全身性そう痒症	1	0
筋骨格系および結合組織障害		1
関節痛	204	1
背部痛	103	0
筋痙攣	11	0
筋痛	187	0
頚部痛	10	0
四肢痛	17	0
腎および尿路障害		0
血尿	3	0
頻尿	11	0
蛋白尿	1	0
生殖系および乳房障害		0
不規則月経	1	0
前立腺炎	1	0
全身障害および投与局所様態		4
無力症	1	0
胸痛	18	0
悪寒	86	1
冷感	4	0
治癒不良	3	0
インフルエンザ様疾患	1	0
注射部位紅斑	108	0
注射部位出血	3	0
注射部位硬結	6	0
注射部位疼痛	21	0
注射部位そう痒感	66	0
注射部位発疹	22	1
注射部位反応	11	0
注射部位潰瘍	1	0
注射部位熱感	9	0
倦怠感	252	3
発熱	258	1
口渇	42	1
注射部位腫脹	15	0
硬結		0
臨床検査		30
アラニン・アミノトランスフェラーゼ増加	40	0
アスパラギン酸アミノトランスフェラーゼ増加	45	0
血中アルブミン減少	3	0
血中ビリルビン増加	96	0
血中ブドウ糖増加	16	0
血中乳酸脱水素酵素増加	43	0
血圧低下	1	0
血圧上昇	10	0

血中尿酸増加	10	0
C－反応性蛋白増加	52	0
好酸球数増加	53	0
γ－グルタミルトランスフェラーゼ増加	46	0
ヘマトクリット減少	215	1
ヘモグロビン減少	235	12
ヘモグロビン増加	1	0
単球数増加	32	0
好中球数減少	239	10
血小板数減少	124	1
赤血球数減少	218	1
体重減少	57	1
白血球数減少	260	1
白血球数増加	5	0
血中アルカリホスファターゼ増加	10	0
総計	8339	90

表２．　PegIFN/リバビリン併用療法(48 週投与)における副作用原因（臨床試験）

	年齢区分（才）				合計
	<40	40−<50	50−<60	60≦	
ヘモグロビン減少	0	1	4	7	12
血小板減少	0	0	1	0	1
好中球減少	4	1	3	2	10
合計	4	2	8	9	23

表３．　PegIFN/リバビリン併用療法(48 週投与)の副作用中止原因となった血球系減少（年齢別）

Ⅱ．研究成果の刊行に関する一覧表

Ⅱ. 研究成果の刊行に関する一覧表

雑　誌

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Ⅲ. 研究成果の刊行物・別刷

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Review

Antiviral therapy for chronic hepatitis C: past, present, and future

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Antiviral therapy for chronic hepatitis C has dramatically advanced since the discovery of the hepatitis C virus (HCV) in 1989 and the introduction of interferon (IFN) monotherapy in the early 1990s. The current standard therapy uses a combination of pegylated IFN and ribavirin. The duration of therapy and response to therapy are HCV genotype-specific. Genotype 1 patients require 48 weeks of the combination therapy for 50% successful viral elimination, while genotype 2 patients require 24 weeks of therapy for 80% or 90% viral elimination. Early viral kinetics after the initiation of therapy is a useful predictor of the sustained virologic response (SVR), which is formally determined at 24 weeks after completion of the treatment. For example, an early virologic response, which is determined by a 2-log reduction of HCV RNA or viral elimination at 12 weeks after the initiation of therapy, is a strong negative predictor of SVR in genotype 1 patients. In contrast, a rapid virologic response of HCV RNA-negative at 4 weeks after the initiation of therapy identifies genotype 2 "super-responders," who may require a shorter period of therapy. Adherence to therapy is one of the most important factors for successful viral clearance. Hematopoietic growth factors such as epoetin and granulocyte-colony stimulating factor help reduce therapy-mediated cytopenia and improve patient compliance, thereby leading to better viral clearance. New types of anti-HCV agents such as HCV protease and polymerase inhibitors are needed for those patients that do not respond to combination therapy.

Introduction

In 1989, the hepatitis C virus (HCV) was discovered in the United States to be the causative agent of posttransfusion non-A, non-B hepatitis by Chiron Corporation (Emeryville, CA, USA).[1] By this discovery, HCV was revealed to be the cause of many hepatic diseases of previously unknown origin. HCV is closely associated with hepatocellular carcinogenesis and death due to chronic liver disease. Epidemiologically speaking, it is estimated that 1.7 million people in Japan and 170 million people worldwide are infected with HCV.[2] Many cases are asymptomatic and result in overt hepatic disease, manifested as hepatic cirrhosis or cancer, only following 20 to 30 years of persistent infection. Thus, HCV infection is of significant concern in terms of public health.

Spontaneous elimination of HCV occurs in approximately 30% of HCV-infected patients within 6 months after infection. However, after this period of time, viral elimination is very rare, with an annual rate of only about 0.2%. Persistent inflammation associated with HCV causes hepatic fibrosis, and as the stage of fibrosis progresses, the risk of cancer increases; annual rates of hepatocarcinogenesis are 0.5% for patients with modest fibrosis and 8% for those with liver cirrhosis.

HCV-associated, progressive hepatic disease can be directly inhibited by interferon (IFN), which is currently the only drug that can eradicate HCV. This review traces the progress of IFN-based therapy for hepatitis C since its introduction and provides a brief overview of the future of HCV treatment.

Introduction of IFN therapy

IFN therapy for hepatitis C dates from 1986, when Hoofnagle et al.[3] reported the normalization of serum alanine aminotransferase (ALT) levels following administration of recombinant human IFNα to patients with non-A, non-B hepatitis. In other words, IFN was shown to be biochemically effective as an anti-inflammatory agent before the discovery of HCV.[4,5]

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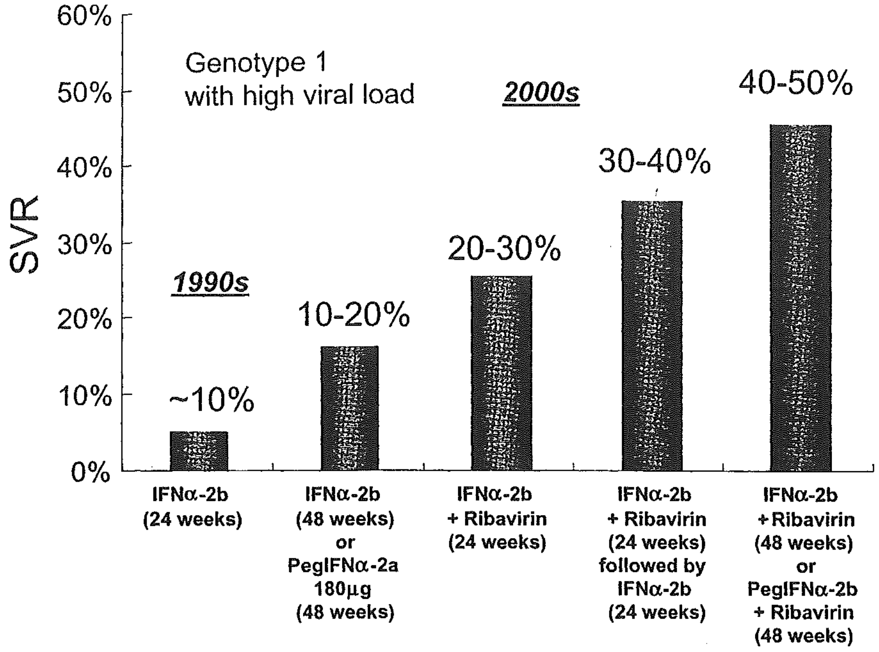

Fig. 1. Milestones of interferon (*IFN*)-based therapy for chronic hepatitis C. Progress in sustained viral clearance for a difficult to treat patient group, with genotype 1 and a high viral load, from the early 1990s. *SVR*, sustained virologic response; *PegIFN*, pegylated interferon

Later, the introduction of a virus identification method using a polymerase chain reaction (PCR) assay revealed cases in which patients became HCV-PCR negative following IFN administration.[6] The normalization of serum ALT levels is associated with viral eradication, with the exception of a few cases. The discovery of these biochemical and virological effects prompted approval of clinical use of IFN against hepatitis C in the United States in 1991 and in Japan in 1992.

The therapeutic responses to IFN can be classified as sustained virologic response (SVR), relapse, or nonresponse. SVR means complete elimination of HCV, which is defined as the loss of detectable HCV RNA during therapy and its continued absence for at least 6 months after the termination of therapy. Relapse is defined as being HCV-negative at the end of IFN treatment but HCV-positive within 6 months after the termination of therapy. Nonresponse is defined as the absence of a HCV-negative condition even with IFN administration. Initial studies showed that after 6 months of 6MU IFN administration to patients with chronic hepatitis C, SVR, relapse, and nonresponse were each observed in one-third of the patients. Subsequent studies revealed that the antiviral effect is determined mainly by viral factors, namely the viral load and the viral genotype.[7,8] Genotypes 1a and 1b are more resistant to IFN therapy than genotypes 2a and 2b, and patients with a high viral load are less likely to respond to IFN than those with a lower viral load. A subgroup analysis of patients treated with IFN monotherapy showed that the SVR rate in genotype 1 patients with a high viral load, accounting for approximately 60% of patients with hepatitis C in Japan, was only 5%. How to improve the therapeutic effect in these patients is the greatest problem for future research and development of IFN therapy (Fig. 1).

Progress of IFN-based therapy

For such resistant cases (patients with genotype 1 and high viral load), extended administration to optimize the total dose of IFN, the introduction of pegylated IFN (PEG-IFN) and coadministration with ribavirin have been used to substantially improve treatment over the past 10 years.

Optimization of the total dose of IFN: extended administration

Two means of increasing the total dose of IFN in resistant cases have been investigated: increasing the dose and extending the administration period. In Japan, patients had usually been given 6MU IFN three times a week for 6 months. Higher doses did not correlate with an increased SVR rate, partly because of the increased incidence of adverse effects and reduced patient compliance. However, extending the administration period proved effective for raising the SVR rate. Kasahara et al.[9] showed that 12 months of administration clearly increased the SVR rate in genotype 1 patients, compared with 6 months of administration. However, in genotype 2 patients, there was no significant difference between 6 and 12 months of administration. The standard dose of IFN used in Europe and the United States, based on early clinical studies, has been 3MU three times a week, with the result that European and U.S. therapeutic results after 6 months of IFN monotherapy are generally lower than those in Japan.[10,11] In Europe and the United States, the superiority of the 6-MU dose over a 3-MU dose has been shown by subsequent controlled studies, and many other clinical studies have shown the superiority of 12 months of therapy over 6 months.[12–14] The SVR rate for genotype 1 patients with a high viral load improved with IFN therapy of extended duration, shown first for IFN monotherapy and later for the combination of IFN with ribavirin.[15–17]

Based on these findings, administration of IFN for 12 months was approved early in Europe and the United States. In Japan, the 6-month limit for IFN therapy was removed in 2002, and self-injection of IFN was approved in 2005. These measures make it easier for patients to undergo long-term treatment.

Development of IFN preparations: introduction of PEG-IFN

The type I IFNs include IFNα, IFNβ, IFNω, and IFNλ, all of which share cell-surface receptor and intracellular pathways of action. IFN agents are used in various preparations. In the United States, recombinant IFNα-2b and IFNα-2a were initially approved. In Japan, in addition to these two preparations, natural IFNα and IFNβ can be used. These conventional preparations are considered to be of equal efficacy, although a few differences in the incidences of neutralizing antibodies and adverse effects have been noted.[18] Subsequently, a special agent, consensus IFN, was developed and put into clinical use.[19] It was designed by selecting the most frequently occurring amino acid at each site of the amino acid sequences of 13 known IFNα subtypes. Consensus IFN is considered to have a potent antiviral effect in genotype 1 patients with a high viral load, but it is still considered to be a conventional IFN agent.

Revolutionary progress in the development of IFN agents was recorded with the development of PEG-IFN and its introduction to clinical use. Pegylation is defined as modification of a drug by the addition of an artificial polymer, polyethylene glycol (PEG), for the purpose of delaying drug elimination, lowering its antigenicity, and modifying the drug's effect. Conventional IFN agents, with approximately 8-h elimination half-lives, require a dosing interval of 1 or 2 days to maintain an effective blood concentration.[20,21] The most beneficial effect of PEG-IFN is that it delays drug elimination, making it possible to maintain a stable blood concentration with once-weekly administration.[22] Currently, two PEG-IFN preparations are available: recombinant IFNα-2a and IFNα-2b, which are covalently bound to 40-kDa PEG and 12-kDa PEG, respectively. Both are thought to have about equal efficacy, but they have not been compared in clinical trials.

European and U.S. controlled studies have shown that PEG-IFN agents are generally more effective, both in monotherapy[23–25] and in combination with ribavirin, than conventional IFN agents.[26,27] In Japan, clinical studies have shown that PEG-IFN agents are not inferior to conventional IFN agents. However, no study has shown PEG-IFN agents to be significantly superior with respect to SVR, partly, perhaps, because the usual dose of control IFN agents used in Europe and the United States is 3MU, which is less than that used in Japan. In sum, PEG-IFN is at least equivalent to conventional IFN in effectiveness, and it appears to be highly tolerable because it can be administered just once a week.

The adverse effects of IFN are classified into two types: those that occur soon after the start of administration, and those that manifest during long-term administration.[28] The former type includes flu-like symptoms, such as a high fever, headache, and myalgia, and abnormal blood test results such as thrombocytopenia and leukopenia. Effects seen with long-term administration include a wide variety of symptoms, such as pruritus, alopecia, fundal hemorrhage, depression, thyroid dysfunction, diabetes mellitus, pulmonary fibrosis, and cardiac arrhythmia. Adverse effects of PEG-IFN are similar to those of conventional IFN and are characterized by mild influenza-like symptoms during the early stage of administration and comparatively severe cytopenia. The occurrence of acute thrombocytopenia in the late stage of administration of PEG-IFNα-2a has also been noted. More caution is needed with respect to the occurrence of adverse effects of PEG-IFN owing to its delayed clearance.

Combination therapy: introduction of ribavirin

Ribavirin, developed in 1972, is a synthetic nucleic acid analog with a purine skeleton. It has antiviral activity in vitro to a wide variety of RNA and DNA viruses, and it is orally administered. Ribavirin has not been approved in Japan as an antiviral agent for monotherapy, but it has been approved in Europe and the United States for various viral diseases, such as severe respiratory syncytial virus infection in children. Its antiviral effect against HCV has not been proved by studies on monotherapy for hepatitis C.[29] In 1998, however, the combination of ribavirin with IFN was reported to have achieved a significantly higher SVR rate compared with IFN monotherapy.[15,16,30,31] These reports were followed by large-scale clinical studies in Europe and United States[26,27] showing that a combination of PEG-IFN and ribavirin produces better results than one of IFN and ribavirin. With both combinations, 48 weeks of administration to genotype 1 patients achieved a significantly higher SVR rate than 24 weeks of administration.[15,16,32] For other patients, no significant difference was seen between groups receiving 24 or 48 weeks of therapy, and the 24-week administration period was reported to be sufficiently effective.

In Japan, a 48-week, multicenter, randomized, controlled study[33] was conducted on combinations of 6 MU IFNα-2b with ribavirin and 1.5 μg/kg PEG-IFNα-2b with ribavirin administered to genotype 1b patients with a high load of HCV-RNA, determined to be 100 KIU/ml or higher using Amplicor (by the original PCR method). Oral doses of ribavirin administered were 600 mg/day for patients weighing less than 60 kg, 800 mg/day for those weighing at least 60 kg but less than 80 kg, and 1000 mg/day for those weighing 80 kg or more. IFNα-2b was administered six times a week for the first 2 weeks and three times a week for the following 46 weeks, while PEG-IFNα-2b was administered once a week. The results for 506 patients indicated high rates of viral elimination by both therapies. The combination of PEG-IFNα-2b plus ribavirin and that of IFNα-2b and ribavirin achieved SVR in 121/254 patients (47.6%) and 113/252 patients (44.8%), respectively, a difference that was not significant. Based on this phase 3 study, 48 weeks of PEG-IFNα-2b and ribavirin combination therapy was approved for genotype 1 patients with a high viral load in Japan in 2004.

The adverse effects of ribavirin include hemolytic anemia and potential teratogenicity. Caution must be exercised with ribavirin administration when there is coexisting anemia or coronary heart disease. Contraception is also required during administration of ribavirin and up to 6 months after the end of its administration. Ribavirin is contraindicated for patients with renal failure, because it is excreted by the kidney and cannot be eliminated by dialysis.

Recent developments in PEG-IFN and ribavirin therapy

Coadministration of PEG-IFN and ribavirin has been established as the standard regimen of antiviral therapy for hepatitis C,[34] and the following questions next arise. How long should the dosing period be for this combination? How can its adverse effects be ameliorated and the treatment successfully completed? To what extent can this combination treatment be applied? Recent developments offer responses to these questions.

Exploring necessary and sufficient dosing periods: the impact of viral kinetics study

Usually the duration of coadministration of PEG-IFN and ribavirin is 48 weeks for difficult cases (e.g., genotype 1 patients with a high viral load) and 24 weeks for other cases, with expected SVR rates of approximately 50% and 80%, respectively.[32] Some studies have suggested that higher doses of ribavirin based on body weight are more effective for genotype 1, while a lower dose (fixed dose at 800 mg/day) is sufficient for viral genotypes other than genotype 1. To date, a variety of factors, both viral and host, that correlate with a sustained response to the combination therapy have been noted (Fig. 2). In contrast to viral factors, however, most host factors do not have a strong impact on the various treatment regimens. Recently, the viral kinetics after the start of therapy has been noted to be a useful early indicator of viral elimination, which is usually determined 24 weeks after the end of therapy.[20] To find out whether SVR is related to the rate of inhibition of viral replication after the start of PEG-IFN plus ribavirin combination therapy, Davis et al.[35] carried out a retrospective analysis of a controlled clinical study conducted by Manns et al.[26] In the clinical study, PEG-IFNα-2b (1.5 μg/kg per week) and ribavirin (800 mg/day) were coadministered to 511 patients with chronic hepatitis C for 48 weeks. If an early virologic response (EVR) is defined as a viral load decrease of 2 log or more or viral elimination after 12 weeks of treatment, then 71.8% of the patients who experienced EVR—74.4% of all patients—achieved SVR. Importantly, none of the patients who did not experience EVR achieved SVR. Similarly, with therapy with PEG-IFNα-2a (180 μg/week) plus ribavirin (1000 or 1200 mg/day, depending on body weight) for 48 weeks ($n = 453$), only 2 of 63 patients who did not experience EVR achieved SVR.[27] These findings show that EVR has negative predictive value, and therefore, if viral elimination is the aim of the treatment and if adverse effects cannot be negligible, the treatment should be discontinued in patients not displaying EVR. This "12-week rule" applies only to patients with viral genotype 1.[36]

The relationship between the time of becoming HCV-negative and SVR has also been examined in Japan in the above-mentioned clinical study[33] of PEG-IFNα-2b plus ribavirin. SVR rates for patients who became HCV-negative at 4, 12, or 24 weeks (23, 121, and 33 patients, respectively) were 100%, 71.1% and 36.4%, respectively. None of the 15 patients who experienced viral elimination after 24 weeks achieved SVR. Therefore, 24 weeks of additional administration to patients with no viral elimination within the initial 24 weeks produces no benefit.

Factors correlated with a successful response to combo therapy

Viral factors

- Non-1 genotypes
- Lower viral load

Host Factors

- Female sex (paradoxically male sex in most Japanese studies)
- Younger age
- Less fibrosis
- Non-African American race
- Absence of hepatic steatosis

Response and adherence to treatment

- Presence of a rapid initial first-phase decline followed by a more gradual second-phase decline in serum HCV RNA levels
- Maintenance of the initial prescribing dosing

Fig. 2. Factors correlated with a successful response to combination therapy with pegylated interferon and ribavirin in chronic hepatitis C. HCV, hepatitis C virus

Genotype 1 patients who do not experience EVR are very intractable, as shown above. In other words, 48 weeks of therapy with PEG-IFN and ribavirin may be too short to maximize SVR in genotype 1 patients.[37] The usefulness of long-term administration for 48 weeks or longer is being investigated to improve the rate of achievement of SVR in such patients. Buti et al.[38] published a promising report on extending therapy with PEG-IFN plus ribavirin to 72 weeks for late virologic responders. They selected nine genotype 1 patients being treated with PEG-IFNα-2b (1.0µg/kg) plus ribavirin (800mg/day) who cleared HCV RNA between weeks 12 and 24 for therapy prolonged to 72 weeks. Eight patients completed therapy, and at week 24 of follow-up, seven maintained SVR and one had relapsed. A Spanish multicenter, randomized controlled study, in which patients with chronic hepatitis C who did not became HCV negative by 4 weeks of coadministration of PEG-IFNα-2a (180µg/week) and ribavirin (800mg/day) (about two-thirds of all patients) were randomized to groups receiving 48 weeks or 72 weeks of therapy, found that the group receiving 72 weeks of therapy achieved a significantly higher rate of SVR than the group receiving 48 weeks of therapy. On the other hand, a recent clinical trial showed that genotype 1 patients who were HCV RNA-negative after 4 weeks of coadministration of PEG-IFNα-2a (180µg/week) and ribavirin (1000 or 1200mg/day) achieved an SVR rate of 66% with a further 20 weeks of therapy.[39] Unfortunately, this study did not randomize the patients to compare 24 weeks of therapy with a 48-week therapy period. The study, however, does show that 24 weeks of therapy can achieve relatively high rates of viral elimination for these genotype 1 "super-responders."

For other, non-1 viral genotypes, studies are being done to identify a dosing period shorter than 24 weeks that can be used to achieve sufficient SVR. In one study, genotype 2 and 3 patients were given PEG-IFNα-2b (1.0µg/kg each week) and ribavirin (1000 or 1200mg/day, based on body weight), and those who experienced viral elimination after 4 weeks of therapy were assigned to 24-week or 12-week therapy groups. The results showed that the SVR rate for the 12-week group was the same as that for the 24-week group, indicating that 12 weeks of combination therapy is sufficient for these patients.[40] Similar data have also been reported for PEG-IFNα-2a (180µg/week) plus ribavirin (800 to 1200mg/day) therapy.[41]

As mentioned above, for treatment of non-1 viral genotypes and some genotype 1 patients, sufficient SVR rates can be achieved and unnecessary treatment avoided by adopting the dosing period by using the early viral inhibition effect as an indicator. The early viral kinetics can be also applied to identify more difficult to treat patients with viral genotype 1, who can then be given longer treatment to improve SVR rates (Fig. 3).

Reducing cytopenic effects and improving compliance: the use of hematopoietic growth factors

Patient compliance has been noted by many clinical studies to be the largest factor contributing to the therapeutic effect of PEG-IFN plus ribavirin combination therapy (Fig. 2). Compliance can be divided into those factors related to patient adherence to the regimen and dose interruptions or modifications mandated by the physician in response to cytopenia, rash, gastrointestinal symptoms, or depression. McHutchison et al.[42] outlined an "80:80:80 rule" in genotype 1 patients; that is, the doses of PEG-IFN and ribavirin and the dosing period should exceed 80% of the initial plan to achieve a sufficient SVR rate. Early dose reduction within 12 weeks is more harmful than later dose reduction. To maximize viral clearance of the PEG-IFN and ribavirin combination therapy, countermeasures are needed against adverse effects to improve patient compliance.

Compared with IFN monotherapy, combination therapy is characterized by additional adverse effects represented by hemolytic anemia. If anemia occurs, the dose of ribavirin must be reduced or the administration of ribavirin must be discontinued. To help avoid this adverse effect, attention is being drawn to drug intervention with erythropoietin. An 8-week, double-blind study was conducted in which epoetin alpha 4000U/week or a placebo was given to patients who experienced a decrease in hemoglobin (Hb) levels to 12g/dl or less during coadministration of PEG-IFN and ribavirin in the United States, and the dose of ribavirin, Hb levels, and quality of life (QOL) were compared at the end of the study.[43] Compared with the placebo group, the reduction in Hb levels was significantly inhibited in the epoetin alpha group; thus, reduction of the ribavirin dose could be avoided. Inhibition of the reduction in Hb levels also improved QOL.[44] Similarly, granulocyte-colony stimulating factor (G-CSF) is expected to be useful for avoiding leukocytopenia induced by PEG-IFN and ribavirin combination therapy. Prevention of adverse effects with hematopoietic growth factors may be a promising measure to allow the maintenance of the therapy protocol and to improve therapeutic outcomes.

Challenging special patient groups: chronic hepatitis C with persistently normal ALT levels

Persistently normal ALT levels are observed in 20%–30% of chronic HCV-infected patients among the general public. Such patients are sometimes called asymptomatic HCV carriers. Most of them present a picture of histologically minimal or mild chronic hepatitis; it is rare for the liver to be normal. Progression of fibrosis is noted in fewer than 10% of the patients. For this reason, the expression "chronic hepatitis C patients with persistently normal ALT levels" is often preferred to "asymptomatic HCV carriers." There was strong resistance against using IFN therapy for such patients in the 1990s[45,46] for both active and passive reasons. The former included a lower viral elimination effect, or SVR, compared with general hepatitis C patients, and the report of abnormal ALT levels in a high percentage of patients due to IFN therapy in early studies of asymptomatic HCV carriers.[47,48] Recent studies have shown that IFN monotherapy[49] and IFN plus ribavirin combination therapy[50,51] can help patients with persistently normal ALT levels achieve the same level of SVR as patients with abnormal ALT levels. The percentage of patients who display an increase in the ALT level in response to IFN therapy is also lower than that in the early studies.[51] Therefore, the active reasons against using IFN therapy for patients with persistently normal ALT levels can no longer be supported. The passive reason, that there is no evidence of improved long-term prognosis in this patient group by IFN therapy, still remains.

HCV patients with normal ALT levels have been not eligible for large-scale clinical studies, causing there to be a deceptively low level of evidence regarding the efficacy of antiviral therapy in such patients. However, the potential importance of antiviral therapy for such patients has been gaining attention in recent years, and an international, multicenter, randomized, controlled study of PEF-IFNα-2a plus ribavirin combination therapy has been conducted.[52] Eligible participants were 491 HCV RNA-positive patients whose ALT levels measured three times or more at intervals of at least 4 weeks did not exceed the upper limit of the normal ALT range. The patients were randomized at the proportion of 3:3:1 into three groups: patients receiving 24 weeks of therapy with PEF-IFNα-2a (180μg/week) and ribavirin (800mg/day), those receiving 48 weeks of PEF-IFNα-2a (180μg/week) and ribavirin (800mg/day), and a control group that did not receive any treatment. Acute exacerbation of ALT levels that exceeded ten times the upper limit was observed in two patients (one in the 24-week therapy group and one in the control group). The results regarding treatment effectiveness were identical to those for chronic hepatitis C patients with high ALT levels previously published by Hadziyannis et al.[32] Thus, a dosing period based on the algorithm established for chronic hepatitis C patients with abnormal ALT levels can be recommended for PEG-IFN plus ribavirin combination therapy for HCV-infected patients with persistently normal ALT levels.

Such findings strongly suggest that HCV-infected persons with persistently normal ALT levels should be considered eligible for IFN therapy. The 2004 American Association for the Study of Liver Diseases (AASLD) best-practice guideline[36] recommended as follows: "Regardless of serum aminotransferase levels, the decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver diseases by liver biopsy, the potential serious side effects, the likelihood of response, and the presence of comorbid conditions." What is crucial is not the ALT level but whether to treat the patient if his/her liver disease is not severe.

Future antiviral therapy for hepatitis C

IFN plus ribavirin combination therapy brought about substantial improvement in comparison with the IFN therapy introduced in the 1990s. This combination may lead to high viral elimination primarily because it decreases the incidence of relapse in patients who have become HCV-negative during the therapy. According to an analysis of patient characteristics by the aforementioned Japanese clinical study[33] of PEG-IFNα-2b plus ribavirin combination therapy for genotype 1b patients with high viral load, SVR rates in treatment-naïve patients, relapsers, and nonresponders were 43.1% (59/137 patients) 62.6% (57/91 patients), and 19.2 (5/26 patients), respectively. The fact that relapsers achieved higher SVR rates than treatment-naïve patients suggests that PEG-IFN plus ribavirin combination therapy maximizes the therapeutic effect of IFN and encourages complete viral elimination in IFN-responding patients. On the other hand, the low SVR rate in nonresponders indicates that PEG-IFN plus ribavirin combination therapy is not always useful in patients who do not respond to IFN. To improve SVR rates in such patients, more-effective antiviral agents other than IFN must be developed. Furthermore, as described earlier, PEG-IFN plus ribavirin combination therapy induces a variety of adverse effects. Clearly, safer and better tolerated therapies are needed.

Promising agents for future anti-HCV therapies are classified as HCV-specific inhibitors targeting its protease and polymerase activities, IFN inducers, or less-toxic ribavirin-like agents. A number of drugs are in preclinical or clinical trials.

HCV protease inhibitors

HCV encodes at least four enzymes required for virus replication. They include NS2/3 autoprotease, NS3 helicase, NS3/4A serine protease, and NS5B RNA-dependent RNA polymerase. Intensive work on developing specific inhibitors has focused on the last two.

SCH 503034 is a novel, orally active HCV protease inhibitor that exhibits potent and specific antiviral activity in HCV replicon assays. Recently, a phase 1b clinical trial was conducted for both monotherapy[53] and combination therapy with PEG-IFNα-2b.[54] SCH 503034 exhibited dose-dependent HCV antiviral activity in genotype 1 patients in whom PEG-IFN therapy had previously been unsuccessful. In combination with PEG-IFNα-2b, SCH 503034 had at least an additive effect on HCV suppression. VX-950 is an orally administered highly selective peptidomimetic inhibitor of HCV NS3/4A protease. In a phase 1b clinical trial, VX-950 was well tolerated for 5 to 14 days in both healthy subjects and patients with viral genotype 1, with no serious adverse effects. VX-950 showed a 4.4-log reduction in median HCV RNA at the end of 14 days of therapy.[55]

In addition of its critical role in virus replication, the NS3/4A protease also plays a role in suppressing the cellular antiviral response. Active NS3/4A prevents the phosphorylation and activation of interferon regulatory factor (IRF)-3 and the triggering of downstream IFN-induced antiviral effector genes.[56,57] IRF-3 activity has been shown to be restored by a HCV protease inhibitor. Thus, an effective protease inhibitor may block not only RNA replication but also the ability of HCV to evade innate antiviral responses.

HCV polymerase inhibitors

Valopicitabine (NM283) is a 3′-valyl prodrug of a nucleoside analog that exhibits anti-HCV activity via inhibition of viral RNA polymerase. Valopicitabine is currently in phase 2 clinical development for the treatment of chronic hepatitis C. In a phase 2a trial, valopicitabine demonstrated potent anti-HCV activity when administered in combination with PEG-IFNα-2b, with 4.5-log serum HCV RNA reduction at 6 months and no obvious viral breakthroughs. In a phase 2b clinical trial, the combination therapy was also effective for patients previously unresponsive to PEG-IFN and ribavirin combination therapy.[58]

Since HCV has a higher intrinsic mutation rate than HIV, resistance is expected to be a problem with the use of any type of HCV-specific inhibitor targeting NS3/4A or NS5B proteins. To suppress the risk of a possible escape mutant, combination therapy with PEG-IFN may be better than monotherapy because the former can more efficiently suppress the levels of HCV replication. In the future, a combination of two or three different types of HCV inhibitors may offer a promising approach, similar to HIV cocktail therapy.

Immune modulators

Successful spontaneous clearance of HCV infection is thought to require both innate (e.g., direct antiviral activities by cytokines and natural killer cells) and adaptive (T cell-mediated) immune responses. Chronic HCV infection is characterized by an inadequate immune response that fails to clear the virus.[59] Immune modulators, alone or in combination with direct antiviral agents such as IFN and HCV inhibitors, represent a possible opportunity to improve HCV clearance.

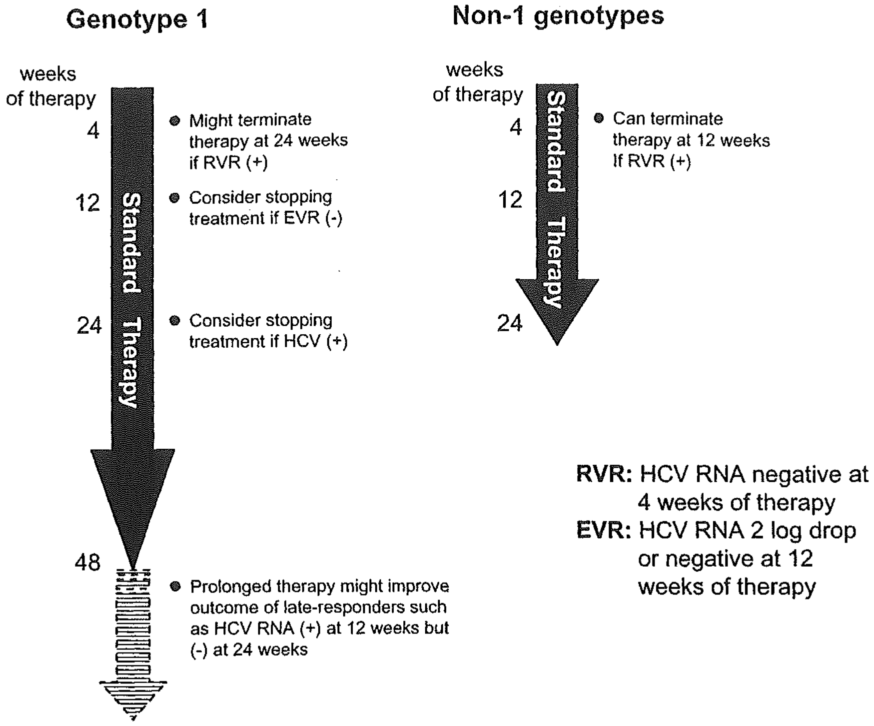

Fig. 3. Various treatment regimens of pegylated IFN and ribavirin combination therapy. *RVR*, rapid virologic response; *EVR*, early virologic response

CPG 10101 is a synthetic agonist of toll-like receptor (TLR) 9. HCV-infected patients receiving CPG 10101 subcutaneously had a more than 1-log reduction in HCV viral load while on therapy.[60] Further development of this agent will continue in conjunction with PEG-IFN and ribavirin.

Isatorbine is a TLR7 agonist. In a proof-of-concept clinical study, intravenous injection of isatorbine once daily for 7 days to patients chronically infected with HCV yielded a significant reduction of serum HCV RNA that correlated with induction of 2′,5′-oligoadenylate synthetase. Recently, the orally available prodrug of isatorbine, ANA975, was developed and studied in healthy phase 1 volunteers and showed promising pharmacokinetics and tolerability.[61]

Ribavirin-like agents

The addition of ribavirin to IFN therapy more than doubled the SVR rate, although its mechanism of action is unknown.[62] Furthermore, higher doses of ribavirin clearly improved response rates in genotype 1 patients.[32,63] However, ribavirin-induced hemolytic anemia is a major obstacle to implementation of a higher dosage regimen and limits its use in patients with comorbidities. To develop a better tolerated combination therapy, ribavirin-like agents lacking a hemolytic effect are needed. Viramidine is a ribavirin prodrug that is metabolized primarily in the liver. In a phase 2 study, fewer patients receiving viramidine developed anemia compared with those given ribavirin, but they also showed lower SVR rates.[64] Phase 3 trials have been undertaken of both PEG-IFNα-2a and PEG-IFNα-2b combined with viramidine in comparison with the combination with ribavirin.

Conclusion: viewpoints other than SVR

IFN treatment of patients with chronic hepatitis C were initially based on observations of its biochemical effects, before the discovery of HCV. Subsequently, evaluation of SVR at 6 months after stopping therapy as a clear end point made it possible to assess therapeutic results in a scientific manner. IFN therapy has been developing over the past decade, with the aim of improving the SVR rate, and higher rates are expected to be achieved with new, more specific antiviral agents.

The question arises as to what the ultimate purpose of hepatitis C treatment is. The answer is that it is the prevention of liver-related death of HCV-infected patients by suppressing progression to decompensated liver disease and liver carcinogenesis (Fig. 4), meaning that hepatitis C is not just an infectious disease, but a potentially serious liver disease. From this point of view, SVR is no more than a surrogate marker—albeit a very strong one—to improve the prognosis of HCV-infected patients. Hepatocellular cancer occurs even in patients

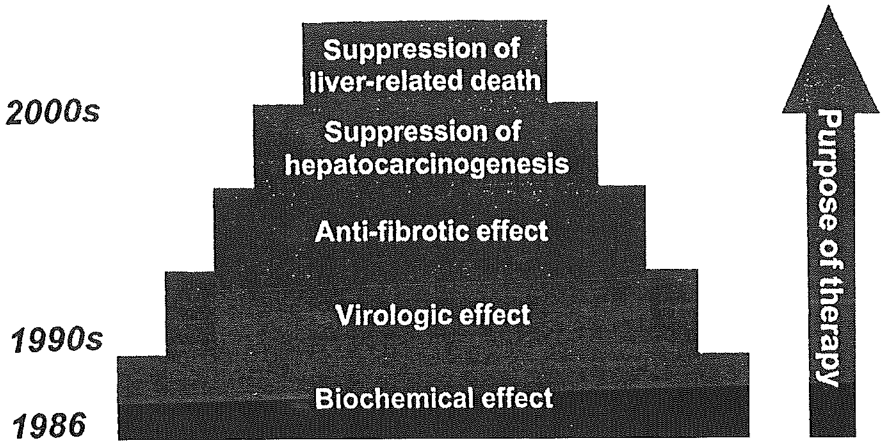

Fig. 4. Effects of IFN-based therapy in relation to the purpose of treatment for chronic hepatitis C. Retrospective analysis of rates of hepatocellular carcinoma and liver-related death after IFN monotherapy have shown a reduction in risk, especially in patients with moderate liver fibrosis[65–69]

who have experienced SVR, although its incidence is substantially lower in those patients than that in untreated patients or nonresponders. Thus, routine hepatocellular cancer screening is essential even after patients have experienced SVR, and early treatment is indispensable if it occurs. On the other hand, the cumulative incidence of hepatocellular carcinoma is clearly suppressed around half in even relapsers at least for 5 years after the termination of therapy compared with that in untreated patients.[65] Therefore, the therapeutic effect of IFN therapy should be evaluated not only on the basis of the SVR rate but also from the more important viewpoint of inhibition of hepatocellular cancer. In this context, repeated IFN therapy, for example every 5 years, for relapsers, and long-term, low-dose IFN therapy for nonresponders should also be considered until a new era dawns of treating hepatitis C with novel anti-HCV agents.

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