hepatotrophic, but not directly cytopathic, and elicits slowly progressive liver injury that results in end-stage liver disease unless effectively eradicated (Liang et al., 2000). Internists and primary care physicians need to be made aware that HCV infection is closely associated with hepatocellular carcinoma (HCC) and death due to chronic liver disease.

The eradication of HCV by antiviral treatment that leads to a sustained virological response (SVR) results in improved liver histology and a higher survival rate (Marcellin et al., 1997; Niederau et al., 1998). Patients who achieved a sustained response have maintained it for 7 to 10 years in almost all cases, and HCV RNA levels are undetectable in the liver of such successful patients, suggesting that an SVR is tantamount to a cure (Lau et al., 1998). Therefore, the primary goal of antiviral treatment of patients with chronic HCV infection is an SVR, defined as undetectable serum HCV RNA by a sensitive molecular assay 24 weeks after the end of the treatment (Hagiwara et al., 1992). Interferon (IFN), the only antiviral agent capable of eradicating HCV, has been widely used for the treatment of patients with chronic HCV infection. A treatment regimen currently in wide use combines IFN with ribavirin and has dramatically improved treatment outcomes.

This review focuses on historical and recent developments in the field and on the use of antiviral drugs in the treatment of patients with HCV infection.

Indications for IFN Treatment

Chronic HCV infection causes mild chronic inflammation of the liver. Ongoing cycles of inflammation, necrosis, and apoptosis eventually lead to fibrosis and, ultimately, cirrhosis, a severe bridging fibrosis with nodular regression (Yano et al., 1996; Poynard et al., 1997; Hayashi et al., 1997a, 2000; Ghany et al., 2003). Although the progression of liver fibrosis may not be linear and the determinants of the progression rate are not known definitively, treatment indications can be based on histological assessment of hepatic lesions. Potential contributing factors to progressive fibrosis include excessive alcohol intake, concomitant diseases associated with liver injury, for example, hepatitis B, steatohepatitis, hemochromatosis, co-infection with HIV, male gender, older age, obesity, immunosuppression, and certain major histocompatibility complex haplotypes (Hayashi et al., 1994a, 1998a; Yano et al., 1996; Furusyo et al., 1997, 2005; Poynard et al., 1997; Alric et al., 1997; Hourigan et al., 1999; Thomas et al., 2000; Monga et al., 2001; Ghany et al., 2003; Crosse et al., 2004; Kubo et al., 2005).

Table 1 shows the clinical features of candidates for successful IFN treatment. Patients who experience a biochemical and virological response to antiviral treatment have considerable improvement in the necroinflammatory components of their liver histopathology, which leads to a decrease in HCC incidence (Nishiguchi et al., 1995; Kasahara et al., 1998; Yoshida et al., 1999; Okanoue et al., 1999; Kashiwagi et al., 2003; Murata et al., 2006). The Consensus Panel of the National Institutes of Health (NIH) in the United States recommended that all patients with chronic HCV infection be considered as potential candidates for antiviral treatment (Sheeff

Table 3 Predictors of successful response to IFN treatment for patients with chronic HCV infection

Non-genotype 1
Low HCV RNA level
Absence of severe fiblosis and cirrhosis
Age 40 years or younger
Male
Lighter body weight
Non-black ethnocity
Absence of liver steatosis
Good adherence
Avoiding of discontined treatment

IFN Monotherapy

IFNs are multifunctional immunomodulatory cytokines whose effects include antiviral activity, inhibition of angiogenesis, regulation of cell differentiation, growth regulatory properties, and enhancement of major histocompatibility complex antigen expression. They have an anti-inflammatory through what has come to be called a cytokine cascade (Kirchner, 1984; Tilg, 1997; Kawakami et al., 2000; Murata et al., 2002; Furusyo et al., 2005). Several types of IFN, recombinant IFN-alpha-2a, recombinant IFN-alpha-2b, natural IFN-alpha, natural IFN-beta, recombinant IFN-beta, and consensus IFN (IFN-alfacon-1), are available for the treatment for patients with HCV infection. Consensus IFN was designed by selecting the most frequently occurring amino acid at each site of the amino acid sequences of 13 known IFN-alpha subtypes. Broadly speaking, IFN-alpha and IFN-beta have been the most widely used IFNs for the treatment of HCV infection. Like IFN-alpha and IFN-beta, IFN-gamma is classified as a type 1 IFN and has shown activity against HCV in cell culture systems (Frese et al., 2002) but does not effectively reduce the HCV RNA level in humans (Soza et al., 2005).

There are differences in the specific activities and potencies of IFNs. The dosage and duration of IFN treatment may vary, but only a few of the IFNs and their approved regimens have been compared head to head. However, monotherapy outcomes, in terms of response rates, generally appear to be similar for the different regimens commonly used to treat patients. An SVR occurs in about 15% to 20% of patients treated with IFN monotherapy for 6 months (about 5% for genotype 1 patients and about 50% for non-genotype 1 patients) (Marcellin et al., 1994; Poynard et al., 1996; Hayashi et al., 1994a, 1998a; Furusyo et al., 1997). Several analyses have found that prolonged courses of IFN, 12 to 18 months, appear to be needed to maximize the chances of having an SVR to treatment, with 25% to 30% of patients responding to prolonged treatment (Poynard et al., 1995), but higher dosages of IFN, greater than 3 million units three times per week, do not seem to substantially improve the rates of sustained response, and a higher dosage has been associated with increased adverse effects (Bennett et al., 1997). IFN monotherapy, especially for patients infected with HCV genotype 1, has had limited success.

Combined Treatment with IFN and Ribavirin

Treatment regimens using a combination of an IFN and ribavirin have significantly improved the treatment outcome (Figure 1) (Lindsay et al., 2001; Luxon et al., 2002; Scott & Perry, 2002; Hugle & Cerny, 2003; Sanchez-Tapias et al., 2006). Combining weekly subcutaneous peg-IFN-alpha treatment with daily oral ribavirin is more effective than monotherapy with standard IFN or peg-IFN-alpha or a combination treatment with a standard IFN and ribavirin (Poynard et al., 1998; McHutchison et al., 1998; Heathcote et al., 2000; Manns et al., 2001; Reddy et al., 2001; Fried et al., 2002; Hadziyannis et al., 2004; Mangia et al., 2005; Furusyo et al., 2006). Pegylation is defined as modification of a drug by the addition of an artificial polymer, polyethylene glycol, for the purposes of delaying drug elimination, lowering its antigenicity, and modifying the drug's effect. Although a standard IFN requires a dosing interval of 1 or 2 days to maintain an effective blood concentration because of its approximately 8-hour elimination half-life, peg-IFN has the great advantage of making it possible to maintain a stable blood concentration with a single weekly administration. At present, two peg-IFNs are available: a weight-based, 1.5-mcg/kg dose of peg-IFN-alpha-2b, and a fixed, 180-mcg dose of peg-IFN-alpha-2a.

Ribavirin, initially synthesized in 1970, is an orally administered nucleoside analogue (a guanosine analogue) with a broad spectrum of antiviral properties that possess activity against several RNA and DNA viruses. When monotherapy with ribavirin is used for chronic HCV infection, the serum ALT level of most patients declines without any significant change in the serum HCV RNA level, even with prolonged treatment (Di Bisceglie et al., 1995; Hoofnagle et al., 1996; Furusyo et al., 2006), suggesting that the biologically beneficial effect is not associated with antiviral activity (Furusyo et al., 2005). The probable beneficial roles of ribavirin in the treatment of chronic HCV infection are an immunologic modulation (a shift from a Th2 to a Th1 response and suppression of interleukin-10 synthesis),

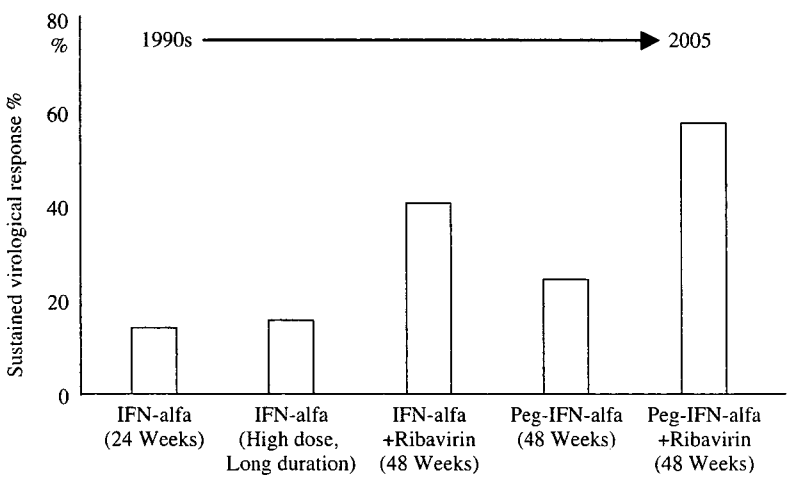

Fig. 1 Improvement of interferon treatment outcome for patients with chronic HCV infection

Table 1 Candidates for antiviral treatment of chronic HCV infection

Widely accepted candidates

1. 18 or more years of age
2. Elevated aminotransferase activity (abnormal ALT level)
3. Presence of moderate to severe fibrosis by biopsy (METAVIR stage 2 or more; Ishak satge 3 or more)
4. Absence of jaundice, acites, encephalopathy
5. Absence of uncontrolled seizure or psychiatric disorder
6. Good compliance and willingness to be treated
7. Infection with genotype 2 or 3 regardless of ALT abonormality

Individually considered candidates

1. Infection with genotype 1 and persistently normal ALT level
2. Presence of no or mild fibrosis by biopsy (METAVIR stage less than 2; Ishak stage less than 3)
3. Recent record of alcohol abuse (Abstinence will be necessary)
4. Injection drug user (Goodl compliance and a substance abuse program will be necessary)
5. Acute hepatitis C (Observation after 2 to 4 months of the onset for waiting the spontaneous clearance)
6. Less than 18 years of age
7. Coinfection with HIV
8. Chronic renal disease
9. Liver transplantation recipient

and Hoofnagle 2002). Treatment should be recommended especially for patients who are at risk of progression to cirrhosis, such as those who are characterized by the presence of HCV viremia, generally persistent elevation of the serum alanine aminotransferase (ALT) level, portal or bridging fibrosis, and moderate inflammation and necrosis of the liver. The following particular patients should be taken into account for antiviral treatment: those having mild liver disease, those with recurrence after transplantation, those who received a liver transplant, those with acute HCV infection, and those with co-infection with HIV. These recommendations are consistent with guidelines set by the American Association for the Study of the Liver, Strader et al. (2004), and the European Association for the Study of the Liver (Alberti & Benvegnu, 2003).

Appropriate Evaluations Before IFN Treatment

In addition to standard tests, special attention should be paid to extrahepatic manifestations, psychiatric disorders, HIV co-infection, excessive alcohol consumption, and excess body weight. As recommended previously (Sheeff and Hoofnagle 2002; Strader et al., 2004; Alberti & Benvegnu, 2003), HCV genotypes and serum HCV RNA levels must be determined before treatment (Table 2). The HCV genotype influences both the treatment indications and the therapeutic strategy, because treatment is more effective and shorter in patients infected with HCV genotypes 2 and 3, for which the efficacy was approximately 80% in clinical trials (Hayashi et al., 1994a, 1998a; Furusyo et al., 2002, 2006). Although the measurement of the HCV RNA level by a qualitative polymerase reaction (PCR) test at baseline is not

Table 2 Appropriate testing before IFN treatment

1.	HCV genotyping
2.	Serum HCV RNA level
3.	Hepatic histology by biopsy (not mandatory)
4.	Testing for HIV infection

commonly done to determine the length of treatment, it may be useful, at least for patients infected with HCV genotype 1 for whom a low HCV RNA level can provide the expectation of an early response, which is a good indicator of the probability of an SVR (Hayashi et al., 1998b; Yamaji et al., 1998; Furusyo et al., 2002).

Liver biopsy, despite the possibility of sampling error, remains the gold standard for evaluating fibrosis and hepatitis activity (Dienstag, 2002). For patients infected with genotypes 2 and 3 who have the probability of a favorable IFN treatment, response is extremely high, and IFN treatment may outweigh considerations of disease severity and the potential for progression in the future. Therefore, some authorities have suggested that it is not necessary to obtain a liver biopsy before treating patients with genotypes 2 and 3. Although a liver biopsy is not absolutely necessary in all cases, it is a useful tool because it is a key parameter for assessing the current status of the liver and because it provides prognostic information concerning disease progression (Dienstag, 2002; National Institutes of Health Consensus Development Conference statement, 2002).

The Background of IFN Treatment

In 1986, before the discovery of HCV, IFN was reported to have a biochemical response as an inflammatory agent in non-A, non-B hepatitis. Hoofnagle et al. reported the normalization of ALT following the administration of IFN-alpha for patients with non-A, non-B hepatitis (Hoofnagle et al., 1986). In the 1990s, IFN-alpha became the most widely accepted form of treatment for chronic HCV infection. The use of IFN was shown to result in a decrease in the serum ALT level and to cause HCV RNA to decline to the undetectable level (Shindo et al., 1991; Hayashi et al., 1994a). However, in many cases the ALT and HCV RNA levels promptly returned to pretreatment levels after cessation of IFN treatment (Hayashi et al., 1994a). An optimal response, an SVR, can be defined as a persistently normal serum ALT level and the absence of HCV RNA from the serum at the end of treatment and for at least 6 months thereafter. Since the first observations of these IFN-produced biochemical and virological effects, studies have reported several host and viral characteristics associated with an SVR (Brouwer et al., 1998; Castro et al., 2002; Berg et al., 2003). The most important predictors of an SVR following IFN treatment are hepatic fibrosis, the HCV genotype, and the pretreatment serum HCV RNA level (Hayashi et al., 1994a, 1998a; Furusyo et al., 2002, 2006). Table 3 shows factors correlated with an SVR to a combination treatment of pegylated IFN (peg-IFN) and ribavirin for chronic hepatitis C. Most of the patients with a good response had only a mild or moderate degree of fibrosis on liver biopsy, had HCV genotype 2 or 3, and had a low baseline HCV RNA level.

inhibition of host inosine monophosphate dehydrogenase activity, depletion of intracellular guanosine triphosphate pools, induction of mutational catastrophe, and a moderate, transient, early direct antiviral effect (Crotty et al., 2000; Cramp et al., 2000; Lau et al., 2002; Dixit et al., 2004). Surprisingly, the addition of ribavirin to IFN treatment leads to a marked improvement in the rate of sustained response (McHutchison et al., 1998; Lau et al., 2002). Patients treated with peg-IFN plus a ribavirin dose of 10.6 mg/kg/day or more had a greater chance of developing an SVR than those treated with peg-IFN plus a lower daily dose of ribavirin (Manns et al., 2001).

According to the most recent large clinical trials, a uniform 48 weeks of a combination treatment with peg-IFN and ribavirin yields the highest rate of sustained response (Strader et al., 2004; Dienstag & McHutchison, 2006). The response to a 48-week peg-IFN plus ribavirin treatment can be divided into three general patterns: a sustained virological response (SVR), relapse, and non-response (Figure 2). The overall sustained response rates were 54–56%. The response rate for genotype 1 patients exceeded 40% for the first time, and some rates were recorded as high as 42–46%. The rates of 76–82% for genotypes 2 and 3 are also impressive. Patients with genotypes 2 and 3 can be treated with a shorter duration (24 weeks) of treatment and with a lower dose of ribavirin with no sacrifice to the response rate (Hadziyannis et al., 2004).

Serum HCV RNA level at baseline is another determinant of the antiviral treatment outcome of patients infected with genotype 1 but is not useful for the other genotypes (Furusyo et al., 2006). A sustained response is consistently higher in patients with a low HCV RNA level, usually defined as 800,000 or fewer IU/ml (Manns et al., 2001; Fried et al., 2002).

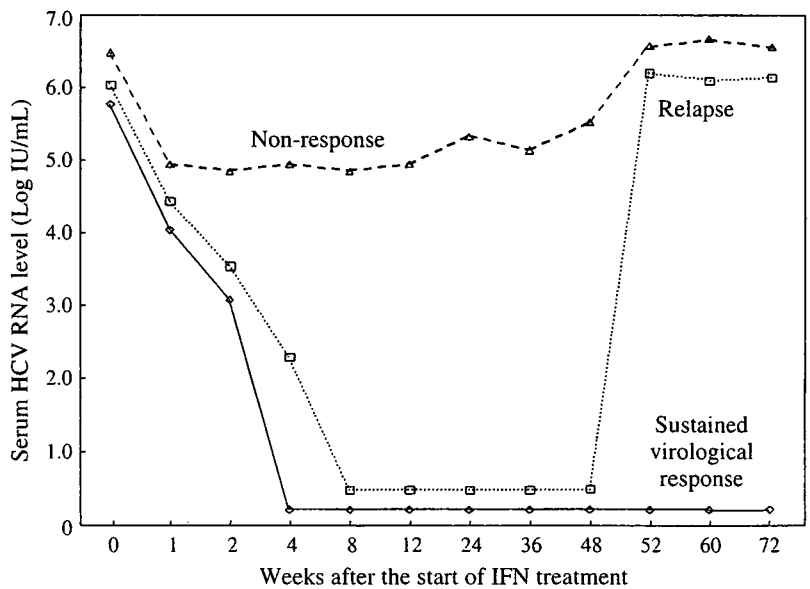

Fig. 2 Three general patterns of the response to a 48-week peg-IFN plus ribavirin treatment

Host factors affect the chance of a sustained response, albeit less so than the genotype. These factors include age, race, gender, obesity, and the degree of hepatic fibrosis and steatosis. African Americans have been shown to have responses rates only one-half to one-third those of Caucasians (Muir et al., 2004). The reasons for the racial differences in response rates to peg-IFN plus ribavirin treatment are not well known.

The sustained response rates for genotypes 2 and 3 are not significantly higher than those achieved for these favorable genotypes with non-peg-IFN combined with ribavirin. However, the combination of peg-IFN and ribavirin is currently considered to be the standard of care for the treatment of previously untreated patients with chronic HCV infection, even for those with genotypes 2 and 3, because the reduction of the injection frequency favors this combination treatment.

Monitoring Serum HCV RNA Level During IFN Treatment

Response to the IFN treatment regimens, including IFN monotherapy, peg-IFN monotherapy, and the combined treatments with ribavirin, is characterized by a two-phase pattern of decreases in the serum HCV RNA level, with an initial rapid decline seen from 24–72 hours after the start of treatment, followed by a gradual decline for several weeks (Neumann et al., 1998). This pattern is believed to reflect an initial inhibition of HCV replication and/or release followed by a different antiviral mechanism (i.e., the loss of infected hepatocytes) (Zeuzem et al., 1998; Buti et al., 2002; Layden-Almer et al., 2003).

In the early 1990s, comparison of assays was problematic because they did not use the same units to represent the amount of HCV RNA (Hayashi et al., 1998b; Furusyo et al., 2002). Recently, this problem has been overcome by the World Health Organization's establishment of an international standard unit for the universal standardization of HCV RNA quantification units (Neumann et al., 1998). Several assays for the quantification of HCV RNA, both PCR and branched DNA techniques, have been developed and have become available for clinical use, especially for the monitoring of the antiviral response to antiviral treatment. These assays are especially useful because the early monitoring of favorable viral kinetics has a direct bearing on the possibility of a sustained response by IFN treatment (Yamaji et al., 1998; Davis, 2002). The monitoring of the serum HCV RNA levels at baseline and at 12 weeks after the start of treatment is most effective when the same quantitative assays are used for both tests. A sustained response can be confirmed by a 2 or more $\log_{10}$ reduction in the HCV RNA level during the first 12 weeks of treatment, which is called an "early virological response" (EVR). The probability of an ultimate sustained response is approximately 70% for patients with an EVR, while the probability is less than 3% for those without an EVR (Davis et al., 2002, 2003). Moreover, even in these reports of patients with a 2 or more $\log_{10}$ reduction of the HCV RNA level at 12 weeks after the start of treatment, 84% of those with undetectable HCV RNA by PCR achieved a sustained response, but a sustained response was achieved by only 21% of those with detectable HCV RNA. These

findings suggest that an SVR is more likely after a rapid and profound reduction of the serum HCV RNA level by IFN treatment.

Management of Side Effects and Educational Guidance

To protect against and control side effects, it is important to carefully monitor the clinical course and laboratory findings during IFN plus ribavirin treatment (Table 4). Flu-like symptoms are often found during treatment but are usually not severe and can be managed with analgesics such as acetaminophen or non-steroidal anti-inflammatory drugs. Marrow suppression, especially leukopenia and thrombocytopenia, which can be induced by IFN, is very important for judging whether or not to continue treatment. Ribavirin contributes additional side effects, the most important of which is hemolytic anemia. When leukopenia, thrombocytopenia, or anemia is found, dosage adjustments may be required to avoid having to discontinue treatment (Nomura et al., 2004a).

Alcohol intake in HCV-infected patients appears to increase the higher fibrosis progression rate (Kubo et al., 2005). Avoiding alcohol during IFN treatment is essential, because alcohol affects the treatment response (National Institutes of Health Consensus Development Conference statement, 2002; Corrao & Arico, 1998). Patients should limit their alcohol intake to fewer than four drinks per week.

IFN has been shown to have an abortifacient effect in animal studies and thus should not be used during pregnancy. Ribavirin is embrytoxic and teratogenic. Strict birth control is necessary by both men and women during treatment and for more than 6 months after treatment.

Table 4 Side effects of antiviral treatment

Interferon-induced

1. Marrow suppression (leukopenia, thrombocytopenia, anemia)
2. Flu-like symptoms (fever, myalgia, headache)
3. General fatigue and irritability
4. Depression and insomnia
5. Weight loss and anorexia
6. Autoimmone diseases (Hypothyroidism and hyperthyroidism, Diabetes mellitus)
7. Rash and pruritis
8. Retinopathy (especially in daibetes patients and hypertention patients)
9. Nausea, vomiting, and diarrhea
10. Hair loss
11. Cough and Plumonary interstitial fibrosis

Ribavirin-induced

1. Marrow suppression (anemia, leukopenia, thrombocytopenia)
2. General fatigue and irritability
3. Weight loss and anorexia
4. Rash and pruritis
5. Nausea, vomiting, and diarrhea
6. Cough

Approach to Other Patient Populations

Acute Hepatitis C

Acute infection with HCV is marked by a high rate of viral persistence, with chronic infection seen in 50–80% of these patients. An important clinical observation about IFN treatment, without ribavirin, of HCV infection is the very high rate of response of patients with acute hepatitis C (Jaeckel et al., 2001). IFN treatment for acute infection with HCV reduces the chronicity rate to 10% or lower (Nomura,et al., 2004b). Strikingly, almost all patients with acute hepatitis C, regardless of genotype or initial viral level, rapidly become serum HCV RNA negative on treatment. A recent study of antiviral treatment of patients with acute hepatitis C reported that a high-dose, short-term treatment was effective (Nomura et al., 2004b). The results of a randomized control study of high-dose, short-term, early treatment (beginning 8 weeks after the onset of acute hepatitis) versus late treatment (beginning after 1 year of observation) showed that 87% of the patients with early intervention achieved a sustained response by the intramuscular, daily administration of 6 million units (MU) of IFN-alpha for four weeks, but only 40% of patients with late intervention had a sustained response (Nomura et al., 2004b). Moreover, all of the patients who experienced a relapse after the initial 4 weeks of treatment received an additional 20 weeks of treatment (6 MU, 3 times weekly) and became SVR, meaning that the early intervention resulted in total 100% SVR, while total 53% of patients achieved SVR after the additional 20 weeks of treatment (Nomura et al., 2004b). Similar outcomes were found for patients on maintained hemodialysis being treated with IFN monotherapy for acute hepatitis C (Furusyo et al., 2004). These findings suggest that nonresponse to IFN treatment might be acquired during the establishment of chronic infection.

Liver Transplantation

Although HCV-related end-stage liver disease represents the most frequent indication for liver transplantation, transplantation is not a clinical cure for hepatitis C. Viral recurrence, as documented by detectable viremia, is universal, and damage to the new liver occurs routinely. Recurrent HCV remains a persistent problem and a leading cause of graft loss. Attempts to prevent reinfection with immune globulin or other agents have not been successful (Charlton, 2003). Histological recurrence with allograft hepatitis owing to HCV occurs in up to 90% of patients by the fifth year after transplantation (Berenguer, 2003). Moreover, up to 42% of patients with HCV-reinfected cirrhosis after transplantation develop decompensation, manifested as ascites, encephalopathy, or hepatic hydrothorax, and less than 50% of these patients survive for one year after they develop decompensation (Berenguer et al., 2000). Clearly, the progression of hepatitis C is accelerated after transplantation as compared with non-transplantation patients. Thus, finding a way to use liver transplantation as a treatment for hepatitis C will be difficult, but if such a treatment is found, it will be clinically important.

Treating patients waiting for transplant when they are on the waiting list and pre-transplant viral eradication represent the ideal. Unfortunately, the results of a peg-IFN plus ribavirin treatment in an NIH trial showed that patients with compensated cirrhosis had a sustained response rate of only 11% (Shiffman et al., 2004). However, the trial results also showed that an initial treatment of low-dose IFN, including peg-IFN plus ribavirin treatment, followed by a slow escalation in dose may be associated with improved tolerability and efficacy in patients with compensated cirrhosis (Shiffman et al., 2004). Additionally, such cirrhosis patients who achieved a sustained response before transplantation or who are transplanted while on treatment but who are undetectable for HCV RNA have good outcomes, with a less than 10% probability of HCV recurrence (Everson, 2005). Thus, IFN treatment could potentially cure some of these patients, but the high discontinuation rate, 27%, should be taken into account when treating patients on a waiting list. After liver transplantation, the tolerability of IFN plus ribavirin treatment is suboptimal, with very high discontinuation of treatment, 37%, because of severe leukopenia and anemia arising from drug-induced bone marrow suppression and renal insufficiency (Gane, 2002; Rodriguez-Luna et al., 2004). A sustained response is achieved by less than 30% of patients after liver transplantation (Rodriguez-Luna et al., 2004). For patients undergoing liver transplantation for chronic HCV infection, the development of new classes of potent, well-tolerated antiviral agents merits a high priority.

Co-infection with HCV and HIV

Because both HCV and HIV are blood-borne viruses and share routes of transmission, HCV and HIV co-infection is particularly common in injection drug users. HIV infection has a detrimental effect on the natural history of HCV infection. The acceleration of liver disease, progression of fibrosis, frequency of cirrhosis, liver failure, and HCC have become substantial sources of mortality and morbidity in patients with HCV and HIV co-infection (Monga et al., 2001; Mohsen et al., 2003).

Ideally, HIV infection should be well controlled with highly active antiretroviral therapy (HAART) before the treatment of HCV infection is initiated. In addition, the management of the chronic hepatitis C of HCV and HIV co-infected patients can be confounded by the difficulty in distinguishing among hepatitis caused by the HCV infection itself, HAART hepatotoxicity, and opportunistic infection involving the liver (Laskus et al., 1998; Kottilil et al., 2004). Patients with HCV and HIV co-infection have lower response rates to peg-IFN plus ribavirin treatment for HCV than do patients with HCV infection alone (Perez-Olmeda et al., 2003). However, HCV and HIV co-infected patients with genotype 2 or 3 achieve a sufficient sustained response, 62–73%, while patients with genotype 1 have a sustained response rate of only 14–29% (Torriani et al., 2004; Chung et al., 2004). Thus, peg-IFN plus ribavirin treatment is optimal for HCV and HIV co-infected patients. However, ribavirin should be avoided if didanosine is critical to the HIV treatment regimen because of the possibility of a drug interaction. Ribavirin can increase the activity and potentiate the toxicity of didanosine (Lafeuillade et al., 2001).

The human T-lymphotropic virus (HTLV-I) is a human retrovirus, as is HIV, and prevalence studies have shown that it infects 10 to 20 million people worldwide

(Kashiwagi et al., 1990). HTLV-1 infection appears to modify the natural progression of HCV infection by leading to a more severe and rapid progression of liver diseases (Kishihara et al., 2001).This occurs because HTLV-1 causes impairment of host immunity and induces functional impairment of cellular immune response (Hayashi et al., 1997b). Moreover, the rate of sustained response to IFN treatment of patients with HTLV-1 and HCV co-infection is significantly lower than for patients with HCV alone (Kishihara et al., 2001). Taken together, further modification of the currently popular treatments is needed for HCV patients co-infected with such human retoviruses.

End-Stage Renal Disease

HCV infection is highly prevalent in patients with end-stage renal disease (ESRD). The prevalence shows a consideration variation, 3–80%, between countries and centers (Hayashi et al., 1991b, 1994a; Furusyo et al., 2001; Fabrizi et al., 2002). A detrimental effect of HCV on patients and graft survival after kidney transplantation has been reported (Bruchfeld et al., 2004). The main complications for such patients are an increased risk of severe infection, liver disease, de novo glomeruonephritis with or without crioglobulinemia, and diabetes (Pereira et al., 1998; Furusyo et al., 2000a; Cruzado et al., 2001; Bloom et al., 2002). As a result of these potential risks of HCV infection of patients with ESRD, the current recommendation is to give antiviral treatment before transplantation with the objective of eradicating the virus.

IFN-alpha monotherapy is generally well tolerated and is more effective for hemodialysis patients with chronic HCV infection than for those with normal renal function (Fabrizi et al., 2003; Russo et al., 2003). This can be partly explained by the phenomenon in which serum HCV RNA levels are lower in hemodialysis patients than in patients with normal renal function (Furusyo et al., 2000b). Maintained hemodialysis affects a lower HCV RNA level in sera. However, a fairly high rate of discontinuation of IFN treatment, over 30%, due to serious adverse events has been reported for these patients (Fabrizi et al., 2003; Russo et al., 2003). The role of treatment for this population and the safety and utility of small doses ribavirin in combination with peg-IFN are currently under investigation. Monitoring plasma ribavirin concentration during ribavirin treatment, ribavirin-induced anemia can be handled by injecting an erythropoietin and supplying adequate iron (Bruchfeld et al., 2003). In several cases, the use of peg-IFN plus ribavirin in ESRD patients was found to be safe, even though side effects were fairly frequent (Sporea et al., 2004; Annicchiarico & Siciliano, 2004; Bruchfeld et al., 2006).

Problems to Be Solved

Despite the great improvement in IFN treatment response, the rate of SVR is far from ideal, and many problems remain: about a 50% rate of nonresponse (especially for genotype 1 patients); adverse effects causing patients to have difficulty

tolerating the treatment regimens; and contraindicated patients in some special settings. Moreover, the probability of success depends on viral and host factors that are often beyond the control of patients and physicians. Recently, it has been reported that extension of treatment with peg-IFN plus ribavirin from 48 to 72 weeks significantly increases the rate of SVR in genotype 1 infected patients with detectable HCV RNA in sera at the week of treatment (Sanchez-Tapias et al., 2006). However, more effective and easily tolerated treatments are desirable.

The epidemiology of chronic HCV infection has seen great change over the last decade, and great progress has been made in the development of new diagnostic methods and treatment strategies, thanks to the combined efforts of academic- and industry-sponsored research. However, a number of issues that have not been completely solved remain, such as the management of the substantial number of nonresponders to IFN treatment, a full understanding of the pathogenesis of liver disease and the mechanisms of chronicity, and severe end-stage liver disease.

Conclusions

Treatments using peg-IFN plus ribavirin have yielded improved rates of SVR, but studies continue to show that the SVR rate is low for patients with HCV genotype 1 infection, for patients with high HCV RNA levels, and for patients with more advanced stages of fibrosis. Future advances in the management of HCV infection will require tremendous efforts to develop more effective treatments for the currently nonresponding populations.

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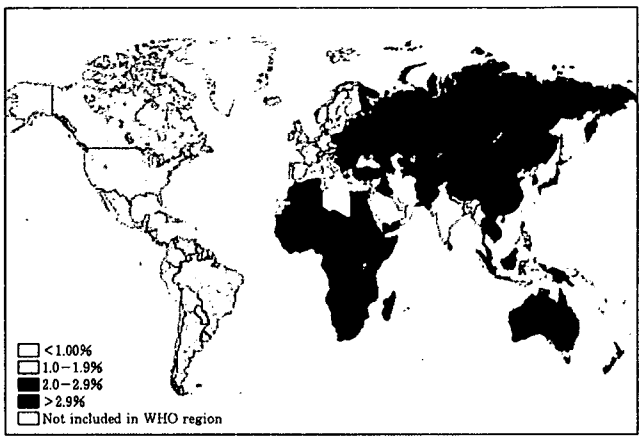
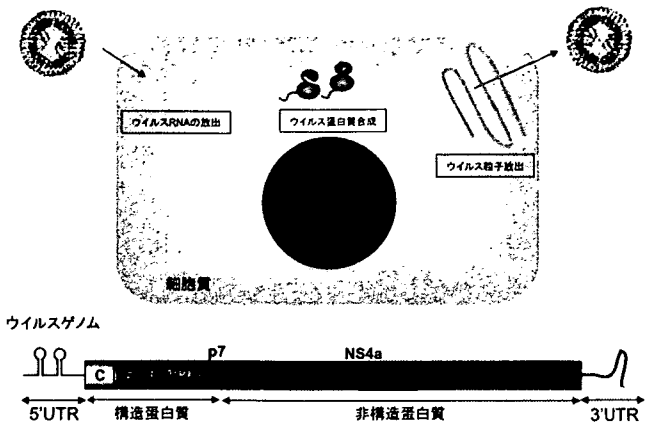
C型肝炎ウイルスの発揮する腫瘍原性

Ⅰ．世界におけるC型肝炎ウイルス感染者の分布

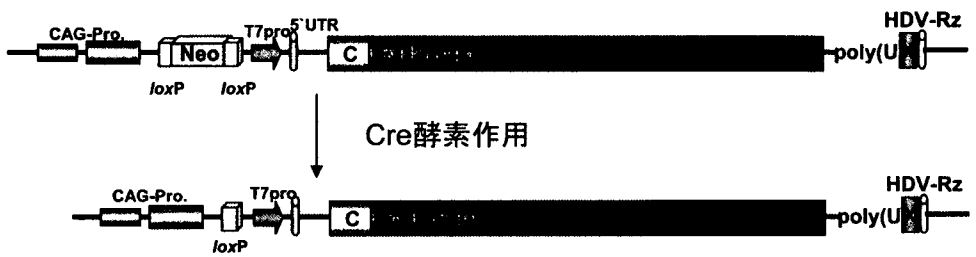


Ⅱ．C型肝炎ウイルスの生活環とウイルスゲノム構造

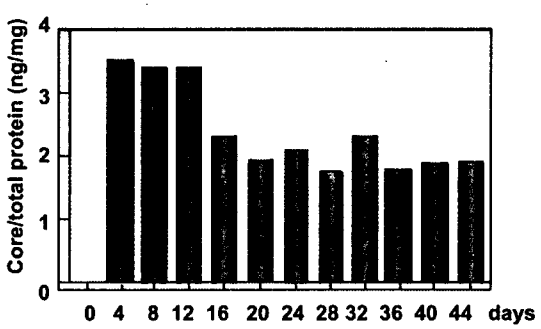


Ⅲ．C型肝炎ウイルスによる腫瘍原性亢進

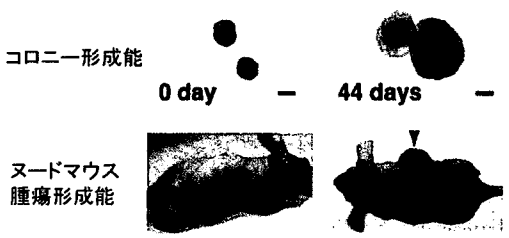
(a) Cre/loxPシステムによる全長HCV発現システム



(b) HCVの持続発現(コア蛋白質)



(c) HCV発現継代細胞の腫瘍原性亢進



(d) HCV発現継代細胞で活性化するシグナル経路