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Review

Epidemiology and Clinical Aspects on Hepatitis C

Makoto Higuchi, Eiji Tanaka and Kendo Kiyosawa*

Second Department of Internal Medicine, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto, Nagano 390-8621, Japan

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CONTENTS:

SUMMARY: Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide, and 2 million persons in Japan. HCV is a major cause of chronic liver diseases, especially hepatocarcinogenesis, and the number of patients with HCV-related hepatocellular carcinoma (HCC) is increasing worldwide as well as in Japan. Most patients with acute hepatitis C develop chronic hepatitis. Spontaneous disappearance of HCV in patients with type C chronic liver disease is uncommon, and it tends to progress to further advanced and more severe liver disease, ultimately to HCC over a period of 30 years in most cases. Chronic liver disease due to HCV infection is commonly associated with extrahepatic manifestation, for example cryoglobulinemia. Antiviral treatment for HCV infection with interferon alone during 24 weeks was associated with a low rate (less than 10%) of sustained virologic response (SVR), especially in patients infected with HCV genotype 1b and high HCV RNA concentration. However, combination therapy of interferon and ribavirin raises the SVR rate. More recently, pegylated interferon used for treatment of chronic hepatitis C resulted in a high SVR rate. These modalities of antiviral treatment will reduce HCC occurrence. So far, there is no HCV vaccine in spite of many efforts.

1. Introduction

Hepatitis C virus (HCV) was discovered as a new viral agent of non-A, non-B hepatitis virus in 1989 by researchers of Chiron Cooperation Group (1). They developed an anti-HCV antibody assay system for diagnosis of HCV infection (2). This finding introduced HCV as a major causative agent of parenteral non-A, non-B hepatitis. Considerable progress has been made regarding knowledge of hepatitis C in the past decade. Hepatitis C is a major health problem not only in Japan but also in the world. It is well known that hepatitis C develops to cirrhosis of the liver and hepatocellular carcinoma (HCC), which are uncontrollable and fatal diseases (3).

To date, many epidemiological observations of hepatitis C worldwide has been reported. Thus, numerous data have accumulated and it has become easy to discuss the global epidemiology of hepatitis C. In addition, numerous clinical aspects including the natural course and treatment of hepatitis C have been discussed in many papers. These make possible a review of the epidemiology and clinical aspects of hepatitis C.

*Corresponding author: Tel: +81-263-37-2632, Fax: +81-263-32-9412, E-mail: kkiyosa@hsp.me.shinshu-u.ac.jp

2. Serological and virologic tests for HCV infection

2-1. Serological tests

Cloning of the HCV genome and sequence analysis has led to the development of antigens and synthetic peptides that have been successfully used in immunoassays to detect antibodies to HCV. Though the sensitivity and specificity of the first generation assay (anti-C100-3) was not significantly high (2,4), they increased in the second and third generation enzyme immunoassays (5). Especially, the third generation assay which detects mixtures of antibodies directed to various HCV epitopes (core[C22-3], NS3[C299], and NS5) has a high sensitivity. The specificity of currently available enzyme immunoassays for anti-HCV is almost 100% (6).

2-2. Virologic tests

Sensitive tests for HCV RNA based on reverse transcriptase polymerase chain reaction (RT-PCR) or other nucleic acid amplification techniques can be used during the window period in acute HCV infection (7). Quantitative assays of HCV RNA can be performed by end-point dilutions of RT-PCR assays, competitive RT-PCR assays, or one of the commercial tests, such as the AMPLICOR Monitor (Roche Diagnostics, Branchburg, N.J., USA) or the QUANTIPLEX or branched DNA (bDNA) assay (Chiron Corporation, Emeryville, Calif.,

USA). These quantitative tests may have utility in determining indications of antiviral therapy and in monitoring viral load in patients undergoing antiviral therapy (6).

Immunoassay using monoclonal antibodies for the detection of the core antigen of HCV have been developed with the claim of sensitivities comparable to those of nucleic acid amplification systems (8,9).

HCV genotypes are distributed differently depending on geography and etiology. HCV genotype is not useful for the assessment of prognosis but is useful for therapeutic management, since it is one of the predictors of sustained response by interferon treatment. Most methods for HCV genotyping are based on the amplification of subgenomic viral fragment by PCR. HCV types can also be determined by serological methods, which are simpler to use but are slightly less sensitive and specific (10).

3. Epidemiology

3-1. Worldwide

3-1-1. HCV carriers and HCV infection

The global prevalence of HCV carriers is estimated to average 3%, ranging from 0.1 to 10% or more in different countries (11). In Europe, the overall prevalence is 1% with a north-south gradient, ranging from 0.5% in northern countries to 2% in Mediterranean countries. Recent studies have shown high prevalence in Eastern Europe, ranging from 0.7% to 5%. In Asia, Mongolia, Vietnam, Myanmar, and China show high prevalence. In Africa, high prevalence is seen in central region countries and Egypt (12). In North America, the prevalence is relatively low. In South America, high prevalence is seen in Brazil (13). The highest prevalence (10% or more) is seen in Mongolia, Egypt, Tanzania, Guinea, and Cameroon as shown in Fig. 1 (11,14). There are reasons for the high prevalence of HCV carriers in each of these regions. For example, in Egypt, the use of parenteral antischistosomal therapy is thought to have contributed to a prevalence of HCV spreading by 22% (12). There are 170 million chronic HCV carriers throughout the world, of whom an estimated 2 million are in Japan, 2.7 million in the United State (U.S.), 5 million in Western Europe.

Until relatively recently, blood transfusion posed a major risk of HCV infection in developed countries. The introduction in 1989 and 1992 of improved blood-screening tests by the detection of anti-HCV antibodies has dramatically decreased the risk of transfusion-associated HCV infection (15). The current risk of contracting the disease from blood in developed countries is very low, with the residual risk resulting from blood donations that occur in the interval between infection and the development of detectable antibodies (the so-called 'window period'). However, the nucleic acid amplification test (NAT) based on PCR assay has been introduced to screen HCV RNA, hepatitis B virus (HBV) DNA, and human immunodeficiency virus 1 (HIV-1) RNA, and has resulted in very rare infection. In the U.S., it has been reported that among voluntary blood donors, blood transfusion, intranasal cocaine use, intravenous drug use, and ear-piercing in men are risk factors for HCV infection (16).

3-1-2. Hepatocellular carcinoma (HCC)

An epidemiological survey conducted in 1985 revealed approximately 320,000 deaths due to HCC worldwide. This number is expected to have reached more than 400,000 at present, of which >80% are confined to Asia and Africa. According to the Gann Monographs on Cancer Research, No. 47, restricted to males, Hong Kong is at the top of the list with 29 deaths as a result of HCC per 100,000 population annually, followed by 24.5 in Singapore and 19 in Japan (17). Of the seven major industrialized nations, Japan stands out with 19 HCC/100,000 population annually, in comparison with 11 in Italy, 9 in France, 6 in nonwhite Americans (2 in white Americans), 4 in Germany, and 2.5 in Canada. HCC is frequently associated with chronic HCV and HBV infection, and both viruses are believed to be causative factors in a large percentage of cases. In geographic regions where HCV and HBV are endemic, such as in Africa, Asia, and Mediterranean regions, HCC is common. In geographic regions where HCV and HBV are not endemic, such as North America and North Europe, HCC is uncommon.

A high prevalence of anti-HCV has been observed in patients with HBsAg-negative HCC in Italy (70 to 79%), Spain (77%), and Japan (75 to 90%). A relatively high prevalence has been observed in France (57%), Florida, U.S. (48%), and a low prevalence in Germany (16%), India (9%),

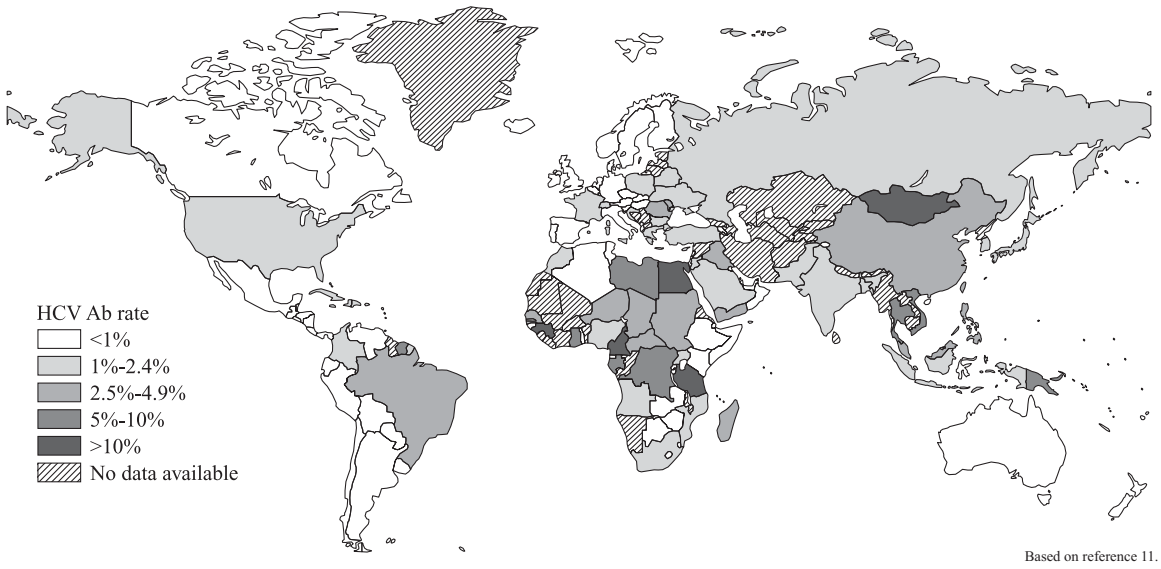

Fig. 1. Hepatitis C virus (HCV) prevalence in the world.

Bangladesh (8%), Taiwan (10 to 23%), Hong Kong (7%), and South Africa (16%) (18).

Recently, several reports have indicated an increase in the rate of HCC in developed countries. The changes in the number of patients with HCC per 100,000 population are 2.1 to 4.0 during a period of 11 years in Australia (19), 7.5 to 10.2 during 16 years in France (males) (20), 4.8 to 10.9 during 25 years in Italy (21), 1.9 to 7.6 during 21 years in Sweden (22), 1.4 to 2.4 during 15 years among the general population in the U.S. (23), and 2.3 to 7.0 during 3 years in veterans infected with HCV in the U.S. (24). Unfortunately, none of the reports regarding the U.S., Sweden, or France included virologic data which could have shed light on the possible roles of the hepatitis viruses in this rise in appearance of HCC incidence. However, a spread of HCV infection should be considered as the most important factor in increasing HCC rates in these countries as seen in Japan (25).

3-2. Japan

3-2-1. HCV infection in Japan

The average prevalence of HCV carriers in Japan is about 2%, with the number estimated at 2 million. According to the study of Yoshizawa (25), the age-specific prevalence of anti-HCV among blood donors are <0.5%, 0.5-1%, 1-2%, 2-3%, 3- 4%, and >4% in individuals <34 years, 35-44 years, 45-54 years, 55-59 years, 60-64 years, and >65 years, respectively. There is a clear increase with age in the prevalence of anti-HCV, reaching its highest rate in individuals >70 years at 7%. This indicates that HCV infection was relatively common in the generation over 45 years old and has seen a decrease in the recent decade. Fifty years ago in Japan there were several characteristic backgrounds regarding its social and medical conditions (25,26).

3-2-2. Increasing HCC in Japan

The recent increase in the incidence of HCC is ascribed to poor socioeconomic conditions intrinsic to Japan in the more distant past (25,26). Although it is unprecedented in other industrialized countries, a similar increase in HCC may well be expected where hepatitis virus infections prevail. A remarkable trend of HCC in Japan is its development preferentially in males in the most productive middle ages of their lives. Figure 2 shows annual deaths due to HCC in Japan stratified by distinct age groups. It has increased sharply since 1975 and continues to do so at present. In 1997, approximately 32,000 patients died due to HCC in Japan. Most of them (about 90%) were infected with HCV (25). For each and every year, the groups below 69 years of age account for the majority. Of the deaths due to malignancies in individuals in their 50s, HCC is the most prevalent cause after stomach cancer.

3-2-3. Reason for the increase of HCC in Japan

We can say that the increase of HCC in Japan depends on the spread of HCV infection. Therefore, we should refer to the way of HCV infection is spread in our country. The history of HCV infection in Japan can be traced back more than 100 years to the Edo era. HCV has spread explosively since the end of World War II, which can be submitted by evidence. Nomura et al. (27) compared incidence rates of HCC between the Japanese who emigrated to Hawaii in early 1900 and age-matched Japanese controls who had stayed in Japan.

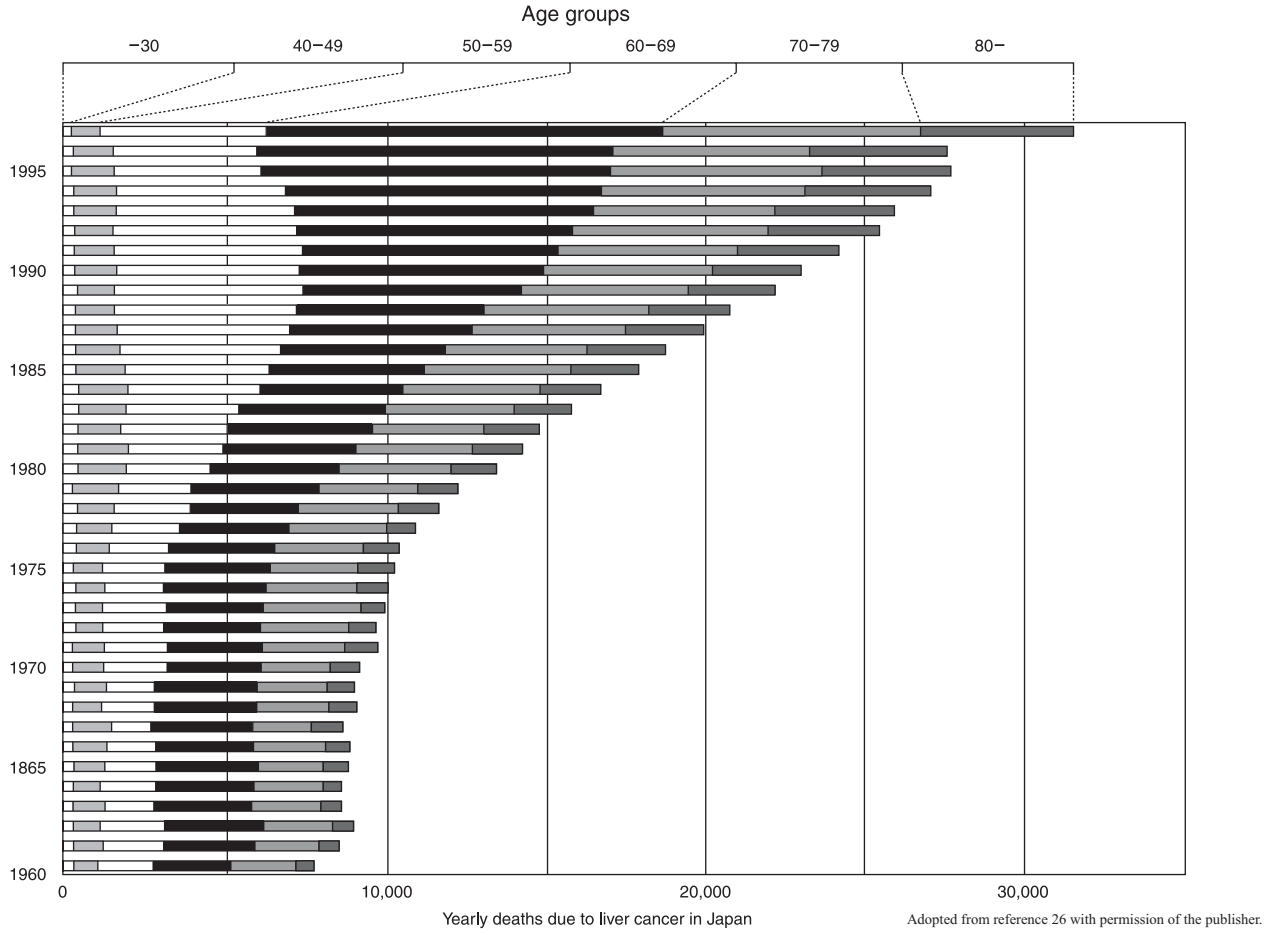

Fig. 2. Yearly death due to liver cancer between 1960 and 1997 in Japan.

Intriguingly enough, the incidence of HCC in Japanese immigrants in Hawaii remained unchanged, both for males and females, from 1960 through 1987. In contrast, the incidence of HCC increased sharply in control male and female Japanese who remained in the same districts from where the residents in Hawaii had emigrated. The etiology was different. HBV infection accounted for 62.5% of male HCC cases in the Hawaii immigrants, and so was much more frequent than for the 2.8% of the control Japanese who had remained in their motherland. As mentioned earlier, HCV is by far the most frequent cause of HCC in the Japanese residents who served as controls.

It is known that the birth date of patients with chronic hepatitis and those with liver cirrhosis in Japan peaks within the decade from 1920 to 1930 (26). The Japanese who were born during this decade reached adulthood some 20 years later in 1940-1950, when drastic changes in the society were occurring in Japan around the end of World War II, 1945, and the period of rapid reconstruction which followed. During this time, tuberculosis and peptic ulcer prevailed as a result of malnutrition, which had been treated surgically needing blood transfusion. As most donors at that time were paid professionals, the occurrence of posttransfusion hepatitis was observed in almost half of the recipients. The blood from the paid donors was called yellow blood, indicating that it was contaminated by hepatitis agents. In addition, because of the confused social background in those years, methamphetamine was habitually injected intravenously by certain subpopulations, who shared used syringes repeatedly (25).

Although the overall prevalence of HCV infection in the general population in Japan is relatively low (about 2%), HCV is highly endemic in some towns and villages (28). These restricted areas of high prevalence may be responsible for the spread of HCV infection. These outbreaks of hepatitis occurred mainly from 1955 to 1980. By far the most frequent cause of hepatitis in these endemics has been identified as HCV infection (29). Recently, 20-40 years since then, these areas emerged with the highest incidence of HCC, which is most likely ascribable to the HCV spread decades ago. The way in which HCV was transmitted widely, but nevertheless remained restricted to these areas, is a matter of conjecture. The overuse of intravenous injections of analgesics, antipyretics, and nutritive agents became a popular medical practice nationwide. It is not hard to conceive that disposable needles and syringes were used more than once in some instances and that the disinfection of medical equipment as not always satisfactory. They would have been efficient vehicles for the transmission of HCV. We cannot ignore the inappropriate medical practices of past decades.

These were recognized as the major routes for HCV transmission in Japan, which is now taking a heavy toll after 30 years or more.

4. Clinical characteristics

4-1. Natural course of hepatitis C

HCV infection is infrequently diagnosed during the acute phase of infection. Clinical manifestations can occur, usually within 4 to 8 weeks after exposure to HCV. However, most patients with acute hepatitis C show either no symptoms or only mild symptoms. Fulminant hepatitis is very rare in cases of hepatitis C. Jaundice, malaise, and nausea have been documented as symptoms of acute hepatitis in type A, B, and E, but not C. The infection becomes chronic in most cases, and chronic infection is typically characterized by a prolonged period in which there are no symptoms. Acute infection leads to chronic infection in the majority of patients (around 80%), and spontaneous resolution of chronic hepatitis C which has been established once is rare (30).

Regarding the natural course of HCV carriers, we published an article entitled "Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus" in 1990 (3). This is the first report which provided the natural history of HCV carriers and the pathogenesis of HCC. Thus, this article has been the second most highly referenced article in the area of hepatology since 1981 to 2000 as described by Di Bisceglie (31). We found that the mean interval between blood transfusion (the presumed source of HCV infection) and diagnosis of HCC was about 30 years, whereas those with cirrhosis but no HCC were on average only 21.2 years and those with chronic hepatitis only 10 years from transfusion. This observation has subsequently been confirmed by several investigators in Japan and other countries. One of them has been made in the U.S. Tong et al. (32) showed that the mean interval after blood transfusion for patients with chronic HCV infection to chronic hepatitis was 13.7 years, more severe chronic hepatitis 18.4 years, cirrhosis 20.6 years, and HCC 28.3 years. Surprisingly, our and Tong's results (3,32) are coincident as shown in Fig. 3. Presently, though these observations are retrospective analysis, it has been generally accepted that the interval between initial HCV infection and the development of cirrhosis and HCC are 20 years and 30 years, respectively.

The prevalence of the development to cirrhosis and HCC from the HCV carrier state remains controversial, because of the lack of long term prospective follow-up study. Seeff et al. (33) traced 568 patients who developed posttransfusion non-A, non-B hepatitis (presumed hepatitis C mostly) in the 1970s and found that their overall mortality after an average 18-year follow-up was 51%, not different from that in matched transfused patients who had not developed hepatitis. In further follow-up study at 25 years (34), they reported that the all-cause mortality approximately 25 years after acute hepatitis C is high but is no different between cases (67%) and controls (65%). When they followed 90 patients who developed hepatitis C, 34 patients (38%) revealed viremia with chronic hepatitis C, 35 patients (39%) with viremia without chronic hepatitis, and 15 patients (17%) with anti-HCV positive

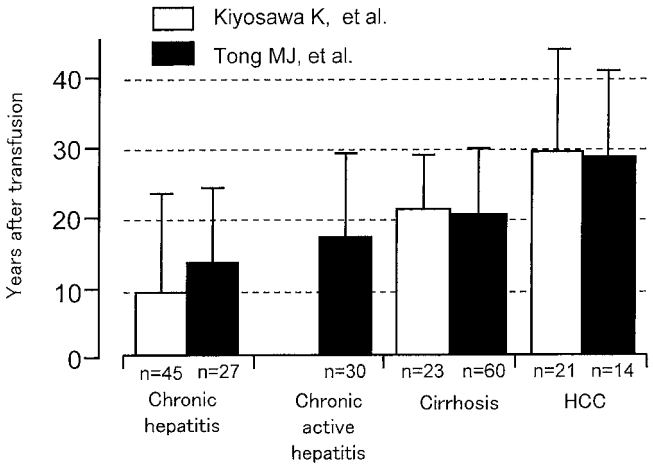

Fig. 3. Comparison of intervals from blood transfusion to diagnosis of type C chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) between United States (reference 31) and Japan (reference 3).

without viremia. Thirty-five percent of 20 posttransfusion hepatitis C patients biopsied for biochemically defined chronic hepatitis displayed cirrhosis, representing 17% of all those originally HCV-infected. Another retrospective prospective follow-up survey of women infected with HCV through contaminated lots of anti-D immune globulin used in Ireland in 1977 and 1978 was completed (35). Seventeen years later, only 2% of 376 women infected in this way had cirrhosis demonstrable on liver biopsy. This suggests that young and/or healthy women at the time infection rarely develop severe liver disease such as cirrhosis from chronic hepatitis C. These two groups' studies (33-35) showing a relatively benign outcome are in contrast with our (3) and Tong's (32) results showing progressive disease in spite of slow progression.

The frequency of HCC development among patients with chronic liver disease, particularly cirrhosis, was determined by many research groups. An incidence of HCC in patients with cirrhosis has been found to occur at a rate of 7%/year or 12.5%/3 years in Japan, and 3%/year in Italy. Ikeda et al. (36), Toranomon Hospital, in Tokyo followed 795 consecutive patients with cirrhosis for up to 17 years and analyzed the cumulative rate of HCC development. It was 19.4%, 44.3%, and 58.2% at the end of the fifth, tenth, and fifteenth years, respectively, in 349 patients with type C cirrhosis. In contrast, it was 14.2%, 27.2%, and 27.2% at the end of the fifth, tenth, and fifteenth years, respectively, in 190 patients with type B cirrhosis. According to Gentilini et al. (37) in Italy reported similar study. It was 4.6%, 24.0%, and 56.2% at the end of the fifth, tenth, and fifteenth years, respectively, in patients with type C cirrhosis. In type B cirrhosis, it was 6.5%, 23.4%, and 31.9% at the end of the fifth, tenth, and fifteenth years, respectively. In both Japan and Italy, the HCC occurrence rate increased steadily over time in patients with HCV-related cirrhosis, and the HCC occurrence rate of patients with HBV was noticeably lower than those of patients with HCV.

The clinical course of patients with type C and type B hepatitis, from initial infection of HCV and HBV to HCC, is compared and shown in Fig. 4. Most patients with HBV-related HCC acquired the HBV infection as newborn infants (mainly via vertical transmission from their HBV carrier mothers). In contrast, most patients with HCV-related HCC acquired type C acute hepatitis as adults through horizontal transmission of HCV. Although there have been reports of HBsAg-positive HCC in children, HBV-related cirrhosis usually develops in patients in their 40s and HCC in their 50s. The concentration of HBsAg and HBV-DNA decrease in serum as HCC progresses. Type C hepatitis typically becomes chronic following an acute episode experienced when patients are in their 30s, and progresses to cirrhosis when they are in their 50s (about 20 years from onset) and HCC 10 years later (about 30 years from onset). HCV-RNA concentration in serum persists at high level in these patients.

As synergistic factors in occurrence of HCV-related HCC, HBV co-infection (38), alcohol intake (39), and aflatoxin ingestion (40) should be considered. HIV-1 co-infection is also considered (41).

4-2. Extrahepatic manifestations

There are many important extrahepatic manifestations of HCV infection (42). Most of them are associated with autoimmune or lymphoproliferative states and may be related to the possibility that HCV is able to replicate in lymphoid cells (43). Cryoglobulins can be found in 50% or more of patients with hepatitis C. Cryoprecipitates usually contain large amounts of HCV antigens and antibodies. Only a small fraction of affected persons (less than 15%) have symptomatic disease. Vasculitis, arthralgia and purpura are included as symptoms. The most severe cases associated with membranoproliferative glomerulonephritis, as well as involvement of the nerves and brain. Presently, it is well known that HCV is the chief cause of essential mixed cryoglobulinemia. Other diseases, including lichen planus (44), Sjogren's syndrome (45), and porphyria cutanea tarda (46), have been linked to HCV infection. However, a definite pathophysiological role of HCV has been difficult to establish.

4-3. Antiviral treatment

In 1989, Davis et al. (47) and Di Bisceglie et al. (48)

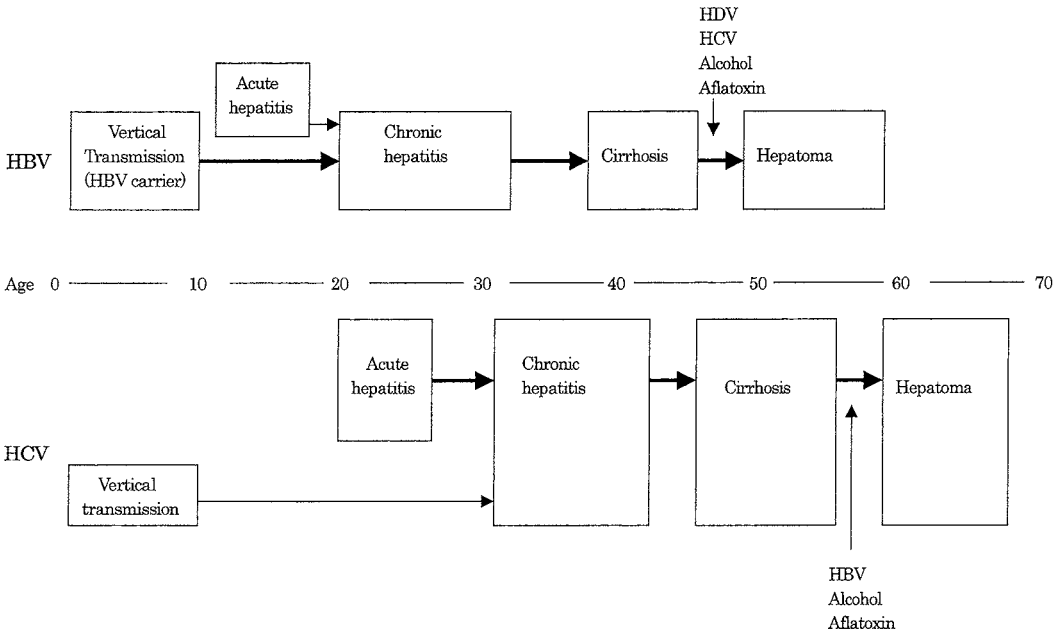

Fig. 4. Clinical course and evolution of disease after hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and synergic cofactors for progression.

reported the successful treatment of chronic hepatitis C with interferon alfa at same time but independently. However, the very high rates of relapse frequently necessitated retreatment. Several kinds of interferons are used, but all appear to have similar efficacy. Recently, combination therapy with interferon and ribavirin has markedly improved clinical outcomes, though less than half of those with HCV infection can be expected to have a favorable response to the agents that are currently available (49,50). More recently, attachment of polyethylene glycol to interferon (pegylated interferon, so-called peginterferon) has been used for treatment for chronic hepatitis C (51,52). Large clinical trials are under evaluation in the U. S. as well as in Japan.

4-3-1. Acute hepatitis C

As acute hepatitis C has a tendency to become chronic hepatitis, it should be considered to treat it with antiviral agents. Several preliminary results suggest that early treatment, even with interferon alone, has a high rate of efficacy (53,54). Jaeckel et al. (55) sought to determine whether treatment during the acute phase could prevent the development of chronic infection on 44 patients who had acute hepatitis C. At the end of both therapy and follow-up, 43 patients (98%) had undetectable levels of HCV RNA in serum and normal serum alanine aminotransferase levels. They concluded that early treatment with interferon alfa 2b alone (5 million U per day for the first 4 weeks, followed by a dose of 5 million U three times a week for another 20 weeks) prevents the development of chronic HCV infection in most patients. Thus, it is recommended that acute hepatitis C be treated with interferon at the early phase of this disease.

4-3-2. Chronic hepatitis C

As described above, since chronic hepatitis C and cirrhosis have a tendency to develop into HCC, the most important aim of antiviral therapy to chronic hepatitis C is to prevent the occurrence of HCC. Thus, all patients with chronic HCV infection are candidates for antiviral therapy. There are many reports that show significant reduction of the occurrence of HCC among patients who achieved complete response (virological and biochemical response) by interferon therapy. These reports came from mostly Japanese investigators (56-60). Though about 30% of patients treated with standard interferon therapy showed complete response, interferon monotherapy has limitations in a large segment of patients especially in cases with HCV genotype 1b, high HCV RNA titer, and severe fibrosis.

Two large, prospective trials from the U. S. (61) and Europe (62) demonstrated that the combination of interferon alfa and ribavirin significantly increases the percentage of previously untreated patients who have a sustained virologic response, from 16% to 40%. Both studies showed that in patients infected with HCV genotype 2 or 3 and in those with low viral loads before treatment, the response was maximal after 24 weeks of treatment, whereas patients infected with type 1 and those with a high viral load before treatment required a course of 48 weeks for an optimal outcome. These findings led to a recommendation that the duration of treatment should be based on the HCV genotype and the pretreatment viral load.

More recently, peginterferon has used in treatment of patients with chronic hepatitis C (51). Peginterferons are given only once a week, and the individual dose is calculated according to patient's weight. These introduce more sustained serum levels of interferon, and consistently induce a higher rate of response than conventional interferons. Presently, peginterferons are replacing the standard formulations (63-65).

It is expected that the rate of sustained complete remission (SCR) will be over 30% with these new modalities in patients with HCV type 1b and high concentration of HCV RNA in serum.

Changes in antiviral treatment for chronic hepatitis C and the estimated rate of sustained virologic response at 24 weeks after the discontinuation of antiviral treatment are summarized in Table 1.

There are many side effects of treatment with interferon and ribavirin as shown in Table 2. Among them, flu-like symptoms, headache, fatigue, fever, anorexia are temporary. Depression, suicide, and autoimmune phenomena such as thyroiditis, interstitial pneumonia are serious. Hemolytic anemia, with an expected hemoglobin decrease of 10 to 30 g/L, is a ubiquitous side effect of ribavirin that reverses with cessation of therapy. Dose adjustment of ribavirin may be necessary in patients with excessive decreases in hematocrit. We should pay more attention these side effects during antiviral treatment

5. Prospects for the future

Infection with HCV is now the most frequent cause of chronic hepatitis, cirrhosis, and HCC in Japan as well as

Table 1. Changes in antiviral treatment for chronic hepatitis C and estimated sustained virologic response (SVR) assessed at 24 weeks after treatment

Age and Antiviral treatment	HCV 1b and High HCV RNA	HCV non-1b and/or low HCV RNA
1990-1997		
IFN alone		
Standard (24 weeks)	<10%	50-60%
Long term (48 weeks)	50%	
1998-		
Combination of IFN & RIB		
Standard (24 weeks)	20%	70%
Long term (48 weeks)	30%	70%
2001-		
PEG-IFN alone		
Standard (48 weeks)	20%	
Combination of PEG-IFN & RIB	45%	

IFN: interferon, RIB: ribavirin, PEG-IFN: pegylated-interferon

Table 2. Adverse events of antiviral treatment

Frequency	Interferon	Ribavirin
Very Common	Flu-like symptoms	Hemolysis
	Headache	Nausea
	Fatigue	
	Fever	
	Thrombocytopenia	
Common	Anorexia	Anemia
	Insomnia	Leukocytopenia
	Alopecia	Nasal congestion
	Depression	Itching
	Irritability	
	Diarrhea	
	Leukocytopenia	
	Autoimmune phenomena	
	Thyroid abnormality	
	Exanthema	
	Interstitial pneumonia	
Rare	Diabetes mellitus	Gout
	Paranoia	
	Suicide	
	Polyneuropathy	
	Retinopathy	

worldwide. The estimated number of chronically infected HCV persons in the world is 170 million. These facts indicate that the prevention of HCV infection and the treatment of HCV carriers are very urgent problems. Despite recent progress, efforts to develop more effective therapies continue. As well, the establishment of an effective HCV vaccine in the near future is highly desirable.

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