Similar to the case of primary biliary cirrhosis, interactions among several genetic factors may be important in the pathogenesis of AIH.[25]

In conclusion, type 1 AIH patients in adolescence and early adulthood show a good response to corticosteroid treatment. However, they may exhibit atypical features, for example, low frequency of HLA DR4 and high frequency of histological acute hepatitis. Thus, a diagnosis of type 1 AIH in adolescence or early adulthood may be difficult and should be made carefully. However, in this study, the study population was small and the data was retrospectively analyzed. In order to confirm these findings, a further study is required.

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CLINICAL STUDIES

Factors associated with adherence to combination therapy of interferon and ribavirin for patients with chronic hepatitis C: importance of patient's motivation and physician's treatment experience

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Keywords
adherence – retreatment – treatment centre – treatment experience

Abbreviations
HCV, hepatitis C virus; IFN, interferon; MU, million units; RT-PCR, reverse transcription polymerase chain reaction; SVR, sustained virological response.

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Abstract

Background/Aims: Adherence to combination therapy with interferon (IFN) or pegylated IFN plus ribavirin for chronic hepatitis C patients is important for a better virological response. However, the impact of the patient's treatment experience and treatment centre on adherence to combination therapy has not been fully analysed. In this prospective study, we analysed the factors that might have an effect on adherence to therapy in patients who had initial or retreatment IFN therapy. *Patients and methods:* We consecutively enrolled 363 patients with chronic hepatitis C; 221 were IFN naïve and 142 were undergoing retreatment. The mean ages of the naïve and retreatment groups were 54.8 and 55.7 years respectively. IFN α-2b was administered daily for 2 weeks, followed by three times per week for 22 weeks, while ribavirin was administered daily. We evaluated the tolerability and response to combination therapy and analysed its relevant factors. *Results:* Of the 363 patients, 189 (52%) achieved 80% adherence. The multivariate logistic regression analysis revealed that retreatment, centre with more patients treated, patient age (< 55 years), male, genotype 2 and dosage of IFN per weight (< 0.13 million units/kg) were associated with achievement of 80% adherence to combination therapy. Accordingly, the achievement of 80% adherence was more frequent in the retreatment (62%) than that in the naïve group (46%) ($P < 0.01$) and in centres with more patients treated (57%) than in those with less patients treated (46%) ($P = 0.03$). *Conclusion:* The present data suggest that the patient's motivation and the physician's treatment experience may be important for a better adherence to combination therapy for patients with chronic hepatitis C.

Approximately 170 million people are infected with hepatitis C virus (HCV) worldwide and HCV is the leading cause of chronic liver disease (1, 2). Because a combination therapy of interferon (IFN) or pegylated IFN plus ribavirin yields a higher rate of sustained virological response (SVR) than IFN monotherapy (3–5), it is currently the recommended form of therapy for patients with chronic hepatitis C (6, 7). A combination therapy, however, tends to be associated with adverse effects more frequently than those occurring with IFN monotherapy, which eventually leads to a dose reduction or discontinuation of therapy in up to 28% of the patients in randomized, controlled trials (3, 4, 8). McHutchison *et al.* (9) reported that HCV-1-infected patients who can be maintained on > 80% of their IFN or pegylated IFN and ribavirin dosage for the duration of treatment in the setting of a clinical trial exhibit an enhanced SVR rate. Therefore, adherence to combination therapy has been considered to be critical to achieve higher SVR rates in these difficult-to-treat patients.

However, we recently reported that dose modification and discontinuation of combination therapy of IFN and ribavirin were frequent among aged patients (10). Thus, deterioration in adherence to combination therapy is a serious problem, especially in aged patients such as in Japan, where patients with chronic hepatitis are 10–15 years older than those in the USA (11).

In this study, we analysed the factors that might have an effect on adherence to combination therapy in patients who had an initial or retreatment of IFN, particularly from two aspects: patient's treatment experience and treatment centre.

Patients and methods

Study design and patients

This nonrandomized prospective study was originally discussed on 12 October 2001 by a committee composed of 22 members

from 18 participating hospitals and universities. The diagnostic criteria for chronic hepatitis C, IFN regimens and follow-up protocols were finalized by the committee on 9 November 2001.

The study design focused on adherence to the therapy from two aspects: patient's treatment experience and treatment centre. Patients were classified into two groups as follows: (i) treatment experience, patients who had previously received IFN therapy (retreatment group) or those who had never received (naïve group) it, (ii) treatment centre, treatment in a centre with 15 or more cases treated per year ($\geq$15 cases/year centre group), or treatment in a centre with $<$ 15 cases treated per year ($<$ 15 cases/year centre group) and (iii) physician's experience in years ($\geq$19 vs. $<$ 19 years). Patients were compared with respect to the safety and efficacy of combination therapy.

Patients were eligible for inclusion if they were adults ($\geq$18 years of age) who were positive for HCV RNA, as determined by a qualitative polymerase chain reaction assay, had exhibited elevated levels of serum alanine aminotransferase above the upper normal limit in the 6 months before entry into the study and had compensated liver function with normal levels of serum albumin, prothrombin time and serum bilirubin. Patients were excluded from the study if they had other underlying causes of chronic liver disease such as hepatitis B, autoimmune hepatitis, primary biliary cirrhosis or drug-induced liver injury, had cirrhosis, had injected drugs or abused alcohol within the previous 6 months, had poorly controlled psychiatric illness or were antihuman immunodeficiency virus positive. Cirrhosis was excluded based on histological, clinical or imaging parameters. The clinical criteria consisted of one or more of the features of portal hypertension, such as hypersplenism, oesophageal varices and ascites or hepatic encephalopathy, whereas the imaging criteria were the findings on ultrasonography or computed tomography of the typical irregular-surfaced liver with a coarse architecture, suggestive of cirrhosis.

Recombinant IFN α-2b (Intron A; Schering-Plough Pharmaceutical Co., Osaka, Japan) and ribavirin (Rebetol; Schering-Plough Pharmaceutical Co.) were the drugs selected for therapy. All participants were scheduled to receive 24 weeks of combination therapy in accordance with the Japanese National Health Insurance rules. Patients were treated with high-dose induction therapy with IFN, because, at the time the study was begun, IFN therapy was routinely limited to a period of up to 24 weeks, as required by the Japanese National Health Insurance. Thus, patients received IFN α-2b by a subcutaneous injection daily for 2 weeks, followed by the same dose given three times per week for 22 weeks and ribavirin was administered daily. Patients weighing $<$ 60 kg received 6 million units (MU) of IFN α-2b and 600 mg of ribavirin, whereas patients weighing 60 kg or more received 10 MU of IFN α-2b and 800 mg of ribavirin. Lower doses of ribavirin rather than higher doses (1000 or 1200 mg/day) were chosen because of the difference in weight between the Japanese and European or American population.

A data sheet that included the clinical, biochemical, virological and histological data of each patient was submitted to the supervisory committee at the Okayama University for approval. Approval for this study was obtained from the ethics committee of each participating institution. Informed consent was obtained from each patient according to the Helsinki Declaration.

Determination of hepatitis C virus RNA levels and hepatitis C virus genotypes

Serum HCV RNA was detected by a reverse transcription polymerase chain reaction (RT-PCR) (Amplicor HCV Test, version 2.0; Roche Diagnostics Japan, Tokyo, Japan) (detection limit 50 IU/ml). The serum HCV load was determined at baseline using the RT-PCR (Amplicor HCV Monitor Test, version 2.0; Roche Diagnostics Japan). HCV RNA genotype was determined by RT-PCR using genotype-specific primers (12) or by the serological grouping of serum antibodies determined by an enzyme-linked immunosorbent assay (SRL Laboratory Co., Tokyo, Japan) according to the method of Tanaka *et al.* (13), assuming that genotypes 1a and 1b corresponded to serological group 1 (genotype 1) and genotypes 2a and 2b corresponded to serological group 2 (genotype 2) (14).

Assessment of safety

Patients were assessed for safety and tolerance during treatment by each attending doctor by monitoring the adverse events and laboratory abnormalities, such as haemoglobin level, white blood cell count and platelet count, at weeks 1, 2, 4, 6 and 8 and monthly thereafter. Adverse events were handled according to the manufacturers' instructions for combination therapy of IFN α-2b plus ribavirin and therapy adjustments were performed. Dose reductions and discontinuation of therapy were carried out, in general, according to the recommendations in the manufacturer's instructions. Further dose reductions or discontinuation of one or both drugs could be performed at the discretion of the investigators at each of the clinical centres for ongoing haematological adverse events, neuropsychiatric, cutaneous and other adverse effects thought to be related to these medications. The doses of IFN α-2b and ribavirin could be increased back to the starting doses if these adverse events resolved. Treatment discontinuation was considered total if both IFN α-2b and ribavirin were discontinued and partial if only ribavirin was discontinued. Reduction of doses for IFN α-2b was defined as a reduction from the standard 6 or 10 to 3 MU, and for ribavirin as a reduction in the dose from 600 to 400 mg or less and from 800 to 600 mg or less, without discontinuation of IFN α-2b.

Adherence to combination therapy was assessed as described previously (9, 15), namely, by calculating separately the actual doses of IFN and ribavirin received as a percentage of the expected dose. Thus, patients who received 80% or more of both their total IFN and ribavirin doses for 80% or more of the expected duration of therapy were considered to be 80% adherent.

Assessment of efficacy

An SVR was defined as serum HCV RNA negativity at 24 or more weeks after completion of IFN treatment, whereas patients who were positive at 24 weeks after completing treatment were considered to have a non-SVR.

Statistics

Differences in the baseline clinical characteristics, safety and efficacy among the patient groups were compared statistically using the *t*-test, Mann–Whitney's *U* test and χ^2 test, as required, on release 6 JMP software (SAS Institute Inc., Cary, NC, USA). The cumulative incidence of dose reduction and discontinuation of IFN and ribavirin, respectively, were estimated using the Kaplan–Meier method and compared using the log–rank test. Univariate or multivariate logistic regression analyses were used to establish the factors contributing to the efficacy and safety of combination therapy. Variables exhibiting statistical

significance ($P < 0.10$) in the univariate analysis were subjected to multivariate analysis. A risk ratio with a 95% confidence interval was denoted for each analysis.

Results

Patient enrollment

A total of 363 consecutive Japanese patients with chronic hepatitis C treated by a combination therapy of IFN plus ribavirin were enrolled in this study between December 2001 and August 2004. The clinical and laboratory characteristics of patients at baseline are shown in Table 1. Significant differences existed in terms of sex, genotype, platelet count and administered IFN dosage per weight between the retreatment and the naïve patients. The ratios of male and genotype 1 in the retreatment group were higher than those in the naïve group. Platelet count and administered IFN dosage per weight in the retreatment group were lower than those in the naïve group. The creatinine level in the ≥15 cases/year centre group was higher than that in the <15 cases/year centre group, and creatinine clearance in the ≥15 cases/year centre group was lower than that in the <15 cases/year centre group. There were more experienced physicians in the ≥15 cases/year centre group than that in the <15 cases/year centre group. The other characteristics were not significantly different.

Safety

Dose reduction and discontinuation rate

The cumulative incidence of dose reduction and discontinuation of IFN and ribavirin in the retreatment group were significantly lower than those in the naïve group respectively ($P < 0.01$) (Fig. 1). The cumulative incidence of dose reduction of IFN and ribavirin and cumulative discontinuation of ribavirin in the ≥15 cases/year centre group were significantly lower than those in the <15 cases/year centre group respectively ($P < 0.01$). On the other hand, the cumulative incidence of dose reduction of IFN and ribavirin and discontinuation of ribavirin were higher in the ≥15 cases/year centre than in the <15 cases/year centre during the first 6 weeks of treatment. However, the incidence was reversed and became higher in the <15 cases/year centre than in the ≥15 cases/year centre after that term (Fig. 2). The cumulative incidence of discontinuation of IFN was similar between these groups.

Adherence to therapy

Of the 363 patients, 189 (52%) achieved 80% adherence. Achievement of 80% adherence in the retreatment group was higher than that in the naïve group (62 vs. 46%; $P < 0.01$) (Fig. 3a). Achievement of 80% adherence in the ≥15 cases/year centre group was higher than that in the <15 cases/year centre group (57 vs. 46%; $P = 0.03$) (Fig. 3b).

Other factors associated with achievement of 80% adherence

The clinical and laboratory variables potentially associated with the achievement of 80% adherence to combination therapy were analysed by a logistic regression analysis. The univariate analysis showed that patient's treatment experience (retreatment), sex (male), patient age (< 55 years), weight (≥60 kg), treatment in the ≥15 cases/year centre, treatment by physician with ≥19 years experience, genotype 2, haemoglobin level (≥14 g/dl) and dosage of IFN per weight (< 0.13 MU/kg) were significantly associated with the achievement of 80% adherence. With multivariate logistic regression analysis, dosage of IFN per weight (< 0.13 MU/kg), patient age (< 55 years), sex (male), patient's treatment experience (retreatment), genotype 2 and treatment in the ≥15 cases/year centre were independently associated with the achievement of 80% adherence (Table 2).

Efficacy

Response to interferon therapy

Of the 363 patients, 124 (34%) achieved SVR. The SVR rates were 27% (39 of 142) and 38% (85 of 221) in the retreatment and the naïve groups, respectively, and were significantly lower in the retreatment group than in the naïve group (P=0.03). The SVR rates were 35% (71 of 203) and 33% (53 of 160) in the ≥15 cases/year centre and the <15 cases/year centre groups, respectively, and were not significantly different. Then, the SVR rates were analysed according to genotype and viral load. In patients with genotype 1 and a high viral load (≥100 kIU/ml), the SVR rates were 13% (14 of 104) and 12% (16 of 132) in the retreatment and the naïve groups, respectively, and were 14% (18 of 133) and 12% (12 of 103) in the ≥15 cases/year centre and the <15 cases/year centre groups respectively. In patients with genotype 2 or a low viral load (<100 kIU/ml), the SVR rates were 66% (25 of 38) and 78% (69 of 89) in the retreatment and the naïve groups, respectively, and were 76% (53 of 70) and 72% (41 of 57) in the ≥15 cases/year centre and the <15 cases/year centre groups respectively. The SVR rates were not significantly different in any of the analyses (Fig. 4).

Other factors associated with achievement of a sustained virological response

The clinical and laboratory variables potentially associated with the achievement of SVR were analysed by a logistic regression analysis. The univariate analysis indicated that retreatment, genotype 2, HCV RNA level (< 100 kIU/ml) and achievement of 80% adherence to therapy were important factors for SVR. Multivariate analysis revealed that low viral load, genotype 2 and achievement of 80% adherence were independently associated with SVR (Table 3).

Discussion

It has been indicated that management of adherence to therapy is quite important for an improvement in the virological response rates (9, 15–18). The present study also demonstrated that HCV RNA levels, genotype and adherence to therapy were independently associated with SVR (Table 3). Among these factors, adherence to therapy is the only variable factor. Thus, it is essential to improve adherence to therapy in order to improve the SVR rates (9).

In the present study, the achievement rate of 80% adherence in the retreatment group was significantly higher than that in the naïve group (Fig. 3a). It has been demonstrated in several studies that a combination therapy of IFN plus ribavirin has a negative effect on the health-related quality of life in patients with chronic hepatitis C (19–22). Therefore, it is suggested that retreated patients had greater motivation for therapy, enough to

Table 1. Baseline characteristics of patients according to patient's treatment experience and treatment centre

Characteristics	All patients ($n=363$)	Treatment experience			Treatment centre		
		Retreatment ($n=142$)	Naïve ($n=221$)	P*	≥15 cases/year centre ($n=203$)	< 15 cases/year centre ($n=160$)	P†
Sex, male/female (% male)	226/137 (62)	100/42 (70)	126/95 (57)	0.01	130/73 (64)	96/64 (60)	0.43
Age (years)‡	55.2 ± 9.7	55.7 ± 8.6	54.8 ± 10.4	0.40	56.0 ± 9.5	54.1 ± 9.9	0.08
Weight (kg)‡	62.3 ± 10.6	63.4 ± 9.9	61.7 ± 11.1	0.14	62.2 ± 10.4	62.5 ± 11.0	0.80
BMI (kg/m^2)	23.8 ± 3.0	24.0 ± 2.9	23.7 ± 3.1	0.38	23.7 ± 2.9	23.8 ± 3.3	0.66
≥15 cases/year centre/ < 15 cases/year centre (% ≥15 cases/year centre)	203/160 (56)	80/62 (56)	123/98 (56)	0.90			
Retreatment/naïve (% retreatment)	142/221 (39)				80/123 (39)	62/98 (39)	0.90
Physician's experience (% ≥19 years)	139/224 (38)	56/86 (39)	83/138 (38)	0.71	91/112 (45)	48/112 (30)	< 0.01
Genotype				< 0.01			0.77
1	257 (71)	114 (80)	143 (65)		145 (71)	112 (70)	
2	106 (29)	28 (20)	78 (35)		58 (29)	48 (30)	
HCV RNA (kIU/ml)§	720 (390–850)	690 (380–850)	730 (403–850)	0.67	670 (360–850)	750 (450–850)	0.11
ALT (IU/L)§	82 (53–122)	79 (53–117)	83 (55–126)	0.44	78 (52–115)	86 (61–128)	0.06
WBC (/μl)‡	5052 ± 1278	4942 ± 1222	5122 ± 1311	0.84	4940 ± 1245	5193 ± 1308	0.06
Haemoglobin (g/dl)‡	14.3 ± 1.4	14.4 ± 1.4	14.3 ± 1.4	0.29	14.4 ± 1.3	14.3 ± 1.4	0.82
Plt (103/μl)‡	155 ± 54	148 ± 50	160 ± 56	0.04	154 ± 52	156 ± 56	0.74
Creatinine (mg/dl)‡	0.73 ± 0.16	0.74 ± 0.16	0.72 ± 0.17	0.25	0.75 ± 0.17	0.70 ± 0.16	< 0.01
CCr (mg/day)‡	99 ± 27	99 ± 25	99 ± 29	0.89	95 ± 26	103 ± 28	< 0.01
IFN/weight (MU/kg)‡	0.13 ± 0.04	0.13 ± 0.03	0.14 ± 0.04	0.01	0.13 ± 0.04	0.14 ± 0.04	0.27
Ribavirin/weight (mg/kg)‡	11.6 ± 1.3	11.5 ± 1.4	11.6 ± 1.8	0.66	11.6 ± 1.2	11.5 ± 1.4	0.74

*Comparison between the retreatment and the naïve groups.

†Comparison between the ≥15 cases/year centre and the < 15 cases/year centre groups.

‡Mean ± SD.

§Median (interquartile range).

ALT, alanine aminotransferase; BMI, body mass index; CCr, creatinine clearance; HCV, hepatitis C virus; IFN, interferon; MU, million units; Plt, platelet count; WBC, white blood cell count.

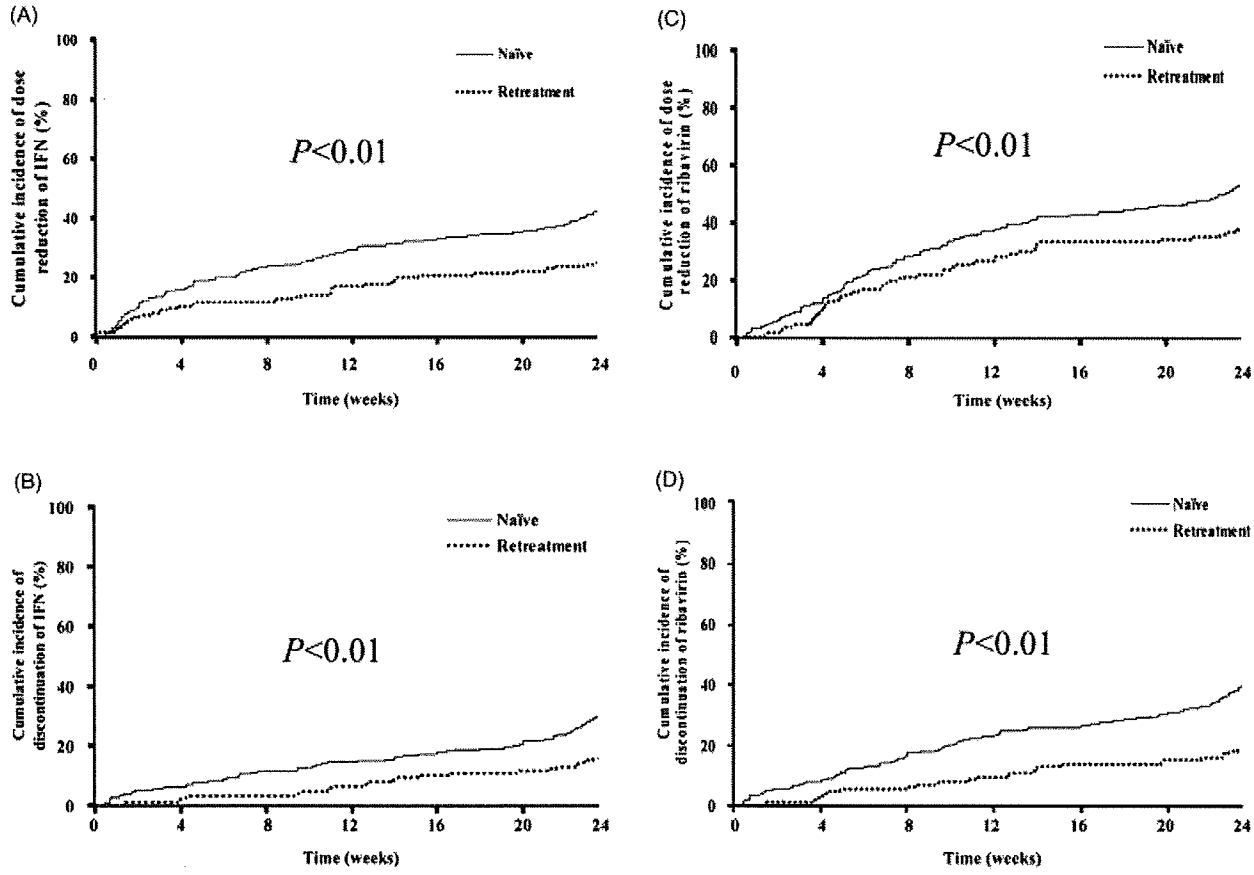

Fig. 1. Cumulative incidence of (a) dose reduction and (b) discontinuation of interferon (IFN) and (c) dose reduction and (d) discontinuation of ribavirin in retreatment and naïve patients. Cumulative incidence of dose reduction and discontinuation of IFN and ribavirin in the retreatment group (broken line) were significantly lower than those in the naïve group (solid line) respectively ($P < 0.01$ for each comparison).

tolerate the deterioration of health-related quality of life during retreatment in contrast to naïve patients. Because poorly motivated patients would not attempt to undergo retreatment, it is also suggested that highly motivated patients were selected for retreatment. Another possible reason is an experience of adverse events and laboratory abnormalities in a previous treatment. It is suggested that only patients who had mild or few adverse events and laboratory abnormalities in a previous treatment attempted retreatment. Motivation for retreatment in patients who had experienced moderate to severe adverse events would be impaired. On the other hand, patients who had higher levels of blood cell counts before treatment might have had fewer laboratory abnormalities in the previous treatment and thus might be selected for retreatment. However, the latter seems not to be the case in the present study, because blood cell counts except platelet counts, which were significantly lower in the retreatment group, were similar between the groups (Table 1).

There are few reports in which adherence and virological response to combination therapy were analysed in terms of treatment centre. We assumed that treatment results should be excellent in centres with more patients treated compared with those with less patients treated because, as the number of treated patients increases, the centre should gain greater experience. As expected, the rate of achievement of 80% adherence in the ≥ 15 cases/year centre was significantly higher than that in the < 15 cases/year centre (Fig. 3b), although more difficult-to-treat patients were treated in the ≥ 15 cases/year centre than in the < 15 cases/year centre (Table 1). On the other hand, it may be expected that the ratio of retreatment patients, who showed better adherence to therapy in the present study, would be higher in the ≥ 15 cases/year centre than in the < 15 cases/year centre by selection bias for treatment candidate. However, this was not the case (Table 1).

Physicians in the ≥ 15 cases/year centre should gain greater experience of treatment than those in the < 15 cases/year centre. On the other hand, there were more experienced physicians in the ≥ 15 cases/year centre group than in the < 15 cases/year centre group (Table 1). Multivariate logistic regression analysis revealed that only treatment in the ≥ 15 cases/year centre was independently associated with better adherence (Table 2). However, it was suggested that these two factors, treatment centre and physician's experience in number of years, were confounding factors. Thus, such experienced physicians could detect adverse events early and appropriately adjust the dose of IFN and ribavirin on time and restrain dropouts. In the present study, dose reduction of IFN and ribavirin was more frequent in the ≥ 15 cases/year centre than that in the < 15 cases/year centre during the initial 6 weeks of therapy. This indicated that experienced physicians in the ≥ 15 cases/year centre treated more difficult-to-treat patients who required early dose adjustment. They might also adjust

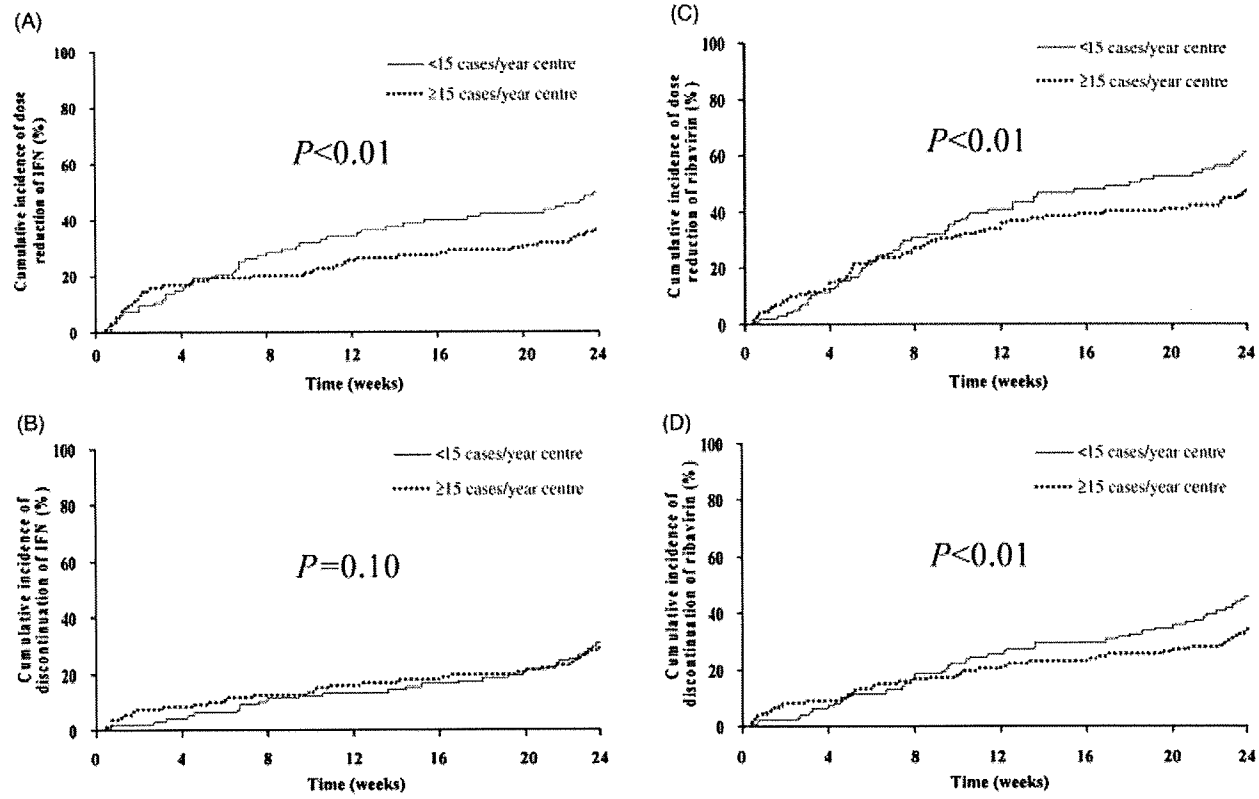

Fig. 2. Cumulative incidence of (a) dose reduction and (b) discontinuation of interferon (IFN) and (c) dose reduction and (d) discontinuation of ribavirin in the ≥ 15 cases/year centre and the < 15 cases/year centre. Cumulative incidence of dose reduction of IFN and ribavirin and discontinuation of ribavirin in the ≥ 15 cases/year centre group (broken line) were significantly lower than those in the < 15 cases/year centre group (solid line) respectively ($P < 0.01$ for each comparison).

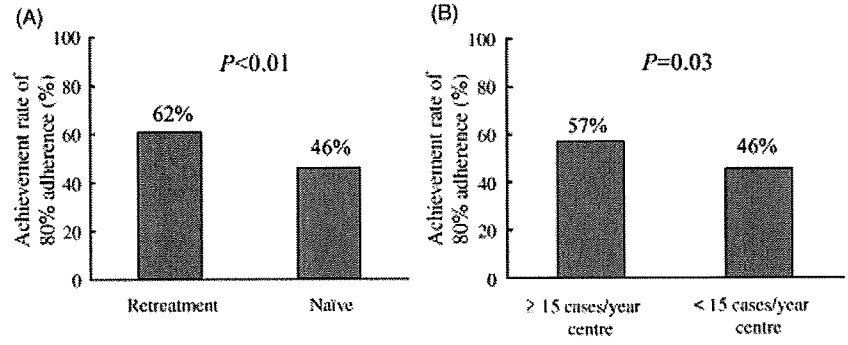

Fig. 3. Comparison of the achievement rate of 80% adherence in the naïve and the retreatment groups (a) and in the ≥ 15 cases/year centre and the < 15 cases/year centre groups (b). The achievement rate of 80% adherence in the retreatment group was higher than that in the naïve group (62 vs. 46%, $P < 0.01$). Achievement of 80% adherence in the ≥ 15 cases/year centre group was higher than that in the < 15 cases/year centre group (57 vs. 46%, $P = 0.03$).

dose at an earlier stage by anticipating a further deterioration of blood cell counts or adverse events in order to avoid complete discontinuation of treatment. Castera *et al.* (23) reported that early detection and appropriate management of psychiatric side effects during pegylated IFN and ribavirin therapy allowed optimizing adherence and virological efficacy. Therefore, it is suggested that experienced physicians promptly and adequately responded to manage adverse events, resulting in an improvement of adherence to therapy and avoidance of discontinuation. The present study also demonstrated that patient age, gender and dose of IFN per weight, besides patients' treatment experience and treatment centre, were associated with adherence to therapy. These findings were in accordance with previous reports in only naïve patients (10).