approximately 3,200 nucleotides (nt), and named by capital Alphabet letters from A to H in the order of discovery [Okamoto et al., 1988; Norder et al., 1992; Stuyver et al., 2000; Araúz-Ruiz et al., 2002]. It has not been established, as yet, whether or not HBV genotypes influence the response to long-term lamivudine and the emergence of YMDD mutants accompanied by breakthrough hepatitis [Zollner et al., 2001; Akuta et al., 2003; Chan et al., 2003; Yuen et al., 2003b; Moskovitz et al., 2005; Thakur et al., 2005].

As in other Asian counties, genotypes B and C have been prevalent in Japan, probably since the prehistoric era [Orito et al., 1989]. Recently, however, infection with genotype A has been increasing predominantly in young men with promiscuous homo- or hetero-sexual contacts [Kobayashi et al., 2002, 2004; Ogawa et al., 2002]. Infection with HBV genotype A can persist, even if contracted in adulthood, in about 10% of cases [Sherlock, 1987; Kobayashi et al., 2006]. These circumstances provided an opportunity to compare the efficacy and side effects of long-term lamivudine, among patients infected with HBV genotypes A, B, and C, in a single Hepatology Center in Metropolitan Tokyo.

MATERIALS AND METHODS

Patients

During almost 10 years from September 1995 through July 2004, 502 patients infected persistently with HBV and diagnosed with chronic liver disease received oral lamivudine 100 mg per day for longer than 1 year. Genotypes were A in 15 (2.6%) patients, B in 38 (7.6%) and C in the remaining 449 (89.4%). The median age was 44 years (range: 18–73 years) and included 407 (81%) men were included. Of these, 426 (84.9%) had chronic hepatitis and the remaining 73 (14.5%) possessed cirrhosis. Chronic hepatitis was diagnosed by liver biopsies performed under laparoscopy, and cirrhosis by liver biopsy and/or ultrasonographic images plus laparoscopic findings. The median serum level of HBV DNA was 7.2 log genome equivalents (LGE)/ml, and HBeAg was positive in 264 (52.6%) of them. They were given lamivudine for a median of 6.9 years (range: 1–10.2 years) and followed for a median of 6.9 years (0.1–31.2); lamivudine was discontinued in only 62 (12.4%) patients.

During and after treatment, the 502 patients were followed monthly for liver function and serum markers of HBV infection. YMDD mutants were determined at the baseline, and monitored yearly as well as at the development of breakthrough hepatitis. The study design conformed to the 1975 Declaration of Helsinki, and was approved by the Ethic Committee of the institution. Every patient gave an informed consent for this study.

Serological Markers of HBV Infection

HBsAg was determined by hemagglutination (MyCell; Institute of Immunology Co. Ltd., Tokyo, Japan) or enzyme-linked immunosorbent assay (ELISA) (ELISA, F-HBsAg; Sysmex, Kobe, Japan), and HBeAg by ELISA (ELISA, F-HBe; Sysmex). HBV DNA was determined by transcription-mediated amplification and hybridization assay (TMA; Chugai Diagnostics, Tokyo, Japan) and the results were expressed in LGE/ml over a detection range from 3.7 to 8.7.

Determination of HBV Genotypes

The six major genotypes (A–F) were determined serologically by ELISA (HBV GENOTYPE EIA; Institute of Immunology). The method is based on the combination of epitopes on preS2-region products that is specific for each genotype [Usuda et al., 1999, 2000]. Genotype G was determined by preS2 serotype for genotype D and HBsAg subtype adw, and H by those for C and adw, respectively; these combinations are specific for genotypes G and H, respectively [Kato et al., 2001, 2004]. Thus, all the eight HBV genotypes were determined serologically.

Determination of YMDD Mutants

YMDD mutants were determined by restriction fragment length polymorphism (RFLP) [Chayama et al., 1998] and Enzyme-Linked Mini-sequence Assay with commercial assay kits (PCR-ELMA; Genome Science).

Statistical Analysis

Categorial variables were compared between groups by the Mann–Whitney U test and Fisher's exact test, and noncategorial variables by the Wilcoxon signed rank test. Loss of HBeAg, HBsAg or HBV DNA, emergence of YMDD mutants and development of breakthrough hepatitis were compared in the Kaplan-Meier life table, and differences were evaluated by the log-rank test with use of the production limit method. Factors independently influencing emergence of YMDD mutants and development of breakthrough hepatitis were evaluated in the Cox proportion hazard model. A P-value less than 0.05 was considered significant. Analysis of data was performed with the computer program SPSS software (SPSS, Inc., Chicago, IL).

RESULTS

Baseline Characteristics of Patients Treated by Long-Term Lamivudine

Patients infected with HBV genotype A, B, or C were compared before they were placed on long-term lamivudine therapy (Table I). Patients with genotype A were significantly younger, had higher levels of HBV DNA and HBeAg more frequently than those with genotype B or C. Men predominated in the patients infected with genotypes A, B, or C. There were no differences in the duration of treatment with lamivudine or severity of liver disease among patients infected with the three HBV genotypes.

TABLE I. Baseline Characteristics of Patients With Chronic Hepatitis B Who Received Lamivudine for Longer Than 1 Year

Features	Genotypes of HBV			Differences (*P*-value)
	A (n = 15)	B (n = 38)	C (n = 449)	
Age (years)	37 (24–49)	47 (24–67)	44 (18–73)	0.015
Men	14 (93%)	34 (91%)	359 (80%)	NS
Treatment duration (years)	2.7 (1.2–5.2)	2.3 (1.0–5.7)	3.6 (1.0–9.6)	NS
Chronic hepatitis	13 (87%)	33 (87%)	383 (85%)	NS
Cirrhosis	2 (13%)	5 (13%)	66 (15%)	NS
HBV DNA (LGE/ml)	8.6 (6.1–8.7)	6.5 (<3.7–8.7)	6.5 (<3.7–8.7)	0.024
HBeAg	11 (73%)	8 (21%)	245 (56%)	0.0001

Clearance of HBV Markers in Patients Treated by Long-Term Lamivudine

Time courses of clearance of HBeAg and HBsAg during long-term lamivudine are compared among patients infected with HBV genotypes A, B, and C in Figure 1a and 1b, respectively. The clearance of HBeAg or HBsAg was no different among patients infected with HBV of three genotypes during the first five years on lamivudine (Fig. 1a,b).

During lamivudine treatment for longer than 192 weeks (>3.7 years), HBV DNA disappeared from serum only in less than half patients with genotype A, significantly less frequently than in patients with genotype B or C; more than three quarters of them lost it (Fig. 2).

Emergence of YMDD Mutants and Development of Breakthrough Hepatitis During Long-Term Lamivudine Therapy

Emergence of YMDD mutants and development of breakthrough hepatitis were compared among patients infected with HBV of the three genotypes. During the first 4 years on lamivudine therapy, YMDD mutants emerged in 89% of patients with genotype A, significantly more often than in those with genotype B or C; such mutants elicited in only less than half of them

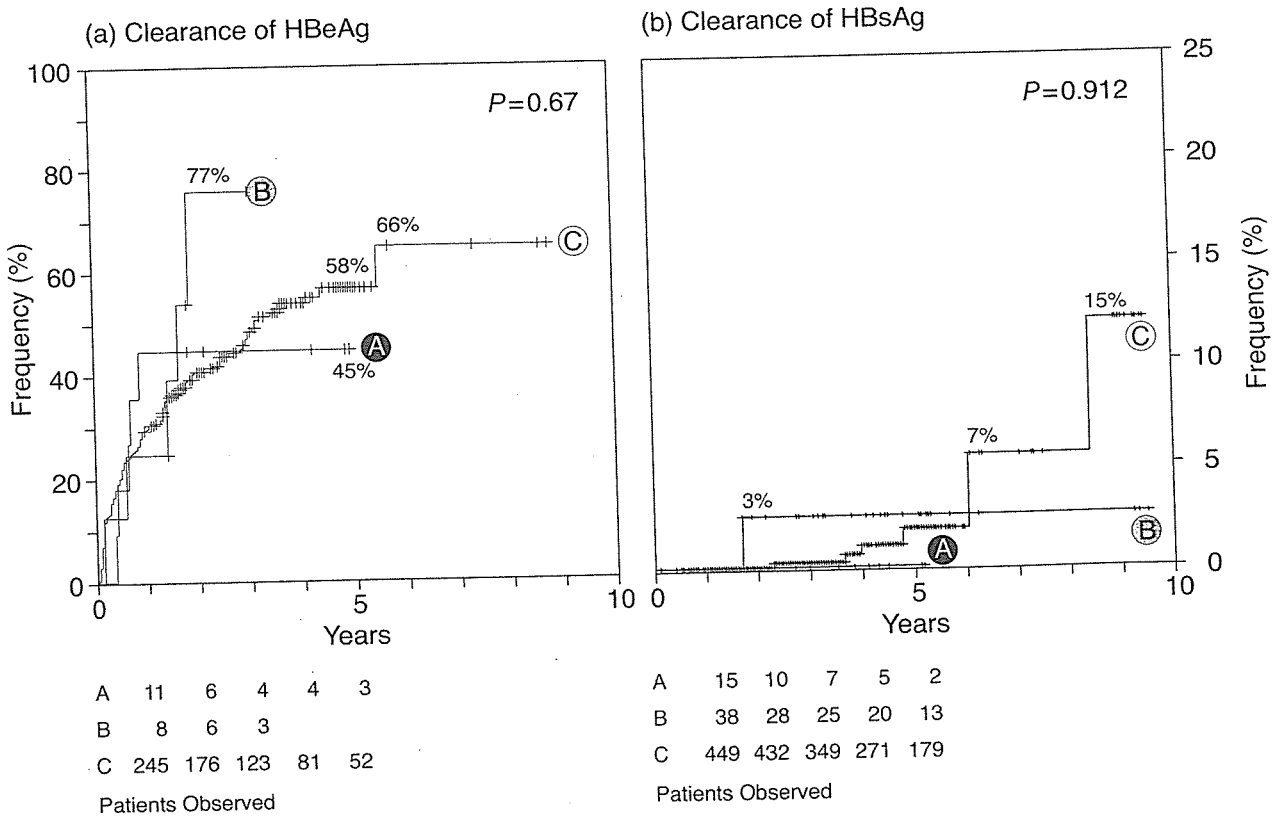


Fig. 1. Serum markers for HBV infection in patients on long-term lamivudine therapy. Patients infected with HBV genotypes A, B, or C are compared for the clearance of HBeAg (**a**) and HBsAg (**b**). Numbers of patients observed at each year are shown below for those infected with genotypes A, B, and C.

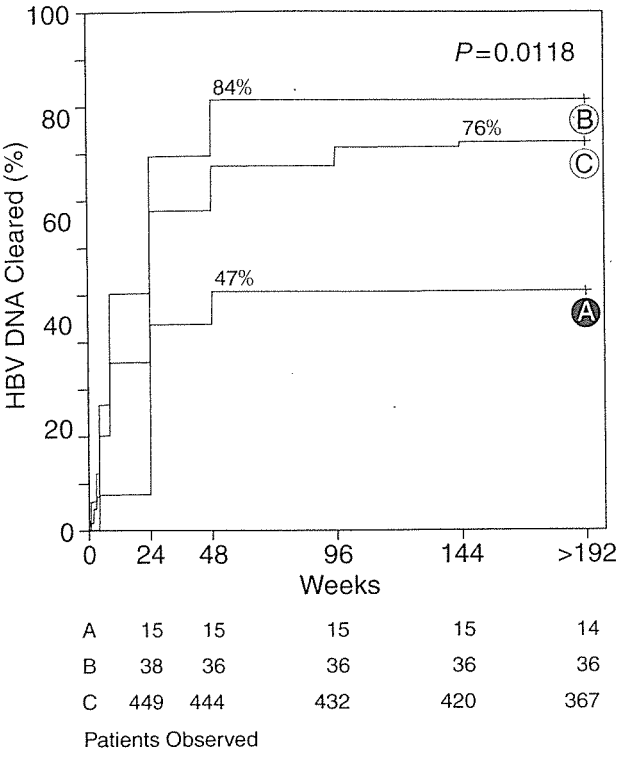


Fig. 2. Clearance of HBV DNA from serum of patients on long-term lamivudine therapy. Patients infected with HBV genotypes A, B, or C are compared. Numbers of patients observed at each year are shown below for those infected with genotypes A, B, and C.

(Fig. 3a). Reflecting the emergence of lamivudine-resistant mutants, breakthrough hepatitis developed twice more frequently in patients with genotype A than B or C (Fig. 3b).

YMDD mutants elicited more often in patients with genotype A than B or C who were positive (82% [9/11] vs. 25% [2/8] or 48% [117/245], $P = 0.037$) or negative for HBeAg (75% [3/4] vs. 30% [9/30] or 33% [68/204], $P = 0.003$).

Factors Influencing YMDD Mutants and Breakthrough Hepatitis

Risks for YMDD mutants and breakthrough hepatitis were evaluated on the nine variables. They included age, gender, liver pathology, cholin esterase, ALT, aspartic transaminase, HBV DNA, HBV genotypes, and HBeAg. In multivariate analysis, only HBeAg at the baseline and genotype A were independent factors significantly increasing the emergence of YMDD mutants (Table II).

Likewise, factors influencing the development of breakthrough hepatitis were evaluated by multivariate analysis (Table III). ALT <500 U/L, HBeAg, cirrhosis (present in about 15% of patients infected with any genotype (Table I)), and HBV DNA > 8.0 LGE/ml at the baseline independently increased the development of breakthrough hepatitis; genotypes did not make significant differences, however.

DISCUSSION

Long-term lamivudine therapy is beneficial for patients with chronic hepatitis B [Lok and McMahon, 2001; Dienstag et al., 2003; Kumada, 2003; Lok et al., 2003], and can retard the progression of fibrosis [Lai et al., 1998; Dienstag et al., 2003; Suzuki et al., 2003b]. Remarkably, treatment decreased the incidence of hepatocellular carcinoma from 7.4% to 3.9% during the median of 2.7 years [Liaw et al., 2004] and from 13.3% to 1.1% during 2.7 years or longer in a multicenter retrospective study [Matsumoto et al., 2005]. Emergence of YMDD mutants and breakthrough hepatitis, however, prohibit long-term treatment with lamivudine [Honkoop et al., 1997; Allen et al., 1998; Chayama et al., 1998; Liaw et al., 1999; Suzuki et al., 1999]. Such adverse events, however, can be managed by timely intervention with other antiviral drugs [Suzuki et al., 2002, 2003b]. Due to merits far outweighing its drawbacks, long-term lamivudine therapy has been favored for the treatment of patients with chronic hepatitis B.

Viral factors can influence the efficacy of lamivudine. Thus pretreatment low HBV DNA levels and absence of serum HBeAg enhance response to lamivudine [Lai et al., 1998; Tassopoulos et al., 1999; Liaw, 2002; Rizzetto, 2002]. Insofar as HBV genotypes make differences in the severity of liver disease and the development of hepatocellular carcinoma [Kao et al., 2000; Orito et al., 2001; Chu and Lok, 2002], they may affect the response to lamivudine, as well. There have been conflicting views, however, on the influence of HBV genotypes on the response to lamivudine [Kao et al., 2002; Chan et al., 2003; Yuen et al., 2003b; Moskovitz et al., 2005]. Geographical distribution of HBV genotypes hampers comparison among three or more genotypes in any single country. Mostly only two genotypes prevail, typified by B and C in Asia, and A and D in Western countries [Lindh et al., 1997; Miyakawa and Mizokami, 2003]. Even when four or more HBV genotypes were compared for response to lamivudine therapy, patients had been assorted from many countries with diverse ethnic backgrounds and distinct modes of transmission [Janssen et al., 2005].

As in the majority of Asian countries, genotypes B and C are common in Japan. Infection with genotype A, however, has increased predominantly in the Metropolitan areas [Kobayashi et al., 2002; Ogawa et al., 2002; Yotsuyanagi et al., 2005]. Genotype A infection tends to persist even when it is contracted in the adulthood [Kobayashi et al., 2002; Suzuki et al., 2005]. These backgrounds gave us the opportunity to compare response to long-term lamivudine treatment and development of YMDD mutants, along with breakthrough hepatitis, among patients of a single ethnicity and infected with HBV genotypes A, B, or C. As a result, some differences surfaced among infections with the three genotypes.

At the baseline, patients with genotype A were younger, and more often positive for HBeAg than those with B or C. Frequent HBeAg in patients with

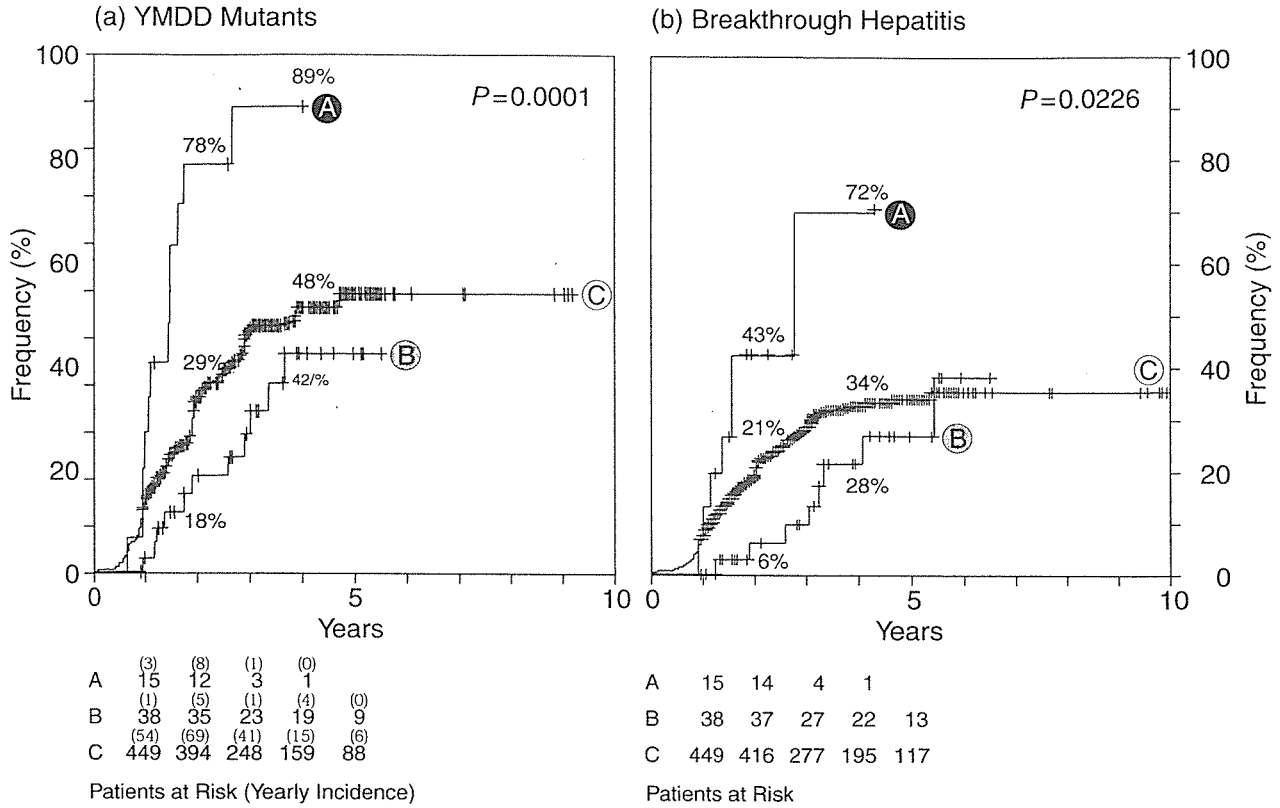


Fig. 3. Adverse events during long-term lamivudine therapy. Patients infected with HBV genotypes A, B, or C are compared for the development of YMDD mutants (**a**) and breakthrough hepatitis (**b**). Numbers of patients at risk at each year are shown below for those infected with genotypes A, B, and C. Development of YMDD mutants during each year is indicated in parentheses.

genotype A may be due to rare precore stop-codon mutation (G1896A) that is unacceptable for HBV DNA of this genotype [Li et al., 1993]. Nucleotide (nt) at the position 1896 is G in the wild-type HBV strains of any genotype, and makes a pair with nt 1858 of T in most of them. Exceptionally, nt 1858 is C in HBV of genotype A. Since a point mutation of G for A at nt 1896 breaks the Watson-Crick pair (C–G) between nt 1858 and 1986 and destabilizes stem-loop structures conforming the 'ε' encapsidation signal, it prohibits the replication of HBV genotype A. In addition, the duration of infection can make differences in the HBeAg status; it is much shorter in patients with genotype A infected in the adulthood than in those with genotype B or C who have been transmitted with HBV perinatally.

During long-term lamivudine therapy, HBV DNA was cleared less often in patients with genotype A than B or C (Fig. 2). In accordance with a poor virological response, YMDD mutants developed more frequently in patients with genotype A than B or C, both in those with (82% [9/11] vs. 25% [2/8] or 48% [117/245], $P=0.037$) and without baseline HBeAg (75% [3/4] vs. 30% [9/30] or 33% [68/204], $P=0.003$).

In multivariate analysis, pretreatment HBeAg and genotype A were significant predictive factors for the emergence of YMDD mutants. In confirmation of previous results [Chien et al., 1999; Liaw, 2002;

TABLE II. Factors Influencing the Emergence of YMDD Mutants*

Factor	Category	Hazard ratio (95% confidence interval)	*P*-value
HBeAg	1: –	1	
	2: +	2.11 (1.53–2.92)	<0.001
HBV genotype	1: B	1	
	2: C	1.23 (0.62–2.42)	0.56
	3: A	2.78 (1.08–7.12)	0.034

*Evaluated by the Cox proportion hazard model.

TABLE III. Pretreatment Variables Influencing the Development of Breakthrough Hepatitis*

Factor	Category	Hazard ratio (95% confidence interval)	*P*-value
ALT	1: ≥500 U/L	1	0.018
	2: <500 U/L	2.56 (1.82–5.56)	
HBeAg	1: –	1	
	2: +	2.11 (1.40–3.16)	<0.001
Pathology	1: Chronic hepatitis	1	
	2: Cirrhosis	1.92 (1.24–2.97)	0.004
HBV DNA	1: <8.0 LGE/ml	1	
	2: >8.0 LGE/ml	1.57 (1.04–2.36)	0.03

*Evaluated by the Cox proportion hazard model.

Kumada, 2003], low ALT levels, HBeAg, severe liver disease, and high HBV DNA at the baseline independently enhanced the development of breakthrough hepatitis (Table III). Breakthrough hepatitis was not influenced by HBV genotypes, however, probably because of the patients with genotype A were fewer than those with genotype B or C (15 vs. 38 or 449). Such great differences in number might have caused a statistical bias in comparison among the three genotypes.

The influence of HBV genotypes on the emergence of lamivudine-resistant mutants has been controversial. Previous studies failed to find differences between infection with genotypes B and C [Yuen et al., 2003a,b; Sun et al., 2005]. The risk of lamivudine resistance is reported to increase in infection with genotype A (represented by HBsAg subtype adw) compared to genotype D (ayw) [Zollner et al., 2001, 2002]; patterns of YMDD mutants differ between infection with genotypes A and D [Zollner et al., 2004]. No differences have been reported on emergence of lamivudine-resistant HBV mutants among infections with genotypes A, B, and C [Akuta et al., 2003; Suzuki et al., 2003a; Moskovitz et al., 2005], although such mutants are more frequent in infection with subgenotype Ba than Bj [Akuta et al., 2003]. The influence of genotype A on the emergence of YMDD mutants found in the present study would be ascribable to larger numbers of patients in comparison or longer duration of lamivudine, or both. Taken together with the report by Zollner et al. [2002, 2001], it does seem that lamivudine resistance occurs more frequently in infection with genotype A than with the other genotypes of HBV.

It has to be pointed out that observed genotype-dependent differences are not readily attributed to genotypes by themselves. Immigration of people and transmission by sexual contact or intravenous drugs have removed national borders in the epidemiology of HBV genotypes, although these are still maintained by perinatal or childhood transmission. Hence the duration of HBV infection differs markedly between imported and domestic genotypes. Even in the present study in patients of a single ethnicity, the duration of infection is much shorter in infection with genotype A than B or C, which would make differences in the response to lamivudine. The exact influence of genotypes on the response to lamivudine can only be evaluated in studies in patients with known duration of infection.

A therapeutic option for patients with genotype A who respond poorly to long-term lamivudine treatment may include adefovir dipivoxil that has a high efficacy unaccompanied by drug-resistant mutants in patients with or without HBeAg [Marcellin et al., 2003; Hadziyannis et al., 2005]. No differences were found, however, in the response to adefovil devoxivil in patients with genotypes A, B, C, and D [Westland et al., 2003]. Patients with genotype A infection may be changed to tenofovir disoproxil fumarate [Kuo et al., 2004] or pegylated interferon that induces a better response patients with genotypes A or B than C or D [Janssen et al., 2005].

REFERENCES

Akuta N, Suzuki F, Kobayashi M, Tsubota A, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H. 2003. The influence of hepatitis B virus genotype on the development of lamivudine resistance during long-term treatment. J Hepatol 38:315–321.

Allen MI, Deslauriers M, Andrews CW, Tipples GA, Walters KA, Tyrrell DL, Brown N, Condreay LD. 1998. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Hepatology 27:1670–1677.

Arauz-Ruiz P, Norder H, Robertson BH, Magnius LO. 2002. Genotype H: A new Amerindian genotype of hepatitis B virus revealed in Central America. J Gen Virol 83:2059–2073.

Chan HL, Wong ML, Hui AY, Chim AM, Tse AM, Hung LC, Chan FK, Sung JJ. 2003. Hepatitis B virus genotype has no impact on hepatitis B e antigen seroconversion after lamivudine treatment. World J Gastroenterol 9:2695–2697.

Chayama K, Suzuki Y, Kobayashi M, Tsubota A, Hashimoto M, Miyano Y, Koike H, Koida I, Arase Y, Saitoh S, Murashima N, Ikeda K, Kumada H. 1998. Emergence and takeover of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy. Hepatology 27: 1711–1716.

Chien RN, Liaw YF, Atkins M. 1999. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Hepatology 30:770–774.

Chu CJ, Lok AS. 2002. Clinical significance of hepatitis B virus genotypes. Hepatology 35:1274–1276.

Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, Crowther L, Condreay LD, Woessner M, Rubin M, Brown NA. 1999. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 341:1256–1263.

Dienstag JL, Goldin RD, Heathcote EJ, Hann HW, Woessner M, Stephenson SL, Gardner S, Gray DF, Schiff ER. 2003. Histological outcome during long-term lamivudine therapy. Gastroenterology 124:105–117.

Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Ma J, Arterburn S, Xiong S, Currie G, Brosgart CL. 2005. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. N Engl J Med 352:2673–2681.

Honkoop P, Niesters HG, de Man RA, Osterhaus AD, Schalm SW. 1997. Lamivudine resistance in immunocompetent chronic hepatitis B. Incidence and patterns. J Hepatol 26:1393–1395.

Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, Simon C, So TM, Gerken G, de Man RA, Niesters HG, Zondervan P, Hansen B, Schalm SW. 2005. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: A randomised trial. Lancet 365:123–129.

Kao JH, Chen PJ, Lai MY, Chen DS. 2000. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology 118:554–559.

Kao JH, Liu CJ, Chen DS. 2002. Hepatitis B viral genotypes and lamivudine resistance. J Hepatol 36:303–304.

Kato H, Orito E, Sugauchi F, Ueda R, Gish RG, Usuda S, Miyakawa Y, Mizokami M. 2001. Determination of hepatitis B virus genotype G by polymerase chain reaction with hemi-nested primers. J Virol Methods 98:153–159.

Kato H, Gish RG, Bzowej N, Newsom M, Sugauchi F, Tanaka Y, Kato T, Orito E, Usuda S, Ueda R, Miyakawa Y, Mizokami M. 2004. Eight genotypes (A-H) of hepatitis B virus infecting patients from San Francisco and their demographic, clinical, and virological characteristics. J Med Virol 73:516–521.

Kobayashi M, Arase Y, Ikeda K, Tsubota A, Suzuki Y, Saitoh S, Kobayashi M, Suzuki F, Akuta N, Someya T, Matsuda M, Sato J, Takagi K, Miyakawa Y, Kumada H. 2002. Viral genotypes and response to interferon in patients with acute prolonged hepatitis B virus infection of adulthood in Japan. J Med Virol 68: 522–528.

Kobayashi M, Arase Y, Ikeda K, Tsubota A, Suzuki Y, Saitoh S, Kobayashi M, Suzuki F, Akuta N, Hosaka T, Someya T, Matsuda M, Sato J, Miyakawa Y, Kumada H. 2004. Wild-type precore and core promoter sequences in patients with acute self-limited or chronic hepatitis B. Scand J Gastroenterol 39:53–59.

Kobayashi M, Akuta N, Suzuki F, Suzuki Y, Arase Y, Ikeda K, Hosaka T, Saitoh S, Kobayashi M, Someya T, Sato J, Watabiki S, Miyakawa Y, Kumada H. 2006. Virological outcomes in patients infected chronically with hepatitis B virus genotype A in comparison with genotypes B and C. J Med Virol 78:60–67.

Kumada H. 2003. Continued lamivudine therapy in patients with chronic hepatitis B. Intervirology 46:377–387.

Kuo A, Dienstag JL, Chung RT. 2004. Tenofovir disoproxil fumarate for the treatment of lamivudine-resistant hepatitis B. Clin Gastroenterol Hepatol 2:266–272.

Lai CL, Ching CK, Tung AK, Li E, Young J, Hill A, Wong BC, Dent J, Wu PC. 1997. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers: A placebo-controlled trial. Hepatology 25:241–244.

Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF. 1998. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 339:61–68.

Li JS, Tong SP, Wen YM, Vitvitski L, Zhang Q, Trepo C. 1993. Hepatitis B virus genotype A rarely circulates as an HBe-minus mutant: Possible contribution of a single nucleotide in the precore region. J Virol 67:5402–5410.

Liaw YF. 2002. Therapy of chronic hepatitis B: Current challenges and opportunities. J Viral Hepat 9:393–399.

Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. 1999. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. Hepatology 30:567–572.

Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J. 2004. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 351:1521–1531.

Lindh M, Andersson AS, Gusdal A. 1997. Genotypes, nt 1858 variants, and geographic origin of hepatitis B virus—Large-scale analysis using a new genotyping method. J Infect Dis 175:1285–1293.

Lok AS, McMahon BJ. 2001. Chronic hepatitis B. Hepatology 34:1225–1241.

Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M. 2003. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 125:1714–1722.

Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL. 2003. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 348:808–816.

Matsumoto A, Tanaka E, Rokuhara A, Kiyosawa K, Kumada H, Omata M, Okita K, Hayashi N, Okanoue T, Iino S, Tanikawa K. 2005. Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: A multicenter retrospective study of 2795 patients. Hepatol Res 32:173–184.

Miyakawa Y, Mizokami M. 2003. Classifying hepatitis B virus genotypes. Intervirology 46:329–338.

Moskovitz DN, Osiowy C, Giles E, Tomlinson G, Heathcote EJ. 2005. Response to long-term lamivudine treatment (up to 5 years) in patients with severe chronic hepatitis B, role of genotype and drug resistance. J Viral Hepat 12:398–404.

Nevens F, Main J, Honkoop P, Tyrrell DL, Barber J, Sullivan MT, Fevery J, De Man RA, Thomas HC. 1997. Lamivudine therapy for chronic hepatitis B: A six-month randomized dose-ranging study. Gastroenterology 113:1258–1263.

Norder H, Hammas B, Lofdahl S, Courouce AM, Magnius LO. 1992. Comparison of the amino acid sequences of nine different serotypes of hepatitis B surface antigen and genomic classification of the corresponding hepatitis B virus strains. J Gen Virol 73:1201–1208.

Ogawa M, Hasegawa K, Naritomi T, Torii N, Hayashi N. 2002. Clinical features and viral sequences of various genotypes of hepatitis B virus compared among patients with acute hepatitis B. Hepatol Res 23:167–177.

Okamoto H, Tsuda F, Sakugawa H, Sastrosoewignjo RI, Imai M, Miyakawa Y, Mayumi M. 1988. Typing hepatitis B virus by homology in nucleotide sequence: Comparison of surface antigen subtypes. J Gen Virol 69:2575–2583.

Orito E, Mizokami M, Ina Y, Moriyama EN, Kameshima N, Yamamoto M, Gojobori T. 1989. Host-independent evolution and a genetic classification of the hepadnavirus family based on nucleotide sequences. Proc Natl Acad Sci USA 86:7059–7062.

Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, Okanoue T, Yotsuyanagi H, Iino S. 2001 . A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV Genotype Research Group. Hepatology 33:218–223.

Rizzetto M. 2002. Efficacy of lamivudine in HBeAg-negative chronic hepatitis B. J Med Virol 66:435–451.

Sherlock S. 1987. The natural history of hepatitis B. Postgrad Med J 63:S7–S11.

Stuyver L, De Gendt S, Van Geyt C, Zoulim F, Fried M, Schinazi RF, Rossau R. 2000. A new genotype of hepatitis B virus: Completegenome and phylogenetic relatedness. J Gen Virol 81:67–74.

Sun J, Wang Z, Ma S, Zeng G, Zhou Z, Luo K, Hou J. 2005. Clinical and virological characteristics of lamivudine resistance in chronic hepatitis B patients: A single center experience. J Med Virol 75:391–398.

Suzuki Y, Kumada H, Ikeda K, Chayama K, Arase Y, Saitoh S, Tsubota A, Kobayashi M, Koike M, Ogawa N, Tanikawa K. 1999. Histological changes in liver biopsies after one year of lamivudine treatment in patients with chronic hepatitis B infection. J Hepatol 30:743–748.

Suzuki F, Tsubota A, Akuta N, Someya T, Kobayashi M, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Miyakawa Y, Kumada H. 2002. Interferon for treatment of breakthrough infection with hepatitis B virus mutants developing during long-term lamivudine therapy. J Gastroenterol 37:922–927.

Suzuki F, Tsubota A, Arase Y, Suzuki Y, Akuta N, Hosaka T, Someya T, Kobayashi M, Saitoh S, Ikeda K, Matsuda M, Satoh J, Takagi K, Kumada H. 2003a. Efficacy of lamivudine therapy and factors associated with emergence of resistance in chronic hepatitis B virus infection in Japan. Intervirology 46:182–189.

Suzuki Y, Arase Y, Ikeda K, Saitoh S, Tsubota A, Suzuki F, Kobayashi M, Akuta N, Someya T, Miyakawa Y, Kumada H. 2003b. Histological improvements after a three-year lamivudine therapy in patients with chronic hepatitis B in whom YMDD mutants did not or did develop. Intervirology 46:164–170.

Suzuki Y, Kobayashi M, Ikeda K, Suzuki F, Arfase Y, Akuta N, Hosaka T, Saitoh S, Kobayashi M, Someya T, Matsuda M, Sato J, Watabiki S, Miyakawa Y, Kumada H. 2005. Persistence of acute infection with hepatitis B virus genotype A and treatment in Japan. J Med Virol 76:33–39.

Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, Hawley S, Barber J, Condreay L, Gray DF. 1999. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Hepatology 29:889–896.

Thakur V, Sarin SK, Rehman S, Guptan RC, Kazim SN, Kumar S. 2005. Role of HBV genotype in predicting response to lamivudine therapy in patients with chronic hepatitis B. Indian J Gastroenterol 24:12–15.

Usuda S, Okamoto H, Iwanari H, Baba K, Tsuda F, Miyakawa Y, Mayumi M. 1999. Serological detection of hepatitis B virus genotypes by ELISA with monoclonal antibodies to type-specific epitopes in the preS2-region product. J Virol Methods 80:97–112.

Usuda S, Okamoto H, Tanaka T, Kidd-Ljunggren K, Holland PV, Miyakawa Y, Mayumi M. 2000. Differentiation of hepatitis B virus genotypes D and E by ELISA using monoclonal antibodies to epitopes on the preS2-region product. J Virol Methods 87:81–89.

Westland C, Delaney Wt, Yang H, Chen SS, Marcellin P, Hadziyannis S, Gish R, Fry J, Brosgart C, Gibbs C, Miller M, Xiong S. 2003. Hepatitis B virus genotypes and virologic response in 694 patients in phase III studies of adefovir dipivoxil. Gastroenterology 125:107–116.

Yotsuyanagi H, Okuse C, Yasuda K, Orito E, Nishiguchi S, Toyoda J, Tomita E, Hino K, Okita K, Murashima S, Sata M, Hoshino H, Miyakawa Y, Iino S. 2005. Distinct geographic distributions of hepatitis B virus genotypes in patients with acute infection in Japan. J Med Virol 77:39–46.

Yuen MF, Tanaka Y, Lai CL. 2003a. Hepatitis B genotypes in chronic hepatitis B and lamivudine therapy. Intervirology 46: 373–376.

Yuen MF, Wong DK, Sablon E, Yuan HJ, Sum SM, Hui CK, Chan AO, Wang BC, Lai CL. 2003b. Hepatitis B virus genotypes B and C do not affect the antiviral response to lamivudine. Antivir Ther 8:531–534.

Zollner B, Petersen J, Schroter M, Laufs R, Schoder V, Feucht HH. 2001. 20-fold increase in risk of lamivudine resistance in hepatitis B virus subtype adw. Lancet 357:934–935.

Zollner B, Petersen J, Schafer P, Schroter M, Laufs R, Sterneck M, Feucht HH. 2002. Subtype-dependent response of hepatitis B virus during the early phase of lamivudine treatment. Clin Infect Dis 34:1273–1277.

Zollner B, Petersen J, Puchhammer-Stockl E, Kletzmayr J, Sterneck M, Fischer L, Schroter M, Laufs R, Feucht HH. 2004. Viral features of lamivudine resistant hepatitis B genotypes A and D. Hepatology 39:42–50.

J Gastroenterol 2006; 41:470–475
DOI 10.1007/s00535-006-1793-2

Journal of Gastroenterology

Efficacy of interferon monotherapy in young adult patients with chronic hepatitis C virus infection

Kiminori Uka, Fumitaka Suzuki, Norio Akuta, Hitomi Sezaki, Yoshiyuki Suzuki, Tetsuya Hosaka, Takashi Someya, Masahiro Kobayashi, Satoshi Saitoh, Yasuji Arase, Kenji Ikeda, and Hiromitsu Kumada

Department of Gastroenterology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan

Background. Suppression of the progression to cirrhosis and hepatocellular carcinoma is important, especially for young hepatitis C virus (HCV)-infected patients. The aim of this study was to analyze the response to interferon (IFN) monotherapy in young HCV patients. ***Methods.*** Between 1989 and 2002, 1021 anti-HCV-positive patients hospitalized at Toranomon Hospital received IFN monotherapy. Among these patients, 144 were ≤35 years of age, while the remaining 877 were 36–73 years old. We retrospectively identified 209 patients with known dates of blood transfusion (i.e., start of HCV infection) among the 1021 patients. IFN treatment lasted 6 months. ***Results.*** HCV RNA level ($P < 0.001$), HCV genotype ($P < 0.001$), age ($P < 0.001$), and liver histology ($P = 0.01$) were identified as determinants of the response to IFN monotherapy in 1021 patients. Moreover, in patients with high viral load and genotype 1b, the sustained virological response (SVR) rate was significantly higher in those aged ≤35 years than in older patients ($P < 0.001$). In patients with genotype 1b with known date of blood transfusion, a longer duration of infection negatively influenced the SVR rate. In the 209 patients, multivariate analysis identified HCV RNA level ($P < 0.001$), age ($P = 0.002$), and duration of infection ($P = 0.049$) as determinants of SVR. ***Conclusions.*** The response of IFN monotherapy is better in patients aged ≤35 years than in older patients, probably because of mild stage histology, the effect of host-related factors, and shorter period of infection. Long-term IFN monotherapy may be suitable for young women who desire to become pregnant or those with anemia.

Key words: HCV, interferon therapy, young patients

Received: September 28, 2005 / Accepted: February 6, 2006
Reprint requests to: F. Suzuki

Introduction

Hepatitis C virus (HCV) frequently causes persistent infection and leads to chronic hepatitis, liver cirrhosis, and even hepatocellular carcinoma (HCC).[1–4] Several studies have reported the effectiveness of interferon (IFN)-based therapy in patients with HCV, particularly with regard to clearance of HCV, normalization of serum alanine aminotransferase (ALT), and reduction of the incidence of HCC.[5–7]

The number of new cases of HCV infection caused by transfusion of infected blood components is decreasing in Japan.[8] However, such cases are still being reported in the United States and other Western countries.[9,10] One of the reasons for this difference is intravenous drug use and the popularity of tattooing. The same trend, however, has been recently reported in Japan.[8] In this regard, it is important to reduce the chance of development of liver cirrhosis and HCC, especially in young infected patients. Accordingly, we believe it is important to evaluate IFN-based therapy in young patients with HCV. Currently, the combination therapy of interferon and ribavirin is widely used for patients with HCV.[11,12] However, ribavirin is reported to be harmful for pregnant and young patients, and sometimes these groups refuse to receive such combination therapy.[13,14]

The present retrospective study was designed to analyze the efficacy of IFN monotherapy in young (≤35 years of age) patients with HCV, because only a few such studies have been reported.[15,16]

Patients and methods

Patients

Between 1989 and 2002, 1021 anti-HCV-positive patients were hospitalized at Toranomon Hospital, Tokyo,

Japan, and received first IFN monotherapy. Patients infected with both HCV and hepatitis B virus (HBV) or hepatitis A virus (HAV) or those with autoimmune diseases, previous IFN treatment for hepatitis, history of heavy alcohol abuse, drug abuse, herbal remedies, liver cirrhosis or HCC on ultrasonography, coexisting cardiac, renal, or pulmonary endocrine conditions were excluded from this study. We also retrospectively identified 209 patients among these 1021 patients for whom the day they had received the blood transfusion was known. The duration of HCV infection was calculated from the day the blood transfusion was received.

Histopathological examination of liver biopsy specimens

The baseline histopathology of chronic hepatitis was classified into four stages according to the extent of fibrosis: stage 0 (F0), no fibrosis; stage 1 (F1), periportal expansion; stage 2 (F2), portoportal septa; and stage 3 (F3), portocentral linkage or bridging fibrosis.[17] No patients with liver cirrhosis (F4) were included in this study.

Serum HCV-RNA marker

Qualitative analysis of HCV-RNA was performed using a branched DNA probe assay (bDNA probe assay, version 2.0; Chiron, Dai-ichi Kagaku, Tokyo, Japan) and a polymerase chain reaction (PCR)-based assay using the protocol provided by the manufacturer (Amplicor HCV Monitor assay version 2.0, Roche Diagnostics, Tokyo, Japan). HCV genotype was classified by PCR, using a mixture of primers for six subtypes known to exist in Japan, as reported previously.[18]

Interferon therapy

Patients received 3 to 18 Mega Units (MU) of IFN-α or -β (Sumiferon, Sumitomo Pharmaceutical, Osaka, Japan; Canferon A, Takeda Chemical Industries, Osaka, Japan; Intron A, Schering-Plough, Osaka, Japan; or Feron, Toray, Tokyo, Japan). The period of IFN treatment was 6 months. After discontinuation of therapy, all patients were followed up for at least an additional 6-month period. A sustained virological response (SVR) was defined as negative HCV-RNA by PCR at 6 months after the completion of IFN therapy.

Statistical analysis

Differences between groups were examined for statistical significance using the Mann-Whitney U test and a χ-squared test where appropriate. Independent predictive factors associated with a SVR to IFN treatment were studied using a stepwise Cox regression analysis. The following seven potential predictors were assessed in this study: HCV genotype (1b vs. other than 1b), HCV RNA level (high vs. low; a high virus quantity was defined as >100 Kiu/ml or >1 Meq/ml; other values were defined as a low virus quantity), liver histology (F1 vs. F2 or F3), duration of infection (≤5 vs. >5 years), age (≤35 vs. >35 years), total dose of IFN (≤624 vs. >624 MU), and sex (M or F). All factors found to be at least marginally associated with SVR to IFN treatment ($P < 0.15$) were entered into a multiple logistic regression. The odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the relative risk confidence. All analyses described above were performed using the SPSS program (version 7.5, SPSS, Chicago, IL, USA).

Results

Efficacy of interferon monotherapy

The SVR rate was 23.6% (134 of 569 patients) of patients with genotype 1b, 70.5% (206/292) of those with genotype 2a, and 48.3% (43/89) of those with genotype 2b. In the high virus load group, the SVR rates were 11.3% (49/432) for patients with genotype 1b, 52.9% (83/157) for those with genotype 2a, and 39.7% (29/73) for those with genotype 2b. In the low virus load group, the SVR rates were 62.0% (85/137) for patients with genotype 1b, 91.1% (123/135) for those with genotype 2a, and 87.5% (14/16 patients) for those with genotype 2b.

Multivariate analysis of predictive factors for response to IFN monotherapy

We explored the predictive factors for response to IFN monotherapy in 1021 patients, and the following variables were entered into the model and could not be removed: HCV RNA level ($P < 0.001$), HCV genotype ($P < 0.001$), age ($P < 0.001$), and liver histology ($P = 0.01$).

Comparison of virological response to IFN between patients ≤35 and >35 years old

Next, we examined the difference between patients aged ≤35 years ($n = 144$) and >35 years ($n = 877$) (Table 1). There was no significant difference in the sex ratio, total dose of IFN, genotype classification, or viral load between the two age groups. With regard to liver histology, more patients aged ≤35 years were classified as mild stage (F1) than those in the other group ($P < 0.001$). We also examined SVR rates according to age (≤35 and >35

Table 1. Comparison between patients ≤35 years old and >35 years old treated with interferon monotherapy

	≤35 years	>35 years	*P* value
Number	144	877	
Age (years)	31 (16–35)	52 (36–73)	
Sex (male/female)	105/39	585/292	NS
HCV-RNA level (high/low)[a]	99/45	602/275	NS
Liver histology (F1/F2/F3/N)[b]	124/18/1/1	513/313/28/23	<0.001
Total dose of interferon (MU)	624 (216–1440)	624 (216–1680)	NS
Genotype (1b/2a/2b/N)[c]	85/38/17/4	484/254/72/67	NS

Data values are expressed as medians with ranges in parentheses unless indicated otherwise
HCV, hepatitis C virus; NS, not significant
[a]High, high viral load ≥100 kiu/ml or ≥1 Meq/ml; low, low viral load <100 kiu/ml or <1 Meq/ml
[b]Liver fibrosis classified as F0, no fibrosis; F1, periportal expansion; F2, portoportal septa; F3, portocentral linkage or bridging fibrosis; N, liver biopsy was not performed
[c]N, not done

Table 2. Comparison of sustained virological response to interferon monotherapy between patients ≤35 years old and >35 years old

	≤35 years	>35 years	*P* value
Low viral load group			
1b	14/22 (63.6%)	71/115 (61.7%)	NS
2a	17/17 (100%)	106/118 (89.8%)	NS
2b	4/4 (100%)	10/12 (83.3%)	NS
High viral load group			
1b	18/63 (28.6%)	31/369 (8.4%)	<0.001
2a	16/21 (76.1%)	67/136 (49.2%)	0.019
2b	9/13 (69.2%)	20/60 (33.3%)	0.0067

years), genotype (1b, 2a, 2b), and viral load (high, low) (Table 2). In the low viral load group, there was no significant difference in SVR rate between the ≤35 and >35 age groups. On the other hand, in the high viral load group, the SVR rate was higher in the younger group than in the older group. In particular, the SVR rate was significantly higher in the ≤35 years group with a high viral load and genotype 1b compared with the respective patients aged >35 years of age ($P < 0.001$).

Relationship between duration of infection and virological response to IFN

Figures 1 and 2 show the relationship between duration of infection and SVR rate for patients with genotype 1b and genotype 2 (2a or 2b) among 209 patients whose infection duration could be assessed based on their history of blood transfusion. For the group with genotype 1b, the longer the duration of the infection, the lower the SVR rate was (Fig. 1). However, no such relationship was identified for the group with genotype 2 (Fig. 2). The duration of infection in patients aged >35 years was longer than that in patients aged ≤35 years (>35, 29 years (median); ≤35, 12 years (median), $P < 0.001$).

For the 209 patients, we explored the predictive factors for response to IFN monotherapy. Univariate analysis showed the following four factors to significantly influence the response to IFN monotherapy: genotype ($P < 0.001$), HCV RNA level ($P < 0.001$), age ($P = 0.019$), and liver histopathology ($P = 0.035$). Since the variables could be mutually correlated, a multivariate analysis was performed. In the last step, the following variables were entered into the model and could not be removed: genotype ($P < 0.001$), HCV RNA level ($P < 0.001$), and age ($P < 0.001$) (Table 3).

We also explored the determinants of the response to IFN monotherapy among the patients with genotype 1b (Table 3). Univariate analysis identified the following four factors as having significantly influenced the response to IFN monotherapy: HCV RNA level ($P < 0.001$), age ($P < 0.001$), duration of infection ($P = 0.014$), and liver histopathology ($P = 0.036$). Since the variables could be mutually correlated, a multivariate analysis was performed. The analysis identified the following three variables as significant and independent determinants of the response to IFN: HCV RNA level ($P < 0.001$), age ($P = 0.002$), and duration of infection ($P = 0.049$; Table 6). Next, we explored the predictive factors

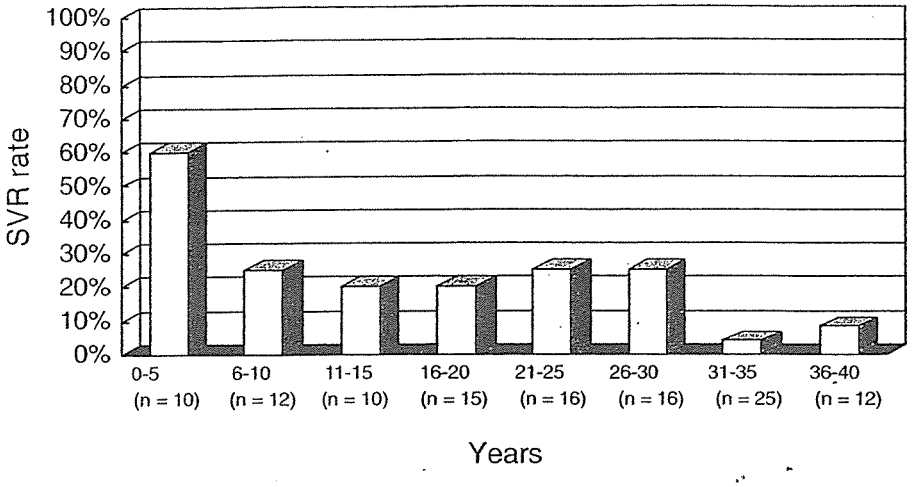


Fig. 1. Relationship between duration of infection and sustained virological response (*SVR*) rate in patients with genotype 1b. The SVR rate was inversely related to the duration of infection. The duration of infection was calculated from the day that the blood transfusion, presumed to have caused the infection, was received

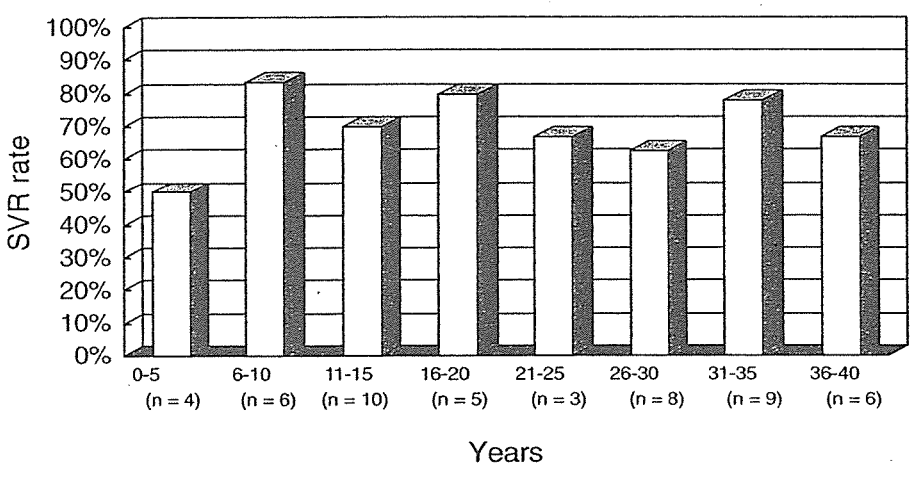


Fig. 2. Relationship between duration of infection and SVR rate in patients with genotype 2. The relationship was not significant in these patients

Table 3. Independent variables that contributed to a complete response to interferon monotherapy among 209 patients with known day of receiving blood transfusion, by multivariate analysis

Variable	Multivariate odds ratio	95% CI	*P* value
Multivariate analysis of all patients ($n = 209$)			
HCV RNA level (high vs. low)	14.618	6.293–33.952	<0.001
Genotype (1b vs. 2a, 2b)	6.573	2.938–14.705	<0.001
Age (≤35 vs. >35 years)	5.416	2.130–13.772	<0.001
Multivariate analysis of patients with genotype 1b ($n = 125$)			
HCV RNA level (high vs. low)	10.120	3.467–29.540	<0.001
Age (≤35 vs. >35 years)	4.944	1.802–13.566	0.002
Duration of infection (≤5 vs. >5 years)	4.467	1.005–19.859	0.049
Multivariate analysis of patients with genotype 2a and 2b ($n = 78$)			
HCV RNA level (high vs. low)	12.089	3.234–45.196	<0.001

95% CI, 95% confidence interval

for the response to IFN monotherapy in patients with genotypes 2a and 2b (Table 3). Among the seven factors examined in univariate analysis, only HCV RNA load was identified as a significant and independent determinant of the response to IFN ($P < 0.001$; Table 3).

Discussion

It has been reported that HCV RNA level, HCV genotype, and liver histology are important determinants of the response to IFN monotherapy in patients with

HCV.[19-21] A few reports also highlight the importance of age in the response to therapy.[22] In our study, a multivariate analysis of predictive factors for response to IFN monotherapy among 1021 patients showed the following variables to be associated with SVR: HCV RNA level, HCV genotype, age, and liver histology. Our study also confirmed the importance of age for achieving a SVR. The latter result is different from that reported by other investigators, and the difference may be explained by the relatively large number of young adult patients (144 patients) in our study compared with the other studies.[23]

In our study, comparison of the response to IFN monotherapy in patients with high viral load according to age showed that the SVR rate of patients aged ≤35 years was significantly higher than that for those >35 years old. In particular, the SVR rate of patients with high viral load and genotype 1b aged ≤35 years was higher than the respective patients aged >35 years. However, no such differences were noted in patients with a low viral load. Thus, in patients with a low viral load, the higher efficacy of IFN may reflect the effect of the drug on virus-related factors and not host-related factors such as age. Why is the SVR rate in patients ≤35 years of age higher than in those >35 years old? One reason is probably liver histology; the liver histology of many young patients was at the F1 stage. Other reasons include the effect of host-related factors and a shorter period of infection, judging from the reported high SVR rate to IFN treatment for acute hepatitis C.[24-27] Considering these reports, we investigated in the present study the efficacy of treatment in patients with known duration of HCV infection.

In the present study, we analyzed patients with a blood transfusion history on the assumption that those patients were infected with HCV by blood transfusion. Among such patients, multivariate analyses also revealed that HCV RNA level, genotype, and age were important determinants of the response to IFN monotherapy. Moreover, the duration of infection and age were independent determinants of the response to IFN monotherapy among patients with genotype 1b.

With regard to the influence of host factors, the biological activity of IFN is mediated, at least in part, by the induction of intracellular antiviral proteins, such as 2′–5′ oligoadenylate synthetase (2′–5′ OAS), dsRNA-activated protein kinase (PKR), and MxA protein.[28,29] It is possible that a larger number of such intracellular antiviral proteins are induced in young patients compared with in older patients. Further in vitro studies are warranted to compare the type and number of antiviral proteins that are induced by IFN therapy in young and old patients.

IFN and ribavirin combination therapy is widely used for the treatment of patients with chronic hepatitis C infection. Such therapy has been reported to increase significantly the SVR rate compared with IFN monotherapy.[11,12] For IFN and ribavirin combination therapy, however, little is known about the effect of age on SVR. In this regard, ribavirin therapy is reported to induce embryonic malformations.[13,14] Therefore, there is an ethical problem with regard to the use of IFN and ribavirin combination therapy, at least in pregnant patients. It is also difficult to recommend the combination therapy for patients with anemia, because such therapy is reported to induce anemia in some patients.[30,31] In these patients, IFN monotherapy is the first choice for treatment. Recent studies reported good SVR rates for IFN monotherapy over 2 years.[32-34] Thus, it is recommended that young HCV patients who must avoid IFN and ribavirin combination therapy should receive long-term IFN monotherapy.

At present, new cases of HCV infection are diagnosed particularly among those who take drugs intravenously and obtain tattoos.[8-10] The spread of intravenous drug use and tattoos among young people is worrisome in Japan and other countries. These trends are expected to be associated with an increase in the number of young HCV-infected patients in the future. To prevent the development of liver cirrhosis and HCC in such patients, early introduction of IFN-based therapy is important.

In conclusion, we have demonstrated in the present study that the response to IFN monotherapy of patients aged ≤35 years is better than that of older patients. Young women who do not intend to become pregnant should be treated with IFN and ribavirin. On the other hand, young women who plan to become pregnant and/or have anemia, should receive long-term IFN monotherapy.

Acknowledgments. This study was supported in part by a Grant-in Aid from the Ministry of Health, Labor and Welfare, Japan.

References

1. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. Hepatology 1998;28:1687–95.
2. Dusheiko GM. The natural course of chronic hepatitis C: implications for clinical practice. J Viral Hepat 1998;5:9–12.
3. Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol 1998;28:930–8.
4. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 1999;22:1228–33.
5. Chayama K, Saitoh S, Arase Y, Ikeda K, Matsumoto T, Sakai Y, et al. Effect of interferon administration on serum hepatitis C

virus RNA in patients with chronic hepatitis C. Hepatology 1991;13:1040–3.
6. Reichard O, Glaumann H, Fryden A, Norkrans G, Schvarcz R, Sonnerborg A, et al. Two-year biochemical, virological and histological follow-up in patients with chronic hepatitis C responding in a sustained fashion to interferon alpha-2β treatment. Hepatology 1995;21:918–22.
7. Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Hepatology 1998;27:1394–402.
8. Moriya T, Koyama T, Tanaka J, Mishiro S, Yoshizawa H. Epidemiology of hepatitis C virus in Japan. Intervirology 1999;42:153–8.
9. Alter HJ, Kruszon-Moran D, Nainan OV. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1998;341:556–62.
10. Mauses S, Berger F, Goeiz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. Hepatology 2004;40: 120–4.
11. McHuchison JG, Gordon SC, Schiff ER, Shiffmann ML, Lee WM, Rustgi VK, et al. Interferon alpha 2β alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485–92.
12. Reichard O, Norkrans G, Fryden A. Randomised double-blind, placebo controlled trial of interferon alpha 2b with and without ribavirin for chronic hepatitis C. Lancet 1998;351:83–7.
13. Kilham L, Ferm VH. Congenital anomalies induced in hamster embryos with ribavirin. Science 1977;195:413–4.
14. Johnson EM. The effects of ribavirin on development and reproduction: a critical review of published and unpublished studies in experimental animals. J Am Coll Toxicol 1990;9:551–61.
15. Prati D, Zanella A, Zanuso F, Vianello L, Della Torre E, Mozzi F, et al. Sustained response to interferon-α2a monotherapy of young blood donors with minimal-to-mild chronic hepatitis C. J Viral Hepat 2000;7:352–60.
16. Casiraghi MA, De Paschale M, Romano L, Biffi R, Assi A, Binelli G, et al. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. Hepatology 2004;39:90–6.
17. Desmet VJ, Gerber M, Hoofnagale JH, Manns M, Sheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513–20.
18. Hashimoto M, Chayama K, Tsubota A, Kobayashi M, Nakano A, Takagi K, et al. Typing six major hepatitis C virus genotypes by polymerase chain reaction using primers derived from nucleotide sequences of the NS5 region. Int Hepatol Commun 1996;4:263–7.
19. Hoofnagle JH, Di Bisceglie AM. The treatment of chronic viral hepatitis. N Engl J Med 1997;336:347–56.
20. Lau JY, Davis GL, Kniffen J, Qian KP, Urdea MS, Chan CS, et al. Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. Lancet 1993;341:1501–4.
21. Tsubota A, Chayama K, Ikeda K, Yasuji A, Koida I, Saitoh S, et al. Factors predictive of response to interferon-alpha therapy in hepatitis C virus infection. Hepatology 1994;19:1088–94.
22. Mamori S, Suzuki F, Hosaka T, Akuta N, Someya T, Kobayashi M, et al. Interferon monotherapy for patients with chronic hepatitis C and normal serum aminotransferase levels at commencement of treatment. J Gastroenterol 2004 ;39:776–82.
23. Tine F, Magrin S, Craxi A, Pagliaro L. Interferon for non-A, non-B chronic hepatitis: a meta-analysis of randomized clinical trials. J Hepatol 1991;13:192–9.
24. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel D, et al. Treatment of acute hepatitis C with interferon alpha-2b. N Engl J Med 2001;345:1452–7.
25. Gerlach T, Zachoval R, Gruener N, Jung MC, Ulsenheimer A, Schraut W, et al. Acute hepatitis C: natural course and response to antiviral treatment (abstract). Hepatology 2001;34:341A.
26. Kamal SM, Ismail A, Graham CS, He Q, Rasenack JW, Peters T, et al. Pegylated interferon α therapy in acute hepatitis C: relation to hepatitis C virus-specific T cell response kinetics. Hepatology 2004;39:1721–31.
27. Nomura H, Sou S, Tanimoto H, Nagahama T, Kimura Y, Hayashi J, et al. Short-term interferon-alpha therapy for acute hepatitis C: a randomized controlled trial. Hepatology 2004;39:1213–9.
28. Fernandez M, Quiroga JA, Martin J, Herrero M, Pardo M, Horisberger MA, et al. In vivo and in vitro induction of MxA protein in peripheral blood mononuclear cells from patients chronically infected with hepatitis C virus. J Infect Dis 1999;180: 262–7.
29. Antonelli G, Simeoni E, Turriziani O, Tesoro R, Redaelli A, Roffi L, et al. Correlation of interferon-induced expression of MxA mRNA in peripheral blood mononuclear cells with the response of patients with chronic active hepatitis C to IFN-α therapy. J Interferon Cytokine Res 1999;19:243–51.
30. Takaki S, Tsubota A, Hosaka T, Akuta N, Someya T, Kobayashi M, et al. Factors contributing to ribavirin dose reduction due to anemia during interferon alpha2b and ribavirin combination therapy for chronic hepatitis C. J Gastroenterol 2004;39:668–73.
31. Nomura H, Tanimoto H, Kajiwara E, Shimono J, Maruyama T, Yamashita N, et al. Factors contributing to ribavirin-induced anemia. Gastroenterol Hepatol 2004;19:1312–7.
32. Arase Y, Suzuki F, Tsubota A, Suzuki Y, Saitoh S, Kobayashi M, et al. Sustained negativity for HCV-RNA over 24 or more months by long-term interferon therapy correlates with eradication of HCV in patients with hepatitis C virus genotype 1b and high viral load. Intervirology 2004;47:19–25.
33. Saracco G, Borghesio E, Mesina P, Solinas A, Spezia C, Macor F, et al. Prolonged treatment (2 years) with different doses (3 versus 6MU) of interferon 2b for chronic hepatitis type C. J Hepatol 1997;27:56–62.
34. Nomura H, Tanimoto H, Sou S, Nagahama T, Hayashi J, Kashiwagi S, et al. Pilot study of prolonged interferon-α retreatment in chronic hepatitis C patients with genotype 1b. Hepatol Res 2003;27:266–71.

Original Paper

Intervirology

Intervirology 2006;49:121–126
DOI: 10.1159/000089372

Received: January 18, 2005
Accepted after revision: March 29, 2005

Efficacy of Interferon Therapy in Elderly Patients with Chronic Hepatitis C

Rikako Koyama Yasuji Arase Kenji Ikeda Fumitaka Suzuki Yoshiyuki Suzuki Satoshi Saitoh Masahiro Kobayashi Norio Akuta Takashi Someya Tetsuya Hosaka Hitomi Sezaki Mariko Kobayashi Hiromitsu Kumada

Department of Gastroenterology, and Hepatic Research Unit, Toranomon Hospital, Tokyo, Japan

Key Words
Chronic hepatitis C · Elderly patients · Interferon · Side effects

Abstract
Objective: We assessed the efficacy and safety of interferon (IFN) monotherapy in 84 elderly patients aged ≥65 years with chronic hepatitis C in a retrospective cohort study. ***Methods:*** Twenty-two of the 84 elderly patients were treated with IFN at a dose of 6 million units daily for 6–8 weeks, 18 patients were treated 2–3 times a week for 24 weeks and 44 patients were treated daily for 2–8 weeks and 2–3 times a week for 16–24 weeks. ***Results:*** A sustained virological response (SVR) occurred in 35.7% (30/84) of the patients by intention-to-treat analysis. Multivariate analysis showed that patients achieved a significant SVR when: (1) serum HCV-RNA level before IFN therapy was <100 KIU/ml ($p < 0.0001$) and (2) staging of liver fibrosis was mild ($p = 0.040$). Eleven (13.1%) patients discontinued the IFN regimen due to adverse events. Regarding factors predicting discontinuation of IFN, univariate analysis showed that patients aged >70 years were prone to drop out of therapy due to adverse events in IFN therapy ($p = 0.009$). ***Conclusion:*** Our results suggest that IFN administration is suitable for 65- to 70-year-old patients with chronic hepatitis C without genotype 1b and high virus load.

Introduction

Hepatocellular carcinoma (HCC) often occurs in patients with hepatitis C virus (HCV)-RNA-positive chronic liver disease [1]. The majority of deaths due to HCC are ascribed to hepatitis viruses, of which 70–80% (corresponding to approximately 30,000/year) are attributed to persistent HCV infection in Japan [2, 3]. The yearly incidence of HCC in patients with HCV-RNA-positive cirrhosis ranges from 5 to 7% [4–6]. In the prevention of HCC, it is important to eradicate HCV-RNA with interferon (IFN) therapy [2, 3, 7]. However, various side effects have been reported in patients treated with IFN [3]. Elderly individuals are defined by the World Health Organization as those aged >65 years, and IFN treatment is mainly given to patients with chronic hepatitis C below 65 years of age because of IFN-related side effects and safety restrictions in Japan. However, in patients with stage F3–F4 disease, progression to HCC was significantly increased compared to patients with F1–F2 liver histology [8]. Thus, to prevent HCC development, it is important to clear HCV-RNA with IFN therapy in elderly patients with stage F3–F4 disease [9]. However, only few studies have targeted IFN therapy in elderly patients with chronic hepatitis C [10–13]. We therefore assessed retrospectively the efficacy and safety of IFN monotherapy in elderly patients with chronic hepatitis C.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0300–5526/06/0493–0121$23.50/0

Accessible online at:
www.karger.com/int

Rikako Koyama, MD
Department of Gastroenterology, Toranomon Hospital
2-2-2 Toranomon, Minato-ku
Tokyo, 105-8470 (Japan)
Tel. +81 3 3588 1111, Fax +81 3 3582 7068, E-Mail rikako@pm.highway.ne.jp

Patients and Methods

Patients

The number of chronic hepatitis C patients treated with IFN monotherapy at the study hospital was 2,630 between 1989 and 2000. Of these, 84 patients met the following criteria: (1) age ≥65 years; (2) IFN administration ≤6 months; (3) alanine aminotransferase (ALT) elevation >2× the upper limits (normal range: 12–50 IU/l) within 6 months; (4) no treatment with corticosteroids, immunosuppressive agents or antiviral agents during the previous 6 months; (5) no hepatitis B surface antigens, antinuclear antibodies or antimitochondrial antibodies detectable in serum by radioimmunoassay, and (6) leukocytes >3,000/mm^3, platelet count >80,000/mm^3 and bilirubin <2.0 mg/ml. Exclusion criteria were a history of alcohol abuse or advanced liver cirrhosis (LC). Subsequently, efficacy and side effects of IFN as well as factors contributing to the eradication of HCV-RNA and the IFN-related dropout rate were assessed. Our study was approved by the institutional ethics review board of our hospital. The physician in charge explained the purpose and method of this clinical trial, as well as potential adverse reactions, to each patient, who later gave his/her informed consent for participation.

IFN Therapy

IFN treatment consisted of 3 or 6 million units of IFN-α or IFN-β given according to one of three schedules. In 22 patients, the daily dose of IFN was administered for 6–8 weeks. In another 18 patients, IFN was administered three times a week for 24–28 weeks. In the third group including 44 patients, daily IFN was administered for 2–8 weeks, followed by three times a week for 16–22 weeks.

Blood and Urine Tests

Blood samples were obtained just before and 24 weeks after IFN treatment. The samples were stored at –80°C until analyzed. Using these blood samples, HCV-RNA levels before IFN monotherapy were analyzed by quantitative PCR assay (Amplicor GT-HCV Monitor, version 2.0, Roche Molecular Systems) [14]. Twenty-four weeks after IFN therapy, HCV-RNA levels were analyzed by the qualitative PCR assay. The lower detection limit of the qualitative assay is 100 copies/ml [15]. The HCV genotype was examined by PCR assay, using a mixture of primers for the six subtypes known to exist in Japan, as reported previously [16].

Definition of Response to IFN Efficacy

The therapeutic efficacy was evaluated 24 weeks after the end of IFN therapy. A sustained virological response (SVR) to IFN therapy was defined as HCV-RNA negativity using a commercial Amplicor HCV qualitative assay (Amplicor HCV, version 2.0, Roche Diagnostic Systems, Basel, Switzerland) at two time points, 3 and 6 months after the completion of IFN therapy. Absence of SVR was defined as no response.

Liver Histology

Liver biopsy specimens were obtained percutaneously or at laparoscopy using a Tohoku-University-modified Vim Silverman needle with an internal diameter of 2 mm (Kakinuma, Tokyo, Japan). Liver histology of chronic hepatitis was classified according to the extent of fibrosis into three stages: stage 1, periportal expansion; stage 2: portoportal septa, and stage 3: portocentral linkage or bridging fibrosis. In addition to LC (stage 4), we classify four stages [17].

Table 1. Characteristics of the study patients at the commencement of IFN monotherapy

Characteristics	
Patients	84
Sex, males/females	38/46
Age[a], years	67 (65–84)
Liver fibrosis, F1/F2/F3/F4/ND	28/30/5/12/9
HCV genotype, 1b/2a/2b/others	35/33/11/5
HCV-RNA[a], MEq/ml	3.9 (<0.2–22)
AST[a], IU/l	60 (22–232)
ALT[a], IU/l	70 (21–369)
Hb[a], g/dl	13.5 (10.8–15.6)
Platelets[a] × 10^4/mm^3	14.5 (8–25.3)
WBC[a]/mm^3	4,700 (2,700–8,400)
IFN regimen, C/I/C+I	22/18/44
IFNα/IFNβ	54/30

C = 6- to 8-week continuous course; I = 24-week intermittent course; C+I = 2- to 8-week continuous course + 16- to 22-week intermittent course.

[a] Medians and ranges.

Statistical Analysis

Efficacy of IFN therapy was assessed by intention-to-treat and per-protocol analyses. Multivariate analysis (multiple logistic regression analysis) was used to establish which factors contributed to the outcome of IFN therapy. Results for each variable were transformed into categorical data consisting of two simple original numbers for multivariate analysis. $p < 0.05$ was considered statistically significant. The variables used for multivariate analysis were age, gender, liver histology, aspartate aminotransferase (AST), ALT (factors associated with patients) and HCV-RNA load and genotype (factors associated with the virus) and the methods of IFN therapy (factors associated with therapy). The SPSS software package (SPSS, Chicago, Ill., USA) was applied.

Results

Patient Characteristics

Table 1 shows the characteristics of the patients. The median age of these 84 patients was 67 years (range, 65–84 years). The IFN regimen was not randomized but decided by physician advice and patient's will.

Efficacy of the IFN Therapy

Eighty-four patients were enrolled in the present study, but 11 patients dropped out due to IFN-related side ef-

Table 2. Factors predicting SVR after IFN monotherapy by univariate analysis

Factors	Category	Odds ratio	95% CI	p value
HCV-RNA	≥1/<1 MEq/ml	1/27.60	5.83–130.78	<0.0001
HCV genotype	1b/2a, 2b	1/3.06	1.15–8.13	0.025
IFN regimen[1]	I/others	1/5.88	1.22–27.03	0.027
Liver histology	F2–F4/F1	1/3.00	1.12–8.06	0.029
Sex	female/male	1/2.12	0.86–5.23	0.104
IFN regimen	others/C+I	1/1.67	0.68–4.12	0.264
ALT	≥100/<100 IU/l	1/2.17	0.50–9.40	0.302
IFN regimen	others/C	1/1.62	0.61–4.31	0.338
AST	≥76/<76 IU/l	1/1.54	0.54–4.35	0.559
IFN	α/β	1/1.33	0.53–3.36	0.542
Age	≥68/<68 years	1/1.09	0.38–3.15	0.873

[1] C = 6- to 8-week continuous course; I = 24-week intermittent course; C+I = 2- to 8-week continuous + 16- to 22-week intermittent course; CI = confidence interval.

Table 3. Factors predicting SVR after IFN monotherapy by multivariate analysis

Factors	Category	Odds ratio	95% CI	p value
HCV-RNA	≥1/<1 MEq/ml	1/42.08	6.18–286.63	0.0001
Liver histology	F2–F4/F1	1/5.97	1.08–32.92	0.040

CI = Confidence interval.

fects. The remaining 73 patients completed the IFN therapy. SVR occurred in 35.7% (30/84) by intention-to-treat analysis.

Next we examined many factors that contributed to SVR by multivariate analysis. Univariate analysis (table 2) showed that patients achieved a significant SVR when: (1) the serum HCV-RNA level before the IFN therapy was ≤100 KIU/ml ($p < 0.0001$); (2) HCV genotype was 2a or 2b ($p = 0.025$); (3) the IFN regimen was not intermittent ($p = 0.027$), and (4) staging of liver fibrosis was mild ($p = 0.027$).

Due to the mutual correlation of these variables, multivariate logistic regression analysis was performed, using four significant variables in the model. Multivariate analysis showed that patients achieved a significant SVR when: (1) the serum HCV-RNA level before the IFN therapy was ≤100 KIU/ml ($p < 0.0001$), and (2) staging of liver fibrosis was mild ($p = 0.040$; table 3).

Table 4 shows the SVR based on virus load, HCV genotype, liver histology and the IFN regimen. In patients with a virus load ≤100 KIU/ml, genotype 2a or 2b, and liver histology of stage 1, SVR was 100% in patients with continuous IFN treatment and in those receiving the continuous + intermittent IFN regimen. On the other hand, in patients with a virus load >100 KIU/ml and genotype 1b, no patients showed SVR.

Safety of IFN Therapy

Of the 84 patients originally included in this study, 11 (13.1%) discontinued the IFN regimen due to adverse events: 5 cases due to general fatigue, 3 cases due to psychiatric disorder, and 1 patient each due to retinal bleeding, conjunctivitis, and leukopenia. These side effects occurred after 49–123 days in general fatigue, 15–141 days in psychiatric disorder, 106 days in retinal infarction, 32 days in conjunctivitis, and 30 days in leukopenia. Eight of the 11 patients stopped the IFN therapy owing to adverse events. Three patients continued IFN therapy at reduced doses. The remaining patients completed IFN therapy without severe side effects.

Cumulative Dropout Rate due to Adverse Events

Figure 1 shows the cumulative dropout rate due to adverse events of IFN. The cumulative dropout rate was

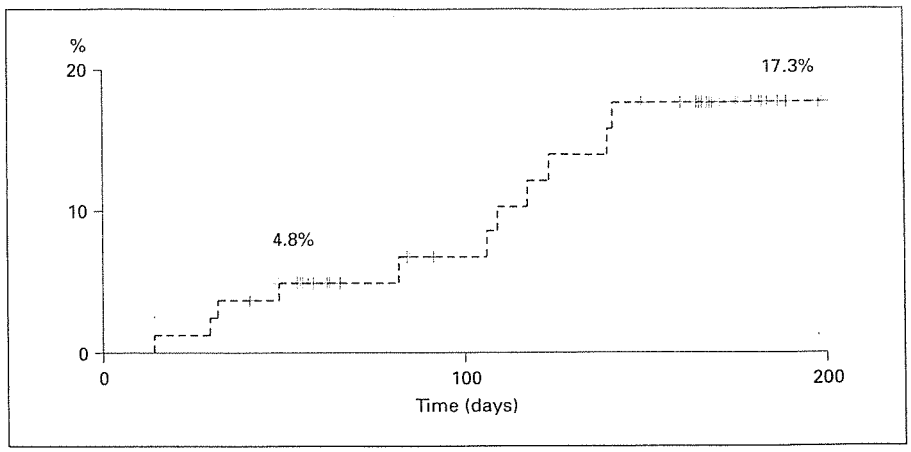


Fig. 1. Cumulative dropout rate due to adverse events during IFN therapy.

Table 4. SVR based on virus load, HCV genotype, liver histology and IFN regimen

HCV-RNA MEq/ml	HCV genotype	Liver histology	Cases	SVR based on IFN regimen[1]
<1	2a, 2b	F1	9	C; 100% (5/5), C+I; 100% (4/4)
<1	1b	F1	4	C+I; 75% (3/4)
<1	2a, 2b	F2–F4	12	I; 33.3% (1/3), C; 50% (2/4), C+I; 40% (2/5)
<1	1b	F2–F4	9	I; 0% (0/2), C; 0% (0/1), C+I; 66.7% (4/6)
≥1	2a, 2b	F1	6	C; 0% (0/3), C+I; 33.3% (1/3)
≥1	1b	F1	6	I; 0% (0/2), C; 0% (0/1), C+I; 0% (0/3)
≥1	2a, 2b	F2–F4	9	I; 0% (0/2), C; 0% (0/1), C+I; 16.7% (1/6)
≥1	1b	F2–F4	12	I; 0% (0/3), C; 0% (0/3), C+I; 0% (0/6)

[1] C = 6- to 8-week continuous course; I = 24-week intermittent course; C+I = 2- to 8-week continuous + 16- to 22-week intermittent course. Numbers of patients who showed SVR/total number of patients and percentages are shown.

4.8% 8 weeks after the initiation of IFN therapy and 17.3% at 24 weeks. We assessed factors predicting dropout based on adverse events in IFN therapy. The following factors were evaluated: sex, age, staging of liver histology, viral load, AST, ALT, Hb, platelet count, HCV-RNA level at the initiation of IFN treatment, and IFN regimen (table 5). Univariate analysis showed that patients aged >70 years were prone to dropout based on adverse events in IFN therapy ($p = 0.009$).

Discussion

Many investigators have reported IFN monotherapy and the IFN-ribavirin combination therapy to be effective for decreasing levels of ALT, reducing and eliminating HCV-RNA levels, improving liver histology and reducing the incidence of HCC in chronic hepatitis C patients [18–22]. However, clearance of serum HCV-RNA is not always attained. Factors predictive of SVR to IFN have been extensively studied, i.e. short duration of the disease, young age, absence of cirrhosis, low HCV-RNA levels and HCV genotype 2a [23–25]. Moreover, owing to IFN-related side effects or occurrence of complications, not all patients could be treated with IFN [26]. The dropout rate due to IFN-related side events might tend to increase in elderly patients. Thus, IFN therapy for chronic hepatitis C has been limited to patients aged less than 60 or 65 years. In Japanese patients >60 or >65 years, anti-inflammatory therapies, e.g. ursodeoxycholic acid or glycyrrhizin, were given. Complications related to these anti-inflammatory agents are few compared to IFN-related side effects.

Table 5. Factors predicting dropout based on IFN-related side effects

Factors	Category	Odds ratio	95% CI	p value
Age	<70/≥70 years	1/5.98	1.57–22.73	0.009
Liver histology	F2–F4/F1	1/3.76	0.46–30.56	0.216
HCV-RNA	≥1/<1 MEq/ml	1/3.01	0.797–11.39	0.104
IFN regimen	C+I/others	1/2.57	0.71–9.21	0.149
IFN	β/α	1/2.56	0.31–21.10	0.381
IFN regimen[1]	others/I	1/2.44	0.69–8.70	0.164
WBC	≥4,000/<4,000/mm^3	1/2.16	0.44–10.99	0.344
Sex	female/male	1/2.12	0.86–5.23	0.104
AST	≥76/<76 IU/l	1/1.97	0.40–3.76	0.407
Platelets	≥15/<15 × 10^4/mm^3	1/1.97	0.47–8.26	0.354
Sex	male/female	1/187	0.53–6.62	0.333
HCV genotype	2a, 2b/1b	1/1.51	0.42–5.47	0.525
Hb	≥13.5/<13.5 g/dl	1/1.51	0.36–6.33	0.574
IFN regimen	others/C	1/1.39	0.13–14.9	0.784
ALT	≥100/<100 IU/l	1/1.34	0.25–7.30	0.738

[1] C = 6- to 8-week continuous course; I = 24-week intermittent course; C+I = 2- to 8-week continuous + 16- to 22-week intermittent course; CI = confidence interval.

However, according to the statistics of the Japanese Ministry of Health, Labor and Welfare, the death rate (per 100,000 people) of HCC in Japan among people >65 years was 72.5 in 1980 and 111.1 in 2002. In the elderly, incidence rates of LC and HCC are increasing in Japan. In general, in patients aged ≥80 years with chronic liver disease, LC is the main risk factor affecting prognosis. In patients without LC, the number of liver-related deaths was lower than in patients with LC [27]. In elderly patients treated with IFN to protect the progression to LC and occurrence of HCC, life expectancy may be prolonged. Especially chronic hepatitis C patients with genotype 2a/2b or genotype 1b and lower virus load show good response to IFN therapy. Even if IFN is given at low doses, these patients could be expected to eradicate HCV-RNA and protect HCC. We, therefore, assessed the efficacy and safety of IFN therapy for chronic hepatitis C in elderly Japanese patients aged ≥65 years.

Regarding the efficacy of IFN therapy, patients who had genotype 2a or 2b, or 1b with low virus load had generally demonstrated high SVR. In the present study, elderly patients having genotype 2a/2b or genotype 1b with low virus load had high SVR. Moreover, with respect to safety of IFN therapy, the dropout rate was low in the IFN-treated elderly patients 8 weeks after initiation of IFN. We would like to recommend daily IFN therapy for 6–8 weeks in elderly patients having genotype 2a or 2b, or 1b with low virus load.

In conclusion, our results suggest that IFN administration is suitable to eradicate HCV-RNA in 65- to 70-year-old chronic hepatitis C patients without genotype 1b and high virus load.

Acknowledgments

The present work was supported in part by grants-in-aid from the Okinaka Memorial Institute for Medical Research and Japanese Ministry of Health, Labor and Welfare.

References

1 Simonetti RG, Camma C, Fiorello F, Cottone M, Rapicetta M, Marino L, Fiorentino G, Craxi A, Ciccaglione A, Giuseppetti R, Stroffolini T, Pagliaro L: Hepatitis C virus as a risk factor for hepatocellular carcinoma in patients with cirrhosis. A case control study. Ann Intern Med 1992;116:97–102.

2 Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, Maeda Y, Shirai Y, Fukuzaki T, Kaji I, Ishikawa H, Matsuda Y, Nishikawa M, Seki K, Matsuzawa Y: Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. Ann Intern Med 1998;129:94–99.

3 Okanoue T, Itoh Y, Minami M, Sakamoto S, Yasui K, Sakamoto M, Nishioji K, Murakami Y, Kashima K: Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: A retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group. J Hepatol 1999;30:653–659.

4 Ikeda K, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, Kumada H, Kawanishi M: A multivariate analysis of risk factors for hepatocellular carcinogenesis: A prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology 1993;18:47–53.

5 Oka H, Kurioka N, Kim K, Kanno T, Kuroki T, Mizoguchi Y, Kobayashi K: Prospective study of early detection of hepatocellular carcinoma with cirrhosis. Hepatology 1990;12: 680–687.

6 Ikegami T, Sugiura N, Ebara M, Saisho H, Ohto M: Development and predictive factors of hepatocellular carcinoma in patients with chronic liver disease over a long follow-up period in Japanese. Jpn J Gastroenterol 1994;91: 1290–1300.

7 Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, Iijima A, Urushihara A, Kiyosawa K, Okuda M, Hino K, Okita K: Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Hepatology 1998;27:1394–1402.

8 Ikeda K, Arase Y, Kumada H: Hepatocellular carcinogenesis and prognosis of elderly patients with chronic hepatits type C (in Japanese). Nippon Rinsho 2001;59:1338–1344.

9 Ikeda K, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, Tsubota A, Arase Y, Murashima N, Chayama K, Kumada H: Long-term interferon therapy for 1 year or longer reduces the hepatocellular carcinogenesis rate in patients with liver cirrhosis caused by hepatitis C virus: A pilot study. J Gastroenterol Hepatol 2001;16: 406–415.

10 Terranova R, Luca S: Treatment of chronic hepatitis C with lymphoblastoid interferon alpha in elderly patients. Eur Rev Med Pharmacol Sci 1997;1:47–52.

11 Terranova R, Luca S: Different types of interferon for the therapy of HCV chronic active hepatitis in the elderly patients. Eur Rev Med Pharmacol Sci 1999;3:45–52.

12 Horiike N, MasumotoT, Nakanishi K, Michitaka K, Kurose K, Ohkura I, Onji M: Interferon therapy for patients more than 60 years of age with chronic hepatitis C. J Gastroenterol Hepatol 1995;10:246–249.

13 Bresci G, Del Corso LD, Romanelli AM, Giuliano G, Pentimone F: The use of recombinant interferon alfa-2b in elderly patients with anti-HCV-positive chronic active hepatitis. J Am Geriatr Soc 1993;41:857–862.

14 Albadalejo J, Alonso R, Antinozzi R, Bogard M, Bourgault AM, Colucci G, Fenner T, Petersen H, Sala E, Vincelette J, Young C: Multicenter evaluation of the COBAS AMPLICOR HCV assay, an integrated PCR system for rapid detection of hepatitis C virus RNA in the diagnostic laboratory. J Clin Microbiol 1998;36:862–865.

15 Doglio A, Laffont C, Caroli-Bose FX, Rochet P, Lefebvre J: Second generation of the automated Cobas Amplicor HCV assay improves sensitivity of hepatitis C virus RNA detection and yields results that are more clinically relevant. J Clin Microbiol 1999;37:1567–1569.

16 Dusheiko G, Schmilovitz-Weiss H, Brown D, McOmish F, Yap PL, Sherlock S, Mcintyre N, Simmonds P: Hepatitis C virus genotypes; an investigation of type-specific differences in geographic origin and disease. Hepatology 1994;19:13–18.

17 Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Sheuer PJ: Classification of chronic hepatitis: Diagnosis, grading and staging. Hepatology 1994;19:1513–1520.

18 McHuchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK: Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485–1492.

19 Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J: Randomised trial of interferon alpha 2b plus ribavirin for 48 weeks or 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426–1432.

20 Reichard O, Norkrans G, Fryden A, Braconier JH, Sonnerborg A, Weiland O: Randomised, double-blind, placebo-controlled trial of interferon alpha 2b with and without ribavirin for chronic hepatitis C. Lancet 1998;351:83–87.

21 Schalm SW, Hansen BE, Chemello L, Bellobuono A, Brouwer JT, Weiland O, Cavalletto L, Schvarcz R, Ideo G, Alberti A: Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C. J Hepatol 1997;26:961–966.

22 McHutchison JG, Poynard T, Pianko S, Gordon SC, Reid AE, Dienstag J, Morgan T, Yao R, Albrecht J: The impact of interferon plus ribavirin on response to therapy in black patients with chronic hepatitis C. Gastroenterology 2000;119:1317–1323.

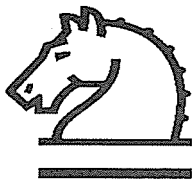
23 Tsubota A, Chayama K, Arase Y, Koida I, Saitoh S, Hashimoto M, Iwasaki S, Kobayashi M, Hiromitsu K: Factors predictive of response to interferon-alpha therapy in hepatitis C virus infection. Hepatology 1994;19:1088–1094.

24 Yoshioka K, Kakumu S, Wakita T, Ishikawa T, Itoh Y, Takayanagi M, Higashi Y, Shibata M, Morishima T: Detection of hepatitis C virus by polymerase chain reaction and response to interferon-α therapy: Relationship to genotypes of hepatitis C virus. Hepatology 1992;16: 293–299.

25 Shiratori Y, Kato N, Yokosuka O, Imazeki F, Hashimoto E, Hayashi N, Nakamura A, Asada M, Kuroda H, Tanaka N, Arakawa Y, Omata M: Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Gastroenterology 1997;113:558–566.

26 Okanoue T, Sakamoto S, Itoh Y, Minami M, Yasui K, Sakamoto M, Nishioji K, Katagishi T, Nakagawa Y, Tada H, Sawa Y, Mizuno M, Kagawa K, Kashima K: Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol 1996;25:283–291.

27 Hoshida Y, Ikeda K, Kobayashi M, Suzuki Y, Tsubota A, Saitoh S, Arase Y, Kobayashi M, Murashima N, Chayama K, Kumada H: Chronic liver disease in the extremely elderly of 80 years or more: Clinical characteristics, prognosis and patient survival analysis. J Hepatol 1999;31:860–866.



Springer

A Long-Term Glycyrrhizin Injection Therapy Reduces Hepatocellular Carcinogenesis Rate in Patients with Interferon-Resistant Active Chronic Hepatitis C: A Cohort Study of 1249 Patients

Kenji Ikeda, Yasuji Arase, Masahiro Kobayashi, Satoshi Saitoh, Takashi Someya, Tetsuya Hosaka, Hitomi Sezaki, Norio Akuta, Yoshiyuki Suzuki, Fumitaka Suzuki, Hiromitsu Kumada

Digestive Diseases and Sciences 2006:51:603-609