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Natural Interferon α Treatment and Interferon α Receptor 2 Levels in Acute Hepatitis C

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Efficacy of interferon (IFN) therapy during the acute phase of hepatitis C infection is promising, although the optimal regimen has yet to be determined. It is not known whether the known prognostic factors for chronic hepatitis C (CHC) influence the effect of IFN in acute hepatitis C (AHC). Seventeen patients with AHC were analyzed for hepatic IFN α receptor 2 (IFNAR2) prior to IFN treatment. All patients were subsequently treated with either 168 million units (MU) or 336 MU of natural IFN α. Seventeen age-matched samples of CHC were provided as controls. The overall sustained response rate was 64.7% (11/17). In patients who received a total dose of 168 MU IFN, the sustained response rate was 28.6% (2/7), and in those who received 336 MU of IFN, the sustained response rate was 90.0% (9/10). The peaks of ALT and HCV-RNA quantity were not associated with the response to IFN. The hepatic IFNAR2 levels were 1.52 ± 0.34 densitometry units and 0.92 ± 0.16 in AHC and CHC, respectively ($P = 0.042$). There was no difference in hepatic IFNAR2 levels between sustained virological responders (SVR) and nonsustained virological responders (NR). The hepatic receptor levels were higher in AHC than in CHC patients. The levels of hepatic IFNAR2 did not differ in SVR and NR, indicating that high-dose natural IFN α treatment is effective for AHC, irrespective of the levels of hepatic IFNAR2.

KEY WORDS: acute hepatitis C; natural interferon α; hepatic IFNAR2.

Hepatitis C infection poses a serious problem all over the world. About 30% of patients with chronic hepatitis C (CHC) will develop cirrhosis within 3 to 20 years, and a large number of these patients will develop complications such as liver failure, portal hypertension, and hepatocellular carcinoma (1). Interferon (IFN) is the most common treatment for chronic hepatitis C virus (HCV) infection but a substantial portion of patients does not respond, and many responders relapse after stopping treatment.

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It is well known that the virological efficacy of IFN monotherapy on chronic hepatitis C (CHC) is only about 30% (1, 2). IFN and ribavirin combination therapy improved response rate up to about 50% (3, 4). Patient selection, depending on the prognostic factors, however, allows virus eradication in a higher percentage of patients. Such prognostic factors include HCV viral load, HCV genotype, NS-5A mutation, and histological progression of the disease (1, 2). Moreover, others (5) and we (6) have reported a correlation between the effect of IFN and hepatic IFN α receptor 2 (IFNAR2), which play a pivotal role in IFN therapy against HCV infection.

Acute hepatitis C (AHC) infection has a tendency to progress to chronic hepatitis in 55–88% (7–10). Because of the high rate of chronic infection resulting from acute hepatitis C, several studies have been conducted to seek an effective therapy during the acute phase which may prevent progression to chronicity (11–14). Several uncontrolled (15, 16) and controlled (12, 14, 17, 18) studies of

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IFN therapy in patients with AHC have been performed aiming to assess the effects of treatment on serum alanine aminotransferase (ALT) level, viral markers, and histological necroinflammation. To increase the statistical power to resolve uncertainty and to improve estimates of effect size, a few meta-analysis based on the results of controlled trials have been performed (19–21). All but one (22) support IFN therapy in AHC, showing effectiveness ranging from 35 to 90%. However, the reason these high virological efficacies of IFN are obtained against AHC infection has not been elucidated to date.

Results of IFN therapy during the acute phase of HCV infection are promising, although the optimal regimen is yet to be determined. Moreover, it is not known whether the known prognostic factors for CHC influence the effect of IFN in AHC. In the current study, we retrospectively analyzed 17 cases of AHC and assessed the efficacy of IFN with respect to pretreatment values including HCV viral load, HCV genotype, and the levels of hepatic IFNAR2.

METHODS

Patient Selection and Diagnosis. Diagnosis of acute hepatitis was based on the finding of elevated values of serum ALT at least five times the normal values, associated with either HCV antibody seroconversion of second-generation ELISA (ELISA III; Ortho Diagnostic System), or positivity of HCV-RNA by reverse-transcription polymerase chain reaction (RT-PCR). Patients for whom other causes of liver disease were suspected were excluded. Seventeen patients (6 males and 11 females) treated at National Nagasaki Medical Center between 1987 and 1999 fulfilled the inclusion criteria.

Liver biopsy specimens obtained from CHC patients between 2000 and 2001 were provided as controls for immunohistochemistry. CHC patients were routinely subjected to liver biopsy at National Nagasaki Medical Center. Seventeen samples were selected of consecutively obtained 74 CHC samples on a crudely age-matching basis.

Written informed consent was obtained from each patient upon enrollment for the study.

HCV Genotype and HCV-RNA Quantification. HCV genotyping was performed by PCR amplification on core region sequences with universal and five subtype-specific primers according to Okamoto *et al.* (23) and their modified version (24). According to this classification, HCV genotypes can be classified into five distinct categories. Genotypes I, II, III, IV, and V correspond to 1a, 1b, 2a, 2b, and 3a in Simmonds' classification (25), respectively.

HCV-RNA quantification was performed by the branched DNA signal amplification method (Quantiplex 2.0; Chiron Diagnostics), which is based on hybridization with specific probes located in the 5′ noncoding region of HCV, with a detection limit of 0.3 Meq/ml.

IFN Therapy and Follow-up. Natural IFN α (Sumiferon; Sumitomo Pharmaceutics, Tokyo) was administered subcutaneously at doses of 6 million units (MU) daily for either 4 weeks (total, 168 MU) or 8 weeks (total, 336 MU). All patients were hospitalized during the treatment. Patients were followed up as outpatients monthly for at least 24 weeks after the end of treatment.

Histological Analysis. All liver tissue specimens were obtained by needle biopsy. Specimens were fixed in 10% formalin, embedded in paraffin, cut to a thickness of 4 μm, and stained with hematoxylin–eosin and Azan. In each patient, the liver biopsy sample confirmed the diagnosis of acute hepatitis.

Analysis for Hepatic IFNAR2 Levels. Liver biopsy samples were evaluated using an indirect immunoperuoxidase staining technique as described previously (6). Briefly, samples embedded in paraffin and cut into 4-μm slices were deparaffinized with xylene and 100, 90, 80, and 70% ethanol, microwaved for 5 min, then subjected to immunostaining using monoclonal anti-IFNAR2. Mouse monochronal antibody against human IFNAR2 (kindly provided by Otuka Pharmaceutical, Tokushima, Japan) at a 1:10,000 dilution was applied to the slide and incubated at 4°C overnight. Standard streptavidin–biotin (Histofine SAB-PO(M) kit; Nichirei, Tokyo) method was utilized for immunohistochemical reaction. As a negative control, normal, nonimmune mouse serum was used instead of the anti-IFNAR2. The staining intensity in each image was quantified by computer-image quantative analysis. The expression intensity was assessed in at least three lobular areas, and the average value for each specimen was determined. The expression intensity in one normal control sample was defined as 1.0 densitometry unit (DU).

Assessment of Efficacy. The treatment was considered to be effective when a sustained virological response (SVR), defined by the absence of detectable levels of HCV-RNA in serum 24 weeks after the end of treatment, was achieved with normal ALT levels. All patients who did not meet the criteria of SVR were defined as nonsustained virological responders (NR).

Statistical Analysis. Data are expressed as mean ± SD. Differences between groups were examined for statistical significance using nonparametric test (Mann–Whitney U test). Chi-square test was also utilized where appropriate. A P value less than 0.05 was considered a statistically significant difference.

RESULTS

General Characteristics of the Patients Studied. The source of infection included blood transfusion (before July 1990; 10 cases; 59%) and needle-stick injury (2 cases; 12%). In five cases (29%), the mode of infection was unclear. The average time from infection to the first signs or symptoms of disease was 43.5 days (median; range, 23 to 180 days). All patents received IFN therapy for 4 or 8 weeks. Genotypes 1b, 2a, and 2b were detected in seven, seven, and one, respectively. All patients completed therapy and follow-up. Patients' clinical backgrounds are listed in Table 1.

Response to IFN Therapy. Overall sustained response rate was 64.7% (11/17). In patients whose total dose of inteferon was 168 MU, sustained response rate was 28.6% (2/7). In patients whose total dose was 336 MU, sustained response rate was 90.0% (9/10). No apparent associations were seen between peak of ALT and HCV-RNA quantity or response to IFN. Although modes of infection were not clear in five patients the time from

TABLE 1. PATIENT CHARACTERISTICS

Patient No.	*Age (yr)*	*Gender*	*Mode of infection*	*Peak of ALT (IU/L)*	*Pre-IFN HCV RNA (Meq/ml)*	*HCV genotype*	*IFN, total dose*	*Effect of IFN*
1	40	F	BT	1154	<0.3	1b	6 MU, 4 weeks, daily (168 MU)	SVR
2	33	F	BT	470	<0.3	2a		SVR
3	35	F	BT	1240	21.8	1b		NR
4	48	F	BT	923	<0.3	1b		NR
5	43	M*	BT	350	0.4	1b		NR
6	44	F	Unknown	1192	1.4	1b		NR
7	64	M	BT	440	1.6	Mixed (1b and 2a)		NR
8	32	M	BT	380	4.3	1b	6 MU, 8 weeks, daily (336 MU)	SVR
9	41	M	BT	395	12.3	Mixed (1b and 2a)		SVR
10	68	M	Unknown	2412	<0.3	2a		SVR
11	32	F	BT	550	<0.3	2b		SVR
12	28	F	Unknown	1238	0.3	2a		SVR
13	30	M	Needle stick	682	0.8	2a		SVR
14	59	F	Needle stick	300	<0.3	2a		SVR
15	24	F	Unknown	1352	10.0	2a		SVR
16	42	F	Unknown	2304	<0.3	2a		SVR
17	33	F	BT	1138	<0.3	1b		NR

Note. SVR, sustained virological responder; NR, nonsustained virological responder; BT, blood transfusion.

infection to initiation of IFN therapy of the SVR and NR groups were among patients whose transmission route was known.

Comparison of IFN Receptor Levels Between AHC and CHC. Because the mean age of consecutive 74 CHC patients admitted to our hospital in 2000 and 2001 was much higher than that of AHA patients, 17 samples were selected on an age-matching basis and were provided as controls for immunohistochemical study. Table 2 shows the levels of hepatic IFNAR2 levels as well as other parameters of these two groups. Male gender was predominant in the CHC group and female gender was more frequent in the AHC group, but the difference was not significant. Hepatic IFNAR2 levels were 1.52 ± 0.34 and 0.92 ± 0.16 DU in AHC and CHC, respectively ($P = 0.042$). The significance was even higher when all 74 CHC patients (0.95 ± 0.06 DU) were included in the analysis ($P = 0.005$: data not shown).

Adverse Events. Therapy was tolerated in all patients. The spectrum of side effects was similar to that reported in previous reports on IFN monotherapy for CHC, including flu-like symptoms, arthralgia, neutropenia, and thrombocytopenia. There were no serious adverse effects during therapy.

TABLE 2. COMPARISON OF PATIENTS WITH CHRONIC HEPATITIS C (CHC) AND ACUTE HEPATITIS C (AHC)

	CHC (n = 17)	*AHC (n = 17)*	P
Gender (male:female)	11:6	6:11	0.086
Age (yr)	42.1 ± 2.1	40.9 ± 9.9	0.755
Hepatic IFNAR2 (DU)	0.92 ± 0.16	1.52 ± 0.34	0.042
Genotype (1b:other type)	9:7 (mixed in 1)	7:10	

Levels of Hepatic IFNAR2 in AHC. Table 3 shows the comparison between SVR and NR for IFN therapy in acutely HCV-infected patients ($n = 17$). There are no significant difference in gender, age, peak ALT levels, HCV-RNA levels, or hepatic IFNAR2. Genotype 1b was more common in NR according to univariate analysis. Total IFN dose (169 vs 336 MU) strongly affected the outcome of acute hepatitis C ($P = 0.009$).

Figure 1 indicates the levels of hepatic IFNAR2 in AHC and CHC. There was no difference in hepatic IFNAR2 levels between SVR (1.43 ± 0.35) and NR (1.70 ± 0.25) patients with AHC, whereas they were both significantly higher than the hepatic IFNAR2 levels of CHC patients ($P = 0.028$ and $P = 0.012$, respectively).

DISCUSSION

Unlike hepatitis A and hepatitis B virus infection, the rate of chronic evolution of HCV infection is very high. The rate of chronicity in HCV infection has been reported

TABLE 3. COMPARISON OF SUSTAINED VIROLOGICAL RESPONDERS (SVR) AND NONSUSTAINED VIROLOGICAL RESPONDERS (NR)

	SVR	*NR*	P
Gender (male:female)	4:7	2:4	>0.999
Age (yr)	39.0 ± 13.4	44.5 ± 11.1	0.410
Mode of infection (blood transfusion:others)	5:6	5:1	0.308
Peak of ALT (IU/L)	1021.5 ± 756.2	880.5 ± 392.4	0.679
HCV-RNA (Meq/ml)	5.5 ± 5.4	6.3 ± 10.3	0.890
Hepatic IFNAR2 (DU)	1.43 ± 0.35	1.70 ± 0.25	0.120
Genotype (1b:other type)	2:9	5:1	0.036
Total dose of IFN (336:168 MIU)	9:2	1:5	0.036

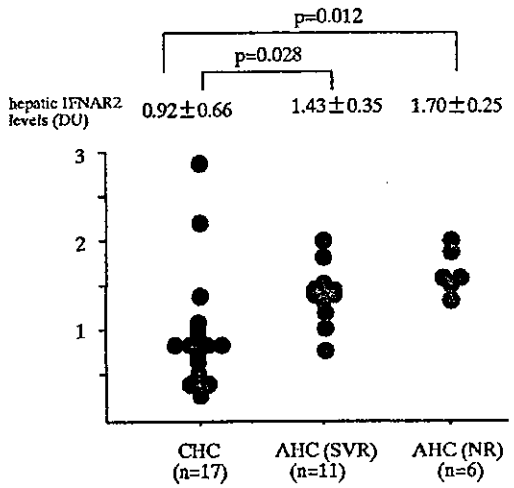

Fig 1. Hepatic IFNAR2 levels in patients with acute hepatitis C ($n = 17$: sustained virological responders, 11; nonsustained virological responders, 6) and chronic hepatitis C ($n = 17$). AHC, acute hepatitis C; CHC, chronic hepatitis C; SVR, sustained virological responders; NR, nonsustained virological responders.

to be 59–88% (7, 8) in transfusion-associated cases and 55–62% (9, 10) in sporadic cases. Once HCV infection progresses to chronic stages, the long-term response to IFN monotherapy is poor. Recently, combination therapy with ribavirin has been established, but it still has limits, including insufficient HCV clearance and significant side effects (26).

On the other hand, high rates of resolution of AHC after IFN therapy have been reported. Hence, it would be rational to challenge stopping infection during the acute phase. For example, recently, a German group (27) reported a nationwide, prospective study in which 44 patients were enrolled. In the study, patients received 5 MU of interferon α-2b daily for 4 weeks and then three times per week for another 20 weeks. Ninety-eight percent of patients had undetectable levels of HCV-RNA in serum at the end of follow-up (24 weeks after the therapy). Based on the results, they suggested that all patients with AHC should be treated, admitting that about 30% of their patients would have had self-limited disease, regardless of whether they received IFN.

Others claim, however, that treating the acutely infected could be harmful, in providing drug therapy for patients whose hepatitis C would have resolved spontaneously (13, 28). Moreover, there is no consensus on the optimal dose, daily versus three times a week injections, or duration of therapy in the setting of AHC.

We reported a comparative study of IFN treatment for AHC in which administration of 6 MU of natural IFN α daily for 4 weeks (total, 168 MU) and 8 weeks (total, 336 MU) was compared. Apparently, the 8-week protocol resulted in a favorable outcome regarding the disappearance of HCV-RNA (90% [9/10] vs. 28% [2/7]).

A total dose of 336 MU of natural IFN α in total is considered to be the "medium" dose in therapy for CHC, suggesting that the amount is safe even for treatment of AHC. Takano *et al.* (12) previously showed a good response (83%) with the same dose of IFN β (336 MU), compared to lower doses, in a randomized, controlled-dose study. Increasing the dose of IFN significantly increased the rate of virological response (as shown in Refs. 12, 14, 18, and 29). Indeed, the German study utilized 440 MU of IFN α2b in total. They admitted that shorter periods of treatment might have been sufficient in patients in whom serum levels of HCV-RNA quickly became undetectable. Thus, the optimal regimen of IFN for AHC should be further elaborated with care.

The reason these high virological efficacies of IFN are obtained against acute HCV infection has not been elucidated. Additionally, factors that determine the virological response rate after IFN therapy are poorly understood. Gursoy *et al.* (30) studied the effects of IFN α2b treatment in hemodialysis patients with acute HCV infection to identify factors that predict the response to this therapy. They found that pretreatment HCV load and genotype were not significantly associated with virological sustained response and that quasispecies heterogeneity was the only parameter that predicted virological response in their 53 patients.

On the other hand, Toyoda *et al.* (31) reported a patient with AHC whose HCV was transmitted by a needle-stick accident from a patient with CHC who had failed to eradicate HCV with IFN therapy. The transmitted HCV was successfully eradicated from the patient with AHC, suggesting some host immune responses in patients with acute viral infections distinct from those in patients with chronic infection.

Human IFN α and β have been considered to elicit their effect via their receptor, IFNAR2 (32). We have reported a strong association between the effect of IFN and the levels of hepatic IFNAR2 mRNA (33) and protein (6) in chronic HCV-infected patients. In the current study, we evaluated if the levels of IFN receptor influence the effect of IFN for those acutely infected by HCV.

As stated above, many studies have shown high resolution rates of AHC after IFN therapy but the reason is yet to be clarified. We conducted a retrospective, immunohistochemical study to clarify whether the IFN receptor levels affect the response of acute hepatitis to IFN therapy. The results indicate that acutely HCV-infected liver expresses higher levels of IFN receptor than does chronically infected liver.

Univariate analysis revealed that there was no difference in the levels of IFN receptor between SVR and NR, suggesting a distinct factor that regulates IFN efficacy. Although the limited number of samples did not allow us to perform multivariate analysis to reveal independent factors associated with the effect of IFN therapy, previous data suggest that genotype is not a strong determinant of IFN efficacy in AHC (27, 30, 31). To reveal the impact of IFN receptors on IFN therapy for AHC, further controlled study is warranted.

In conclusion, we showed that the higher-total dose regimen was superior to the lower total dose in the treatment of AHC. The hepatic receptor level was higher in AHC patients compared to CHC patients, suggesting that the IFN receptor is one of the causes of the high resolution rate of IFN α. The levels of IFNAR2 did not differ in SVR and NR, indicating that high-dose natural IFN α treatment is effective for AHC, irrespective of the levels of hepatic IFNAR2.

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Global Burden of Disease (GBD) for Hepatitis C

The Global Burden of Hepatitis C Working Group

Hepatitis C virus (HCV) infection is now a global public health issue. However, the global burden of disease attributable to HCV infection is unknown. The objectives of this WHO informal consultation included the following: (1) defining a strategy to estimate the global burden of disease (GBD) associated with HCV infection in terms of morbidity and mortality, (2) describing the natural history of HCV infection in terms of morbidity and mortality, and (3) identifying areas for which more research is needed. The GBD project is an attempt to examine all causes of morbidity and mortality using an approach common to all conditions. The World Health Organization (WHO) already has estimated the burden of disease associated with hepatitis B virus (HBV) infection and is now about to conduct the same analysis for HCV infection. A review has been conducted to estimate the prevalence of HCV infection by age, gender, and region. These figures can be used to estimate incidence, although there are a number of areas of uncertainty. Combined with natural history parameters, incidence estimates could be used to estimate the future burden due to current infections. However, the present model is not validated and requires calibration before it can be used. A consensus was reached over the strategies to be used to (1) estimate the current burden due to past infections and (2) estimate the future burden due to current infections. Provisional expert consensus was reached over natural history parameters and cofactors that influence them. However, systematic literature reviews and meta-analysis are preferable for obtaining estimates to be included in models. Areas deserving future research include (1) obtaining a better estimate of HCV infection prevalence by age groups, (2) characterizing the various morbidity states associated with HCV infection and their disability weights, (3) understanding the long-term natural history of HCV infection beyond 20 years after infection, and (4) estimating the prevalence (and numbers of) of HCV infection among the drug-using population worldwide. A working group was created to address unmet needs and to assist the WHO in estimating the GBD associated with HCV infection.

Keywords: *Hepatitis C virus; global burden of disease; World Health Organization; morbidity; mortality; GBD project*

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MODELING HEPATITIS C GLOBAL BURDEN OF DISEASE

A Global Perspective on Hepatitis C

Hepatitis C has become an issue of global importance. It is not only of concern to industrialized countries. In Egypt, for example, the impact of hepatitis C virus (HCV) infection exceeds that of HIV. This World Health Organization (WHO) informal consultation on the global burden of disease (GBD) caused by HCV infection was organized for two reasons:

- The WHO needs burden of disease estimates to make policy decisions.
- The world is concerned with hepatitis C and is eager for proper guidance.

In the past, the WHO estimated the prevalence of HCV infection worldwide and published the results in

the *Weekly Epidemiological Record*. However, these estimates need to be revised. In addition, preliminary, unpublished estimations of the global burden of disease have been made but need improvement.

This meeting has addressed three key areas:

1. the strategy to estimate the global burden of morbidity and mortality associated with HCV infection;
2. the natural history of HCV infection, including "healthy individuals," morbidity, and mortality; and
3. the areas for which more research is needed.

About the Global Burden of Disease

Rationale of the GBD Project

National and international health policies should be based on accurate and meaningful health information. However, much of the information collated cannot be directly translated into policy. Health data from routine statistics or epidemiological studies are often fragmented, frequently concentrate on fatal health outcomes, and may only be partially available. Studies that investigate particular conditions may exaggerate claims on mortality. This is largely a reflection of comorbidity, in which several coexisting pathologies contribute to and compete for the cause of death. Moreover, traditional statistics use a variety of different measures, which do not permit direct comparisons of the cost-effectiveness of different interventions. The GBD project addresses these problems using a single metric, the disability-adjusted life year (DALY).

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DALY is the measure used to quantify the health gap. It combines years of life lost (YLLs) and years lived with disability (YLDs) for varying degrees of severity; time itself becomes the common metric for death and disability. Years of life lost are weighted according to age (because a year of life lost does not have the same value at all ages) and discounted by 3% per year. Considering weighting and discounting, the value of an early death is reduced to approximately 75% of its original value in 10 years. GBD does not take into account the fact that life expectancy may increase over time in the future. There is not enough evidence to modify that in future projections. Japan, the country with the longest life expectancy, is being used.

GBD estimates age-specific death rates by sex using a variety of sources of data on mortality (vital registration,* surveys,† and epidemiological studies). From these, life tables can be derived using standard methods. The number of deaths abstracted from the life tables provides a "mortality envelope," which serves to limit the total number of deaths from all specific causes. GBD uses a grading system to estimate data quality and conducts uncertainty analyses to reflect this quantitatively.

Goals

The goals of the GBD project are to

- decouple evidence from advocacy,
- use both fatal and nonfatal measures of health outcomes, and
- use a single metric to estimate burden and cost-effectiveness.

Objectives

The objectives of the GBD project are to

- estimate mortality by age, sex, and regions for 130 causes of deaths and their sequelae;
- estimate other epidemiological parameters;
- evaluate risk factors; and
- project burden of disease into the future.

Classification of Outcomes

For the purpose of GBD, health outcomes are classified as follows:

1. communicable, maternal, perinatal, and nutritional diseases;

* The quality of vital registration varies from region to region. This quality is high in established market economies and the former socialist republics of Eastern Europe but low in many other places. However, the trend is toward improvement.

† Including Demographic and Health (DHS) surveys.

2. noncommunicable diseases; and
3. injuries.

This classification is used to prevent diseases from being counted twice.

Currently, hepatitis C virus infection is only counted as "acute and chronic hepatitis" (in group 1) as the data have not yet been made available to divide the chronic outcomes (hepatocellular carcinoma and chronic liver disease that are in group 2) into various causes (e.g., hepatitis B virus [HBV] infection, HCV infection, alcohol, and others). This could be revised if data are made available. However, the model ultimately needs to be built up from both ends and report on incidence and prevalence using the natural history model.

Modeling Hepatitis B from the WHO's Point of View

Methods Used

One of the main input parameters of the hepatitis B model is the prevalence of chronic infection. This decision was made because (1) no estimates of incidence were available, and (2) the majority of the burden of disease attributable to HBV infection occurs during adulthood as a consequence of chronic infection acquired early in life. Mortality and morbidity from hepatocellular carcinoma and cirrhosis were estimated among patients chronically infected (HBsAg positive). Age- and gender-specific mortality rates among chronically infected patients that were derived from Gambian studies were applied to the prevalence of HBsAg in the population by age, sex, and region. The Gambian project generated good-quality data based on extensive surveillance. The Taiwan province of China generated very similar estimates. In addition to the burden estimates for mortality associated with chronic infection, additional work is ongoing to estimate the burden associated with chronic morbidity and acute HBV infection.

Results

The GBD hepatitis B model estimates that, in 2000, there were approximately 360 million persons with chronic HBV infection, nearly 5.7 million cases of HBV-related clinical disease, and just over half a million of HBV-related deaths. This represents current burden due to past infections that should be differentiated from future burden due to current infections. Accounting for background "competing" mortality is important in the case of HBV and other chronic infections because after infection, death and disability occur later in life. This is particularly important in sub-Saharan Africa as the background HIV-related mortality is high (Figure 1) and will be increasingly important in Asia. In the absence of HIV infection, expected chronic HBV death rates in Botswana would approach that of Singapore.

In terms of mortality, hepatocellular carcinoma and cirrhosis dominate. In terms of morbidity, acute hepatitis dominates. However, this does not take into account chronic active hepatitis, and therefore morbidity may have been underestimated. The characterization of chronic morbidity in terms of annual episode incidence, duration, and level of disability is planned for the near future. The impact of cofactors of hepatocellular carcinoma, including aflatoxin, alcohol, and other viral hepatitis infection, has not been investigated but should be addressed using case control methodologies. However, it is unclear whether a better reflection of these factors would substantially improve disease burden estimates. Rather, expanding the geographical scope of research into HBV's attributable fraction in cirrhosis and hepatocellular carcinoma is likely to be more productive given the lack of information in this area.

Modeling Hepatitis B in Switzerland

In Switzerland, the global burden of HBV infection was estimated to help guide decisions in the area of immunization. In contrast to the prevalence-based approach used for the WHO global model, a decision tree approach was used based on experience with the model developed for the United States by the Centers of Disease Control and Prevention (CDC). This model could

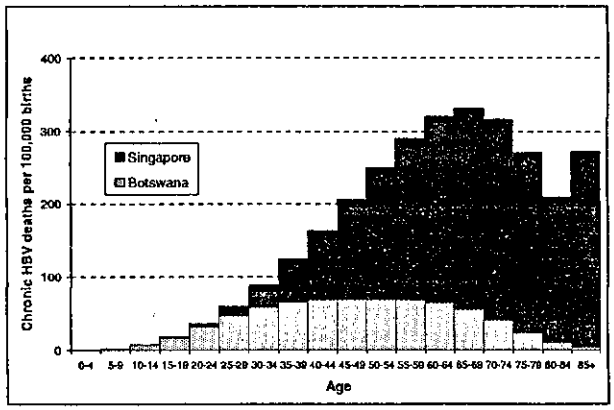

Figure 1. Background mortality does matter: Expected chronic hepatitis B virus (HBV) deaths in the 2000 birth cohort in Botswana and Singapore in the absence of hepatitis B vaccination. From Gay NJ, Edmunds WJ, Bah E, Nelson CB: Estimating the global burden of hepatitis B. *Geneva, Swizerland: World Health Organization, Department of Vaccines and Biologicals, 2001.*

be applied to hepatitis C. However, (1) data are not yet available, (2) background mortality has not been considered, and (3) DALYs have not been calculated. Besides Switzerland, the model may have been used in Liechtenstein and by private economists. For use in Asia, the model would have to be updated to take into account mutants and perinatal infection.

Global Prevalence of HCV Infection

Objective

The objective of the study was to estimate the prevalence of HCV infection by age, gender, and region and to update the estimate previously generated by WHO.

Methods

A literature search was carried out using Medline and other sources. The results of studies that included patients whose risk of HCV infection was thought to be similar to the general population were incorporated in a database. Studies were considered regardless of whether supplemental testing was conducted. Both English and non-English publications were considered. Surveys done since the late 1980s were assumed to be representative of the year 2000. First, country-specific studies were reviewed to obtain an overall estimate where possible, placing greater weight on community surveys and studies including supplemental testing. Second, gender- and age-specific prevalences were estimated. Countries lacking data were associated with other countries on the basis of epidemiologic similarities. Regional estimates were derived by weighting the country-specific estimates by overall population.

Results

Data from more than 300 studies representing all of the regions were considered in deriving estimates of the prevalence of HCV infection. Overall preliminary results suggest that the prevalence of HCV infection is approximately 2.2% worldwide. While the individual estimates from the different regions have undergone some change, the overall picture is still similar, with the WHO African region and the WHO Eastern Mediterranean region having the highest prevalence of HCV infection (Figure 2). Future work will focus on uncertainty analysis.

Discussion

Approximately one-quarter of the studies used represented community surveys, while one-third represented blood donors. No single approach was used to adjust these estimates as the mode of recruitment of

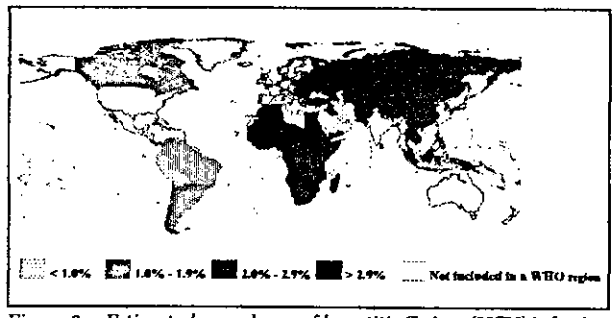

Figure 2. Estimated prevalence of hepatitis C virus (HCV) infection by region (preliminary).

blood donors differs tremendously depending on the region. However, none of the regional estimates relied exclusively on studies conducted among blood donors. In selected industrialized countries, another approach has been previously used to (1) estimate the size of the population in high-risk groups (e.g., injection drug users), (2) estimate the prevalence of HCV infection among these high-risk groups, and (3) compile these estimates to adjust the estimated prevalence in the general population. For example, this approach was considered useful in Switzerland, where community-based studies did not capture injection drug users. While this approach could work in industrialized countries where community-based studies may underestimate prevalence by not including injection drug users, it may not be useful in developing countries where unsafe medical injections are a main risk factor of infection. However, because there are emerging outbreaks of injection drug use in a number of developing and transitional countries, a mechanism to include this factor into a sensitivity analysis should be identified. The Evidence and Information for Policy (EIP) WHO cluster has estimates of the number of injection drug users by region. These figures could be used to adjust the HCV infection prevalence estimates in certain areas. Ideally, data should include estimates of both current and prior injection drug use. In the United States, for instance, most of the prevalent HCV infections were associated with former rather than current injection drug use.

Modeling the Incidence of HCV Infection

Difficulties in Estimating HCV infection Incidence

Precise estimation of the incidence of HCV infection is not possible given available data. Because direct mea-

surement of incidence is difficult, there are few published studies in which this has been attempted. Estimation of incidence from available prevalence data is the most practical approach for estimating incidence on a global scale, although results are sensitive to assumptions, particularly those regarding past trends in incidence. In addition, age-specific estimation of incidence is not possible because of the paucity of precise, age-specific data.

Impact of Past Trends on Incidence

The incidence of HCV infection is probably a function not only of age but also of time. Following the Second World War, there was an increase of use of injections, blood products, and injection drug use. However, in the past 10 years, in some industrialized countries, the incidence of new infections has decreased, presumably reflecting a decrease in percutaneous exposures. These temporal trends need to be taken into account when estimating incidence from prevalence.

Other important sources of uncertainty in the incidence model include the rate at which seropositive individuals lose detectable antibody (seroreversion) and whether persons with HCV infection have higher underlying mortality rates. The first of these, seroreversion, will cause the model to underestimate incidence if not taken into account. The second, differential mortality rates, will have the same effect. To take these issues into account, one should estimate survival functions for each of the birth cohorts that make up today's population, as well as for the subpopulation of people infected with HCV, which is not practical. There is evidence, for example, that injection drug users have higher mortality rates than their non-drug-using counterparts. In the model proposed for this project, background mortality is assumed to be the same for infected and noninfected people.

Unresolved Issues

Key unresolved issues include the following:

1. Using or not using a seroreversion rate. A 1% seroreversion rate per year may be too high. There was a 7% loss of antibodies after 25 years in a transfusion study.[1] Seroreversion may happen among nonviremic patients during the first 10 years after infection. If seroreversion does occur, then the prevalence in the population underestimates the proportion of the population ever infected.
2. Deciding on incidence trends.
3. Deciding on age-specific incidence estimates.

Natural History of HCV Infection

Revisiting the Natural History of HCV Infection

A decision tree can summarize the natural history of hepatitis C. However, an agreement needs to be reached regarding the parameters to use. A systematic review of natural history studies was conducted and published in 2001.[2] Risk of cirrhosis varied according to the type of recruitment (highest for blood transfusion and liver centers, lowest for blood donors and community studies). Overall, it was suggested that for persons who acquire HCV infection in young adulthood, less than 10% are estimated to develop cirrhosis within 20 years. While higher estimates have been used in the past in many published models, the lower estimates probably reflect reality better at a population level and should be preferred. In essence, the model is homogeneous and averages the influence of cofactors.

Uncertainties beyond 20 Years

While natural history is reasonably known for up to 20 years, we need assumptions to go beyond that point. The assumption made was linearity of progression. Linearity may be the safest assumption to date in the absence of specific data. That the disease could accelerate was hypothesized in the studies published by Poynard et al.[3] However, this interesting hypothesis was based on cross-sectional data, and there are no data to test it. Uncertainty about the long-term prognosis could be addressed using a number of approaches, including (1) population-based vital statistics data matched with incidence that we believed may have occurred in the past and (2) registry of infections based on notification of chronic cases matched with cancer registries.

The outcome of most discussions about the natural history of HCV infection is summarized later in "B. Natural History of HCV Infection, Including Morbidity and Mortality" (see p. 26).

Using DISMOD for Hepatitis C Global Burden of Disease

The DISMOD computer software was created because (1) variables are observed with different degrees of reliability (mortality > prevalence > incidence), (2) data come from different sources, and (3) other disease characteristics may be stable across populations and thus be useful for the estimation of missing parameters.

DISMOD can be used to compute incidence on the basis of prevalence, check internal consistency or estimates, or change age groups.

Limitations of DISMOD for HCV Infection

DISMOD works best for chronic diseases (e.g., asthma). It is less adapted for infectious disease such as hepatitis C because HCV infection does not produce disability in itself. It is the complication (i.e., cirrhosis) that does.

Using DISMOD for HCV Burden of Disease

We decided to use two computer software programs—DISMOD to obtain incidence and the "HCV Natural History Programme," a "homemade" MS-Access-based application—for the remainder of the modeling. The HCV natural history program includes a natural history model that is based on the parameters proposed by Dore et al[4] (up to the stage of cirrhosis) and the parameters proposed by Sagmeister et al[5] (after cirrhosis). These figures can be plugged into incidence estimates.

Results

Preliminary runs of the model suggest that 1% of cirrhosis prevalence in 2000 worldwide is caused by HCV infection. This is obviously a gross underestimation since the prevalence of HCV infection among patients with cirrhosis is much higher. We need to identify the cause of this discrepancy. Options include the following:

- Revise incidence trend scenarios. Because the incidence estimates were based on prevalence and because the incidence may have declined, thereby increasing the duration of infection, this trend scenario could have influenced the results and may explain the underestimation.
- Test the "acceleration" natural history scenario in the model.
- Calibrate the model on the basis of the fraction of chronic liver disease and hepatocellular carcinoma attributable to HCV infection in epidemiological studies.
- Introduce cofactors. However, there are few data to estimate the proportion of infected people in each cofactor category. A possibility would be to try a 100% cofactor-present case scenario as a starting point.

Models are more sophisticated in the postcirrhosis phase, but it is the pre-cirrhosis phase that is most important and that is subject to the highest source of uncertainty.

Natural History of Hepatitis C in Japan

The incidence of posttransfusion acute hepatitis C decreased in Japan in the early 1990s. However, the overall incidence of acute HCV infection has been stable, accounting for about 8% to 9% of acute hepatitis cases. Among patients dying from hepatitis C, 82% of deaths are caused by hepatocellular carcinoma. The average age of diagnosis for hepatocellular carcinoma is 62 years.[6] Persons transfused in their 20s do not develop hepatocellular carcinoma before the age of 60. Factors associated with the development of hepatocellular carcinoma include initial age (older or younger than 50 years on diagnosis), stage of fibrosis, inflammation activity, and interferon treatment. Gender is not associated with risk. Among Japanese patients with hepatocellular carcinoma associated with HCV infection, 80% have cirrhosis. The incidence of hepatocellular carcinoma from all causes increased from less than 10,000 in 1958 to more than 30,000 in 1994, with the highest increase of incidence among persons between 60 and 69 years of age. The Japanese data differ from the experience in the rest of the world.[1,7,8] This could suggest that ethnicity is a cofactor that explains the high rate of hepatocellular carcinoma among Japanese. However, there could be other factors of importance, including environmental ones.

DISCUSSIONS ON PARAMETRIC DECISIONS

A. Strategy to Estimate the Global Burden of Morbidity and Mortality Associated with HCV Infection

Two different issues need to be distinguished: the burden of disease in 2000 due to past HCV infection and the future burden of disease due to HCV infections contracted in 2000.

The Burden of Disease in 2000 Due to Past HCV Infections

The proposed approach includes the following:

1. Obtain the overall number of deaths from chronic liver disease and hepatocellular carcinoma in 2000 from the GBD.
2. Estimate the prevalence of HCV infection among chronic liver disease and hepatocellular carcinoma in 2000 by age, gender, and region.

3. Estimate the prevalence of HCV infection in 2000 by age, gender, and GBD region.
4. Estimate the fraction of chronic liver disease and hepatocellular carcinoma attributable to HCV infection on the basis of numbers 2 and 3 and on the basis of available attributable fraction studies.
5. Add to the mortality estimate a morbidity estimate based on the assumption that before dying, each patient has an average number of years alive with decompensated cirrhosis or hepatocellular carcinoma.*

Mortality and morbidity associated with acute hepatitis are considered negligible when compared to the burden associated with the chronic outcomes.

The Future Burden of Disease Due to HCV Infections in 2000

The proposed approach includes the following:

1. Estimate the prevalence of HCV infection in 2000 by age, gender, country, and GBD region.
2. Model the incidence of HCV infection in 2000 by age, gender, country, and GBD region on the basis of prevalence.†
3. Estimate the future morbidity and mortality associated with the natural history of HCV infections acquired in 2000.
4. Include prevalence, incidence, natural history parameters, and background mortality into a DISMOD model to ensure internal consistency and estimate future mortality and morbidity in DALYs due to HCV infections in 2000.

B. Natural History of HCV Infection, Including Morbidity and Mortality

All these parameters are derived by experts using established methods:

Proportion of Infected Persons Who Develop Acute Hepatitis with Jaundice‡

Estimate	25%[9,10,§]

Proportion of Infected Persons Who Develop Chronic Infection (RNA Positive)

Estimate	75%[11]
Uncertainty	50%-85%

This value tends to be lower among younger people and higher among older people.

Proportion of Chronically Infected Persons Who Develop Cirrhosis ~20 Years after Infection

Good evidence is available to document this parameter. A number of studies suggest that this parameter is age dependent:

For persons infected younger than age 40 years	
Estimate	5%[2]
For persons infected age 40 years or older	
Estimate	20%[12]

Proportion of Chronically Infected Persons Who Develop Cirrhosis ~40 Years after Infection

In contrast to the estimate for the two first decades, little evidence is currently available to document the natural history after the first two decades. Thus, this parameter is somewhat speculative. Expert consensus suggests that this parameter is age dependent:

For persons infected younger than age 40 years	
Estimate	20%
Uncertainty	10%-30%
For persons infected age 40 years or older	
Estimate	40%
Uncertainty	30%-50%

The effect of age at infection on the disease progression beyond 20 years is unknown. Assuming a linear inference to project the risk of progression to cirrhosis after 20 years implies that only age at infection matters. Under an alternative scenario, it is possible that the fibrosis progression in someone infected younger than age 40 years could accelerate as that person ages and reaches an age group for which progression to cirrhosis after 20 years of infection is higher.

* Use progression rates from transplantation lists to cross-check/validate progression rates from the natural history model.

† Incidence estimates are not needed to estimate the current burden due to past infections that will appear in the next World Health Report. However, incidence is needed for the Global Burden of Disease (GBD) 2000 study report that will come out in 2003 and for the estimation of the future burden due to current infections.

‡ Chronic and acute hepatitis C may need to be redefined. The traditional 6-month cutoff time may be outdated.

§ The death to case ratio is close to 0%.

Annual Rate of Hepatocellular Carcinoma among Patients with Cirrhosis

Estimate	1.6%[12-15]
Uncertainty	1.5%-2.5%

Japan and the Taiwan province of China fall outside this range with a rate of > 7%.

Annual Death Rate among Patients with Hepatocellular Carcinoma

A number of studies suggest that this parameter depends on access to treatment:

In industrialized countries	
Estimate	80%[16,17]
In developing countries	
Estimate	90%

The annual mortality rate of patients with HCV in Japan is significantly lower (~10%).[6,18-20]

Annual Rate of Decompensation among Patients with Cirrhosis

Estimate	4%[12,13]

Annual Death Rate among Patients with Decompensated Cirrhosis

A number of studies suggest that this parameter depends on access to treatment:

In industrialized countries	
Estimate	15%
In developing countries	
Estimate	30%

Factors that May Affect the Natural History of HCV Infection

Consistently normal ALT levels. Consistently normal alanine aminotransferase (ALT) levels are associated with slower fibrosis progression.

Steatohepatitis. Limited evidence suggests that steatohepatitis may affect fibrosis progression. Steatohepatitis, rather than obesity, seems to be the important cofactor. However, one intervention study from Brisbane, Australia, suggests that reducing weight reduces fibrosis progression.[21-24]

HIV coinfection. The influence of HIV infection depends on CD4 count. The relative risk for the development of cirrhosis among HIV and HCV coinfected patients is around two.[25,26]

HBV coinfection (HBsAg). Chronic HBV/HCV coinfection (HBsAg and anti-HCV positive) is uncommon globally, although it may be emerging in China. Coinfected patients have a higher risk of hepatocellular carcinoma than those who are only infected with one virus. However, it is unclear whether this high risk reflects a combined effect of the two viruses in the absence of interaction or some synergistic effect. The anti-HBc alone/anti-HCV serological profile is common. Some evidence suggests that the presence of anti-HBc alone might increase the risk of hepatocellular carcinoma among patients with chronic HCV infection.[27]

Alcohol intake. Intake of more than 50 g alcohol/day accelerates progression to cirrhosis with a relative risk of about three.[28,29]

Therapy. Globally, the proportion of viremic patients who undergo therapy is low, industrialized countries included. In Australia, for example, less than 10,000 people have been treated, while estimates suggest that there are 170,000 people infected. At the present time, effective treatment is not administered to all patients (e.g., in correctional facilities, developing countries). In addition, the proportion of viremic patients who will clear infection under treatment is variable, although improvements have been made for all genotypes, especially for genotypes 2 and 3. Sustained virological response is associated with improvement in necro-inflammatory lesions and fibrosis, but the effect on overall survival is still unclear. Thus, the impact of therapy is unlikely to affect the natural history of HCV infection at the population level at the present time. However, this analysis should be revised if improved treatment protocols become available and better therapy coverage is achieved.

Smoking. Preliminary evidence suggests that smoking may influence the development of hepatocellular carcinoma.

Factors that Probably Do Not Affect the Natural History of HCV Infection

Viral load. Evidence suggests that in general, viral load does not influence disease severity or progression.

Genotypes. Most studies suggest that in general, genotypes do not influence disease severity or progression.

C. Areas that Need Further Research

To better estimate the global burden associated with HCV infection, more research is needed in the following areas.

Estimates of HCV Prevalence

The quality and coverage of population-based estimates of HCV prevalence should be improved. The two critical elements for survey quality are (1) use of a representative sample and (2) use of accurate diagnostic tests. Because age-specific estimates of prevalence are important to estimate incidence trends and burden of disease, these surveys should attempt to estimate the prevalence of infection according to age. Stratification by gender should also be done.

Morbidity

Morbidity associated with chronic liver disease must be better characterized so that disability weights can be applied. This will allow a more precise estimation of DALYs. In that respect, the histological lesion of cirrhosis must be differentiated from (1) the disease that results from decompensated cirrhosis and (2) chronic hepatitis and/or chronic infection. The Australian system could be used as a basis for classifying health states of chronic hepatitis and its consequences (see Table I). In industrialized countries, knowledge of one's infection status is a major determinant of altered quality of life due to the uncertain progression of the disease and the increased anxiety caused by this uncertainty. Treatment may also need to be addressed. GBD needs a qualitative description of the range of potential symptoms, from severe to mild, that a patient may experience in one of the health states rather than a quantified estimate of disability. These figures will be useful to hepatitis B burden, too. Extrahepatic manifestations of HCV infection will not be addressed as they are uncommon (although the association between HCV infection and non-Hodgkin lymphoma needs confirmation by further studies to define the presence or absence of a causal relationship).

Natural History Parameters

Natural history parameters should be estimated using a systematic literature review and meta-analyses. In addition, research needs to better describe (1) the risk of fibrosis progression beyond 20 years, (2) the risk of fibrosis progression in developing countries, (3) spontaneous clearance of hepatitis C virus infection, and (4) the patients who do or do not progress to cirrhosis (e.g., normal aminotransferase levels, gender, ethnicity,* obesity, toxins, environmental factors).

Table I Health States Used for Hepatitis C Virus Infection by the National Centre in HIV Epidemiology and Clinical Research of Australia

Mild, chronic hepatitis, undiagnosed
Mild, chronic hepatitis, diagnosed
Moderate, chronic hepatitis, undiagnosed
Moderate, chronic hepatitis, diagnosed
Compensated cirrhosis, undiagnosed
Compensated cirrhosis, diagnosed
Liver failure
Hepatocellular carcinoma

HCV Infection among Injection Drug Users

The prevalence of HCV infection should also be estimated when estimating the size of the population of injection drug users and the prevalence of HIV infection among them.

CONCLUSIONS

The WHO needs burden of disease estimates to make policy decisions. A working group was created to address unmet needs and assist the WHO in estimating the global burden of disease associated with HCV infection. This meeting has addressed the strategy that will be used to estimate the global burden of morbidity and mortality associated with HCV infection and has tried to define the parameters that will be used for the natural history of HCV infection, including morbidity and mortality in the model. Areas for which more research is needed to improve modeling have also been defined.

The authors and the World Health Organization wish to thank the Viral Hepatitis Prevention Board (VHPB) and the Fondation Mérieux for assisting with the organization of the meeting and Mr. Socrates Litsios for editorial comments.

* In the United States, there is a difference between African Americans and Caucasians. However, there are no data regarding Africans living in Africa. Genotype could be a cofactor. There is no information regarding Australian Aborigines.

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Efficacy of early retreatment with interferon β for relapse in patients with genotype Ib chronic hepatitis C

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Abstract

Background: Interferon (IFN) retreatment for hepatitis C virus (HCV) relapsers has been effective under some conditions. We conducted a randomized, controlled trial of IFN β retreatment for HCV relapsers after IFN α. *Patients and methods:* We gave IFN β 6MIU therapy to 43 patients who had relapse of HCV after the 24 weeks IFN α monotherapy. The 43 patients were randomly assigned to two groups: Group A started retreatment within 4 weeks after relapse; and Group B started retreatment 24 weeks or more after relapse. *Results:* Nine patients showed sustained virological response (SR) to the retreatment. All of these patients were in a low viral load subgroup. The SR rate in Group A (8/22, 36%) was significantly higher than in Group B (1/21, 5%) ($P = 0.0128$). Among patients with lower viral load, the SR rate in Group A (8/10, 80%) was also significantly higher than in Group B (1/8, 13%) ($P = 0.0076$). *Conclusion:* The retreatment with IFN β is effective for patients with HCV low viral load, and the sooner after the relapse the retreatment is started, the better the clinical results will be.

Keywords: Interferon α; Interferon β; Retreatment; Chronic hepatitis C; Genotype 1b

1. Introduction

Chronic hepatitis due to persistent infection with the hepatitis C virus (HCV) often progresses to cirrhosis and hepatocellular carcinoma [1]. Interferon (IFN) represents an effective therapy for many patients with chronic hepatitis C [2,3]. A sustained virological response (SR) with IFN treatment depends on many factors, including viral genotype, viral load, presence of hepatic fibrosis, age, gender, and mutations in IFN susceptibility determinants in the nonstructural 5A (NS5A) region of the virus [4–7]. HCV genotype and viral load are particularly important factors in predicting treatment response [2,4,5,8].

Resistance of the HCV genotype 1b to treatment with IFN has been frequently reported in Japan [8–10]. Many patients infected with genotype 1b fail to eliminate HCV after treatment with IFN monotherapy. In addition, many patients eliminate HCV during the treatment but can not prevent later relapse. Alberti et al. reviewed several prospective studies [11]. Their report generally described patients other than genotype 1b (genotype 1b, 11%; other, 41%), significantly higher alanine aminotransferase (ALT) levels at time of retreatment, treatment with IFN for at least 12 months, and retreatment with IFN in patients who relapsed.

Recently, a combination of IFNα2b and ribavirin has been used for retreatment of patients who relapsed after initial treatment with IFN alone. This combination has been proven more effective than IFNα2b monotherapy [12]. However, this combination therapy is limited because ribavirin is contraindicated in many patients [13].

This study is suggesting an effective new retreatment regimen. The study evaluated differences in efficacy of reattempting therapies, one was starting immediately after the relapse and the other was starting after 24 weeks, in patients

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who relapsed after initial treatment. All patients were diagnosed as chronic hepatitis C with genotype 1b and were initially treated with natural IFNα. Patients with relapse were then randomly assigned to two groups. One group began retreatment with a 6 week course of natural IFNβ starting immediately after relapse. The other began retreatment with the same regimen starting 24 weeks after relapse. We now report on the significant differences in the treatment responses.

2. Patients and methods

2.1. Selection of patients

The patients involved in this study were treated at ShinKokura Hospital from January 1997 to December 1999. Each patient was positive for HCV-RNA based on reverse transcription nested polymerase chain reaction (RT-nested PCR) test [14] and diagnosed as chronic hepatitis C from findings on a liver biopsy performed within 3 months. Only adult patients with HCV genotype 1b were eligible for this study. Patients with cirrhosis, autoimmune hepatitis, alcoholic liver diseases, or hepatitis B surface antigen positives by an enzymelinked immunosorbent assay (Abbott Japan, Co. Ltd., Tokyo, Japan) were also excluded. Patients ranged in age from 20 to 69 years. The study design and IFN treatment were explained, and written informed consent was obtained from all of the patients prior to enrollment. All procedures in this study were conducted in accordance with the Helsinki Declaration of 1975 (1983 revision).

2.2. Study design and treatment regimens

Natural IFNα (Sumiferon, Sumitomo Pharmaceutical Industries Inc., Osaka, Japan) was used as the initial treatment. The dose was 6 million international units (MIU) by intramuscular injection, administered once daily for 2 weeks, followed by three times a week for 22 weeks (total dose: 480 MIU). Patients who were HCV negative at completion of the initial treatment but who later experienced relapse were randomized into one of two treatment groups by using an enveloped enrollment sheet method. In Group A, retreatment was initiated within 4 weeks after relapse. In Group B, retreatment was started 24 weeks or more after relapse. Twenty two of the 43 relapsed patients after initial treatment were assigned to Group A (low viral load: 10 patients) and the others were assigned to Group B (low viral load: 8 patients). Table 1 shows the baseline of clinical profiles of the patients. No statistically significant differences in any baseline profiles were observed between Groups A and B. Measurement of viral load prior to retreatment demonstrated low viral load in 18 of the 43 patients. The retreatment regimen was natural IFNβ (6 MIU per day) (Feron, Toray Industries Inc., Tokyo, Japan), administered once daily by intravenous injection for 6 weeks (total dose: 252 MIU).

Table 1
Clinical characteristics of patients receiving retreatment

	Group A ($n = 22$)	Group B ($n = 21$)	Total ($n = 43$)
Age (years)			
21–49	13	11	24
50–69	9	10	19
Gender			
Male	15	13	28
Female	7	8	15
Viral loads			
<100 (kcopies/ml)	10	8	18
≥100 (kcopies/ml)	12	13	25
Liver tissue			
Mild hepatitis	11	16	27
Severe hepatitis	11	5	16
Serum ALT value			
<2 × ULN	14	16	30
≥2 × ULN	8	5	13

This table shows the clinical characteristics of patients before retreatment with IFNβ. Patients were randomly assigned to Group A or Group B, and classified into subgroups based on liver histology: mild hepatitis (HAI score ≤ 10) and severe hepatitis (HAI score ≥ 11). ULN: the upper limit of the normal range (40 IU/l). HAI: histological activity index.

SR was defined as serum ALT levels below the upper limits of the normal level (ULN: 40 IU/L) and negative HCV-RNA at 24 weeks after retreatment. Any clinical findings other than SR were considered nonresponse (NR). The subsequent followup period was 1 year.

HCV viral load was measured just before the start of retreatment. Viral load was measured with Amplicor-HCV monitor assay (Roche Molecular Diagnostics, Tokyo, Japan) [15]. Low viral load was defined as <100 kcopies/ml, and high viral load as ≥100 kcopies/ml. Serum ALT levels, hemoglobin concentration, white blood cell count, and platelet count were measured at 4-week intervals from the start of treatment until 24 weeks after completion of retreatment. If serum ALT levels again increased to ≥2 × ULN after completion of treatment, HCV-RNA was assayed. Hepatic inflammation and fibrosis were assessed using the Knodell histological activity index (HAI). Patients were classified into two subgroups: mild hepatitis (HAI ≤ 10) and severe hepatitis (HAI ≥ 11) [16]. Treatment with IFN was discontinued if the hemoglobin concentration decreased below 9.0 g/dl, if the white blood cell count decreased below 1500 mm^{-3}, if the platelet count decreased below 50,000 mm^{-3}, or if symptoms such as severe malaise was observed.

2.3. Statistical analysis

Differences between the groups were analyzed with Fisher's exact test. In the determination of predictive factors for IFN retreatment efficacy, simple logistic regression analysis was performed. Logistic analysis was performed

for age (21–49 years versus 50–69 years), gender (male versus female), time of starting retreatment (Group A versus Group B), HCV-RNA level (<100 kcopies/ml versus ≥100 kcopies/ml), liver histology (HAI score 2–10 versus 11–22), and serum ALT value (< 2 × ULN versus ≥ 2 × ULN). Probability values of <0.05 stands for statistically significant.

3. Results

3.1. Relationship between predictive factors and efficacy of IFN retreatment

The results of univariate analysis for predictive factors associated with SR in the 43 retreated patients were: age (P = 0.2607), gender (P = 0.2185), time of starting retreatment (P = 0.0482), viral load (P = 0.0020), hepatic histology (P = 0.3910), and serum ALT level (P = 0.6043). Both "viral load" and "time of starting retreatment" were significant predictive factors (Table 2).

3.2. Results of IFN retreatment by viral loads

Table 3 shows the results of IFN retreatment by viral loads. SR was observed in nine retreated patients (21%), all of whom had low viral load prior to retreatment. The SR rate was significantly higher in Group A (8/22, 36%) than in Group B (1/21, 5%) (P = 0.0128). Among the patients with low viral load, SR was observed in 8 of 10 patients in Group A (80%) but only in 1 of 8 patients in Group B (13%, P = 0.0076). Serum ALT at 24 weeks after retreatment was below ULN in 10 patients in Group A (45%), but only in 3 patients in Group B (14%, p = 0.0279). In evaluation after retreatment (24 weeks after completion of retreatment), among the HCV-RNA positive patients, 4 of 5 with serum ALT below ULN eventually had a rise in serum ALT to above ULN the during followup for 1 year. However, no patients with SR had a relapse during 1 year of followup after retreatment.

No discontinuations or withdrawals occurred during the 6 weeks of retreatment with IFNβ.

Table 2
Results of univariate analysis for predict factor of retreatment

Factor	Chi-Square	P-value	Odd ratio	95% Confidence limits
Age	1.2648	0.2607	0.385	0.073–2.034
Gender	1.5039	0.2185	3.356	0.488–23.084
Time of starting retreatment	3.9016	0.0482	5.970	1.014–35.147
Virus loads	9.5104	0.0020	18.86	2.915–125.102
Histology	0.7358	0.3910	1.959	0.421–9.110
Serum ALT level	0.2686	0.6043	1.527	0.308–7.569

Cutoff values for liver histology were HAI score of 11 and viral load of 100 kcopies/ml. Patients were divided into Group A or Group B based on time of starting retreatment.

Table 3
Results of sustained virologic response rate for interferon retreatment by viral loads

	Group A (n = 22) SR/n (%)	Group B (n = 21) SR/n (%)	Total (n = 43) SR/n (%)
Viral loads			
<100 (kcopies/ml)	8/10 (80)**	1/8 (13)**	9/18 (50)
≥100 (kcopies/ml)	0/12 (0)	0/13 (0)	0/25 (0)
Total	8/22 (36)*	1/21 (5)*	9/43 (21)

This table summarized analysis of data from Fisher's exact test. SR: Sustained virologic response, (%):Sustained virologic response rate.
** P < 0.01 (Group A vs. Group B).
* P < 0.05 (Group A vs. Group B).

3.3. Safety

No clinically significant decreases in hemoglobin concentrations, white blood cell counts or platelet counts were observed during initial treatment and retreatment. No symptoms such as severe malaise or adverse reactions requiring discontinuation of IFN treatment were observed.

4. Discussion

Our study was characterized by [1] time of starting retreatment [2], change to a different types of IFN for retreatment [3], short duration of retreatment and small total dose (252 MIU), and [4] absence of any treatment discontinuations or withdrawals. Based on data from previous studies evaluating efficacy of retreatment [11–13,17], the present study targeted retreatment in HCV relapsers after IFN therapy.

Genotype 1b chronic hepatitis C is often resistant to IFN treatment. All patients in this study were initially treated with IFNα. Only the HCV relapsers were retreated with IFNβ. For patients with low viral load, the SR rate with retreatment early after relapse (Group A) was about 80%. Unfortunately, as in previous reports [18], the response rate was poor when retreatment was initiated after 24 weeks or more from the relapse. Our data supports that retreatment should be started after HCV recurrence as soon as possible for patients with low viral load. HCV load may rise from 4 to 8 weeks after completing treatment with IFN but then decrease [19]. Retreatment in Group A was probably started at a time of decreased HCV load, thus resulting in a high SR rate. In Group B, however, retreatment was started 24 weeks or more after HCV recurrence. This resulted in a low SR rate, like those reported with other retreatment regimens.

Not only IFNα, but IFNβ is also used for treatment of chronic hepatitis C in Japan. The IFNβ standard regimen is daily administration for 6–8 weeks. The IFNα regimen is a combination of daily administration followed by intermittent administration for a total of 24 weeks. SR rates for each

regimen are almost the same in chronic hepatitis C treatment [17]. Barbaro et al. compared IFNβ monotherapy to a combination of IFNα and ribavirin for retreatment of IFNα nonresponders, and found that the HCV negative rate was higher with IFNβ [21]. In another study, patients who did not convert to HCV-RNA negative during treatment with IFNα later did convert to HCV-RNA negative after treatment was switched to IFNβ [22]. Thus, a switch to a different type of IFN (e.g., IFNβ) can be effective in patients with no response to IFNα.

IFNβ demonstrates a potent antiviral effect against HCV. A short 6-week course of IFNβ shows an HCV-RNA negative turning ratio of about 90%, but the rate of recurrence is high [20]. Therefore, a longer course of therapy has been tried in genotype 1b patients resistant to IFN [23,24]. Watanabe et al. reported that IFNβ and IFNα sequential therapy has better results than IFNα monotherapy [25]. However, IFNβ costs more than IFNα in Japan, and longterm treatment can become a considerable financial burden on patients [24]. Our results show that higher efficacy can be achieved over a short period (6 weeks) and with a small total dose (252 MIU) for patients with low viral load if retreatment is started sooner after relapse. In addition, the shorter duration of therapy increases patient quality of life and helps to reduce the financial burden from the perspective of insurance coverage.

A combination of IFN and ribavirin has been used for retreatment of patients with genotype 1b HCV. However, the use of ribavirin in many patients is limited because of contraindications and adverse effects. In our study on IFNα and IFNβ, no clinically significant decreases in hemoglobin concentrations, white blood cell counts or platelet counts were observed, and no serious adverse reactions requiring discontinuation of treatment were noted.

In this randomized controlled study, combination use of two types of IFN provided effective treatment for patients with low viral load HCV genotype 1b, if we start sooner after the relapse of HCV. Retreatment in our study was relatively short term, using a small total dose, and was highly tolerable. This retreatment regimen shows promise for effective treatment and improving quality of life in patients with low viral load HCV genotype 1b.

5. Conclusion

In this study, we show that retreatment with IFN-β is effective in low viral load genotype 1b patients, if we start sooner after the relapse of HCV.

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