Pegylated interferon α (IFNα) in combination with ribavirin (RBV) is currently recommended as the first-line "standard-of-care" treatment for chronic hepatitis C virus (HCV) infection. This combination therapy has drastically improved the rate of sustained virological response (SVR) from < 20% to > 60%: 40%-60% of "difficult-to-treat" genotype 1 and 4 patients with 48-wk treatment, and 70%-90% of "easy-to-treat" genotypes 2 and 3 patients with 24-wk treatment [1-5].

A recent trend in the treatment strategy of chronic HCV infection is the development of individualized treatment regimens based on strong predictors of SVR to IFN-based treatment, such as HCV genotype [2-4,6-10] and the initial virologic response to treatment [9,11-19]. The pegylated formulation prolongs the half-life of conventional IFNα by covalently binding it to the polyethylene glycol (PEG) molecule, leading to improvement in the overall rate of sustained virological response (SVR) from < 20% to > 60%: 40%-60% of "difficult-to-treat" genotypes 1 and 4 patients with 48-wk treatment, and 70%-90% of "easy-to-treat" genotypes 2 and 3 patients with 24-wk treatment [1-5].

A recent trend in the treatment strategy of chronic HCV infection is the development of individualized treatment regimens based on strong predictors of SVR to IFN-based treatment, such as HCV genotype [2-4,6-10] and the initial virologic response to treatment [9,11-19]. Meanwhile, alternative options, such as modified regimens with currently available medications, novel modified IFNα and RBV or combinations with specifically targeted antiviral therapy for HCV (STAT-C) agents, are currently being investigated for the growing number of patients for whom current “standard-of-care” treatment has failed. For the
foresurable future, however, peg-IFNα and RBV appear to remain the backbone of “standard-of-care” treatment.

This review addresses and summarizes some issues and epoch-making topics in the treatment of chronic HCV infection, and discusses more optimal and highly individualized therapeutic strategies for patients infected with HCV.

**FACTORS ASSOCIATED WITH SVR**

SVR is defined as an undetectable qualitative HCV RNA level (by using a qualitative polymerase chain reaction assay) at 24 wk after the completion of treatment. Identification of factors predictive of SVR, including host-, virus- and treatment-related elements, provides relevant insights about the mechanisms of action of IFNα and RBV. So far, numerous factors have been identified as significant predictors of SVR or non-SVR. Strong predictors of the response to non-pegylated IFNα monotherapy, such as HCV genotype, pretreatment viral load and fibrosis stage, are also significantly associated with the outcome of peg-IFNα plus RBV combination therapy. Most importantly, by recognizing these factors, therapy can be tailored to individual needs, helping to make decisions regarding whether treatment should be initiated, continued or stopped. Individualized treatment regimens determined according to outcome predictors should increase the SVR rate and reduce unnecessary patient and social burdens, such as medical costs, side effects/adverse events associated with treatment, and treatment-related absenteeism.

**Host-related factors**

A number of pretreatment factors are known to reduce the SVR rate: older age, presence of cirrhosis or advanced fibrosis, African American race, overweight, obesity, diabetes, low alanine aminotransferase (ALT), abnormal baseline fasting glucose, low level of cholesterol, low hemoglobin, low platelet count, insulin resistance and hepatic steatosis[2,4,6,20,29]. The contribution of gender to treatment outcome is controversial as it varies among studies[26,29,32].

The response to treatment of patients with genotype 1 has been reported recently to be strongly associated with a single nucleotide polymorphism (SNP) near the interleukin-28B (IL28B) gene that resides on chromosome 19 and encodes IL28B or IFN-λ-3[3,14]. Patients with favorable genotypes at the SNPs (such as rs12979860[33], rs12980275 and rs8099917[25,34]) near the IL28B locus are more likely to achieve SVR than those with unfavorable genotypes. At present, the SNPs near the IL28B locus seem to be one of the strongest pretreatment predictors of SVR to peg-IFNα plus RBV or triple combination therapy including STAT-C agents, in addition to the HCV genotype. The population distribution of the favorable SNP genotype is significantly more prevalent in the Caucasian and Asian populations than in African Americans. Specifically, rs12979860 shows close correlations with the SVR rate and ethnicity: rs12979860 C-allele frequency is the highest in East Asians who show the highest rate of SVR among diverse ethnic groups[33]. Therefore, racial differences in treatment outcome may arise from divergence in host genomic genotype related to treatment response. Individualized therapeutic strategies should always consider ethnicity of individual patients as well as SNPs. However, it is highly unlikely that SNPs could be used alone to define different treatment strategies, since approximately 30%-40% of patients do not have the favorable genotype CC of rs12979860[33].

**HCV-related factors**

HCV genotype, pretreatment viral load and initial virologic response are strong independent predictors of SVR to IFN monotherapy[6-15,18,19,35]. These factors also have significant and independent impact on treatment outcome of conventional IFNα/peg-IFNα plus RBV combination therapy or triple combination therapy with telaprevir[24,4,10,7,21,22,28,29,36-44]. Patients infected with “easy-to-treat” genotypes 2 and 3 respond much better than those with “difficult-to-treat” genotypes 1 and 4. Furthermore, those with low pretreatment viral load respond much better than those with high pretreatment viral load, although the cutoff value that discriminates between high and low viremia varies among studies. The earlier the serum HCV RNA becomes negative during the initial phase of treatment, the greater the likelihood of achieving SVR.

Although there are relatively few data regarding genotypes 4, 5, and 6, HCV genotypes can be ranked, in a decreasing order of susceptibility to IFN-based treatment, as follows: genotypes 2, 3, 4 and 1. Furthermore, genotype 1a rather than 1b and genotype 2a rather than 2b are likely to respond better to IFN-based therapy. Interestingly, resistant variants against telaprevir (an NS3/4a protease inhibitor) and viral breakthrough occur more frequently in genotypes 1a than in 1b for telaprevir alone or in combination with peg-IFNα (with or without RBV)[30-42]. The different frequency results from nucleotide differences at amino acid position 155 of the nonstructural (NS3) protease region between genotypes 1a (aga, encodes R) and 1b (ega, also encodes R). The amino acid substitution of R with K at the position (R155K), which is most frequently related to telaprevir resistance, requires only one nucleotide substitution in genotype 1a and two substitutions in 1b. Similarly, the emergence of the resistant mutant R155K against boceprevir (an NS3 protease inhibitor) differs between genotype 1a and 1b[46]. Thus, HCV subgenotype as well as HCV genotype should be taken into consideration in triple combination therapy with peg-IFNα/RBV/STAT-C agent.

Two recent reports discuss the influence of wild and mutant types in the core or NS5 region of the HCV genome on treatment outcome of peg-IFNα plus RBV combination therapy in Japanese patients with genotype 1 and high pretreatment viral load[37,40].

**Treatment-related factors**

The doses of both peg-IFNα and RBV are important and have significant impact on SVR[3]. The likelihood of SVR increases as RBV dose (measured in mg/kg) increases[2,9], patients who receive peg-IFNα-2b plus a RBV dose of
10.6 mg/kg per day or more have a greater chance of achieving SVR than those receiving lower RBV doses[2]. Furthermore, the moving average of SVR rates increases as RBV dose increases up to about 13 mg/kg, and is almost level between 13 and 15 mg/kg. Combination therapy with peg-IFNα-2a plus RBV for 48 wk is more effective in HCV genotype 1 patients if the ribavirin dose is 1000 or 1200 mg/d rather than 800 mg/d[4]. In many cases, hemoglobin concentrations decrease drastically due to RBV-related hemolytic anemia (especially during the first 4 wk), and it may be necessary to reduce RBV dose and/or to initiate the use of erythropoietin. Any reduction in the RBV dose during the first 12-20 wk of therapy could have a larger negative influence on SVR rates than reductions in peg-IFNα dose[21,40,60], although maintaining RBV exposure over the whole duration of therapy is crucial[47,49]. Furthermore, a reduction in peg-IFNα dose during the first 12 wk could reduce the rate of early virologic response (EVR, defined as at least a 2-log decrease from the baseline levels or no detectable viremia) by 10%, but an additional reduction in RBV dose during this time was shown to decrease the EVR rate by another 37%[44].

Adherence is important to achieve SVR[49] and patients who take at least 80% of the prescribed total dose of the two drugs for at least 80% of the planned time are considered to be adherent (the “80/80/80” rule). For genotype 1 patients with unfavorable factors, more intensive therapy is recommended including a higher dosage of RBV and a longer duration of treatment or the use of STAT-C agents (such as telaprevir) as the initial therapy. Recent direct comparative trials, retrospective and meta-analysis studies demonstrated that treatment with peg-IFNα-2a is a significant and independent contributor to SVR in patients infected with genotype 1 or 3, compared to treatment with peg-IFNα-2b[25,36,38,29], although the largest head-to-head trial (IDEAL study) failed to find a significant difference in SVR rates between the two peg-IFNα formulations[29].

On-therapy response
HCV kinetics during the early phase of treatment are closely associated with SVR or non-SVR[11-15,18,19]. Patients with rapid virological response (RVR), defined as undetectable HCV RNA levels at treatment week 4, have a better likelihood of achieving SVR, and this is a strong independent on-therapy predictor[19,27,50,54]. The viral response is influenced by host-, virus- and treatment-related factors: young age, lean body, low baseline viral load and HCV genotype[53]. Conversely, the probability of SVR is less than 5% in patients with a minimal fall in viral load of < 1 log10 from the baseline level at treatment week 4, even when peg-IFNα and RBV are combined with telaprevir[2].

EVR is an important on-therapy indicator of the final treatment outcome: 65% of EVR patients have been reported to show SVR[9]. Those with no detectable viremia at week 12 (complete EVR) had SVR compared with those who had only a 2-log decrease from the baseline level (75% vs 33%). In contrast, a lack of EVR was associated with no SVR in 97% of the patients[8]. Such viral suppression during the initial phase is of crucial importance to resolve persistent viremia.

RESPONSE-GUIDED THERAPY
The extent of reduction in HCV RNA during the initial treatment phase is closely associated with the likelihood of achieving SVR[11-19]. The more rapidly HCV RNA becomes negative during treatment, the higher the rate of SVR. This fact suggests that the rapidity of viral response could be used to modify the duration of treatment, and hence the design of response-guided therapy (RGT). RGT is a dynamic treatment algorithm that involves individualized treatment based on the virologic response. Based on the briskness of the viral response, the treatment duration of 48 wk could be shortened to 24 wk or extended to 72 wk in patients infected with genotype 1 or 4, whereas 24-wk duration could be reduced to 12-16 wk in “easier-to-treat” genotype 2 or 3 patients. The rationale for extending the duration of treatment is to increase the likelihood of achieving SVR and to reduce virological relapse after treatment[6,50]. Conceivably, the shortened treatment would improve the overall tolerability and reduce exposure to unnecessary medication and economic burden. Likewise, a shorter therapy would avoid premature termination of treatment, while maintaining satisfactory SVR rates.

Genotype 1 or 4
The time points usually used to decide whether treatment should be stopped or continued are treatment weeks 4, 12 and 24, which constitute the basis for RGT[1,19]. Among genotype 1 or 4 patients with RVR, the likelihood of SVR is approximately 80%-90% when treated for 48 wk[19,27,51,56,64]. The existence of this patient subpopulation encouraged investigators to shorten the treatment duration to 24 wk without lowering the SVR rate. In patients with RVR treated for 24 wk, the SVR rate was 79%-89% for genotype 1 and 86%-87% for genotype 4[50,52,55,64]. Specifically, these studies showed that abbreviated 24-wk regimens are best suited to genotype 1 or 4 patients with low baseline viremia who achieve RVR.

In contrast, patients who respond later have a lower likelihood of SVR and greater probability of virologic relapse when treated for 48 wk[2,3,5,18,19,45,46]. Furthermore, the likelihood of achieving SVR is little or none in patients who do not show EVR or undetectable HCV RNA at week 24. Accordingly, a 12-wk stopping rule is widely accepted in patients who fail to achieve EVR[1]. However, the negative predictive value for SVR in such patients could be reduced from over 95% to 85% by extending the treatment duration to 72 wk. Several studies investigated whether extending treatment to 72 wk increases the SVR rate in patients without RVR randomized to 48- or 72-wk regimens (Table 1)[6-38,61]. In genotype 1 patients without RVR (including those with EVR who become HCV RNA-negative for the first time at treatment week 24, so called slow viral response), prolongation of treatment from 48 to 72 wk increases the likelihood of achieving
SVR and reduces the probability of relapse. The rates of virologic response at the end of treatment and adverse events are similar between 48- and 72-wk regimens, although the rates of withdrawal from treatment and subsequent follow-up are higher in the latter than in the former.

However, some issues should be noted and carefully addressed to interpret the results of randomized controlled trials (RCTs), because they have differed in treatment regimens, criteria and time points for randomization, and study population. Firstly, to resolve these differences, investigators should identify patients who will benefit from 72-wk treatment, and the best time points and the response criteria to be used to prolong the duration of treatment. Secondly, it may be better to distinguish between “complete” (undetectable HCV RNA) and “partial” (> 2-log HCV RNA drop from baseline but detectable viremia) EVRs. Currently, we comply with the following recommendation for the extended 72-wk treatment in clinical practice: when patients do not achieve complete EVR but have slow viral response, they are advised to prolong the treatment to 72 wk. In the near future, it should be clarified whether extension of treatment to longer than 72 wk further would increase the SVR rate. Thirdly, it is not always clear whether patients with genotype 1 and 4 are treated in an identical manner in RGT, because the number of studied genotype 4 patients has been very small.

**Genotype 2 or 3**

Patients with genotype 2 or 3 are more susceptible to peg-IFNα plus RBV treatment than those with genotype 1 or 4, and the current recommendation advocates a 24-wk treatment course, because more than 80% of the former group will attain SVR. Several small studies showed that the treatment duration could be shortened from 24 to between 12 and 16 wk without adversely affecting outcome in patients with RVR at week 4. However, the results of large trials clearly indicated that shortening the treatment duration to 16, 14, or 12 wk significantly lessened the SVR rates, because of a higher rate of virological relapse. The results of these studies suggest that patients with RVR have high probability of achieving SVR regardless of treatment duration, but that the risk of relapse increases with abbreviated treatment. Still, the pros and cons of the abbreviated treatment do not allow the making of a firm conclusion at present. Conversely, there is little information on the most suitable duration of treatment for patients with genotype 2 or 3 who do not achieve RVR. In this regard, there is a need to verify whether treatment week 4 is appropriate for prediction of outcome in genotype 2 or 3 patients, because the susceptibility to IFN-based therapy at the recommended duration of treatment apparently differs between genotypes 1/4 and 2/3.

Interestingly, there is ample evidence that peg-IFNα plus RBV treatment is more beneficial in patients infected with genotype 2 than those with genotype 3. This suggests that the two genotypes are not a homogeneous group, and that treatment regimens should perhaps be tailored or individualized for each genotype, with a special emphasis on the duration of treatment. Strictly speaking, the susceptibility to IFN-based treatment somewhat differs between sub-genotypes (e.g. genotype 1a vs 1b or genotype 2a vs 2b). For instance, treatment with peg-IFNα alone for 4 and 12 wk produced SVR rates of 91% and 100%, respectively, in genotype 2a patients with low viral load who became HCV RNA-negative at treatment week 14. Such subgrouping of patients with some strong predictors could further shorten the treatment duration with preservation of a high SVR rate.

Virologic response at critical time points, viral load at baseline, and HCV kinetics during the initial treatment phase provide useful information for tailoring or individualizing treatment to a given individual, leading to substantial reductions in both patient and society burdens without adversely affecting treatment outcomes.

**DIFFERENCES BETWEEN PEG-IFN α-2a AND α-2b**

PEGylation of therapeutic proteins modifies immunologic, pharmacokinetic and pharmacodynamic properties. PEGylation technology has been applied to improve these properties of conventional IFNα, to even out large fluctuating serum concentrations, and to resolve the inconvenient dosing regimens associated with conventional IFNα. The structure and size of the PEG moiety and covalent binding modes characterize the properties of the
modified biomolecule. Peg-IFNα-2a has a large, branched 40-kDa monomethoxy PEG, comprising two linked 20-kDa chains, attached to the lysine residues of IFNα-2a via amide bonds that are not susceptible to hydrolysis, and consists of 4 major positional isomers[60]. In contrast, peg-IFNα-2b is pegylated with a small, linear 12-kDa monomethoxy PEG moiety and involves 13 positional isomers, with the main isomer linked to His-34 of IFNα-2b via a urethane bond that is unstable and susceptible to hydrolysis[60]. These differences between the two peg-IFN formulations have an impact on the pharmacokinetic/pharmacodynamic properties.

Pharmacokinetic properties

The absorption half-life for peg-IFNα is longer than for unmodified IFNα (50 h and 4.6 h for 2a and 2b, respectively)[60-62]. The absolute bioavailability of peg-IFNα-2a is at least 60%. The time to maximum concentration (Tmax) is 78-80 h after a single dose and 45 h after multiple doses of peg-IFNα-2a, while Tmax times are 15-44 h and 22-29 h, respectively, in dosing of peg-IFNα-2b. The serum concentration after a single dose of peg-IFNα-2a is sustained up to 168 h (elimination half-life, 65 h), and up to 48-72 h (elimination half-life, 40 h) for peg-IFNα-2b. At steady phase, which is attained 5-8 wk after initiation of treatment, the peak-to-rough ratio of serum concentrations of peg-IFNα-2a and -2b is 1.5-2.0 and > 10, respectively, indicating that serum concentrations of peg-IFNα-2a are sustained during the 1-wk dosage interval. Since variations in the peak-to-rough ratios for peg-IFNα-2b are greater than for peg-IFNα-2a, viremia levels tend to fluctuate more with peg-IFNα-2b than peg-IFNα-2a (at least within the initial 4 wk of treatment). The volume of distribution is dependent on the body composition because of the wide distribution of peg-IFNα-2b throughout body fluids and tissues, whereas peg-IFNα-2a exhibits restricted distribution with the highest concentrations in the liver. Thus, peg-IFNα-2b requires weight-based dosing, while peg-IFNα-2a is used at a fixed dose.

Pharmacodynamic properties

Comparative studies of the initial viral kinetics after treatment have shown either a greater HCV RNA decline in patients treated with peg-IFNα-2a than those treated with peg-IFNα-2b[73] or vice versa[74], or no difference[75]. Pharmacodynamic profiling studies of the two formulations also showed conflicting results. Single dosing induced a similar degree or pattern of activity of 2'-5'-oligoadenylate synthetase and serum protein levels of neopterin and β2-microglobulin, indicating no difference between both types of peg-IFNs (plus RBV)[76]. In contrast, another study showed that peg-IFNα-2b up-regulated IFN response genes significantly more than peg-IFNα-2a during the first 72 h after single dosing of each peg-IFNα, both administered without RBV[77]. The enzymatic activity and serum protein levels were assayed in the former study, while RNA transcription was measured in the latter study. Furthermore, the methods and duration applied to evaluate various indicators differed between the two studies. Peg-IFNα was administered in combination with RBV during the evaluation period in the former, but not in the latter. Collectively, it is difficult to draw definite conclusions by simply comparing the results of relatively small studies, which have varied in several respects including the aforementioned differences.

Head-to-head comparison

Which of the peg-IFNs is more effective in combination therapy RBV for chronic hepatitis C? So far, several head-to-head studies have compared peg-IFNα-2a vs -2b in combination with RBV (Table 2).

Two investigator-initiated, independent, single-center,
randomized, controlled, head-to-head trials compared peg-IFN-2a vs -2b in combination with RBV for 48 wk (genotype 1 or 4) or 24 wk (genotype 2 or 3). Peg-IFN-2a plus RBV produced a significantly higher SVR rate than peg-IFN-2b plus RBV in treatment-naïve patients. In a prospective observational cohort study (PROBE, sponsored by Roche), the rate of SVR was higher in genotype 1 patients treated with peg-IFN-2a than with peg-IFN-2b (36% vs 29%, P = 0.02). In a retrospective observational cohort study (PRACTICE), matched pair analysis also showed a significant difference in the SVR rate between peg-IFN-2a and -2b treatments (59.3% vs 53.0%, P = 0.008). An observational retrospective cohort study at the Veteran Hospitals in the United States also reported that treatment with peg-IFN-2a was associated with a higher likelihood of SVR than treatment with peg-IFN-2b (25% vs 18%, P < 0.001). These studies have highlighted the superiority of peg-IFN-2a over peg-IFN-2b in the critical end-point of efficacy.

In contrast, the largest multicenter, randomized, head-to-head trial (IDEAL study, sponsored by Schering-Plough) showed no statistical difference in SVR rates among treatment arms with low-dose (1.0 µg/kg per week) or standard-dose (1.5 µg/kg per week) peg-IFN-2b or peg-IFN-2a (180 µg/wk), in combination with various RBV regimens (38.0%, 39.8% vs 40.9%, respectively). However, there were some differences between the IDEAL and other studies that could be described as critical limitations: (1) RBV regimens differed in initial doses and dose reduction rules between the treatment arms or studies; (2) the IDEAL study compared treatment regimens but did not directly evaluate the difference between the two peg-IFNs; (3) the dosing rules seem inappropriate by current standards in some studies; and (4) the IDEAL study included higher proportions of overweight, obese, and black/Latino patients. Using the same dosing and dose reduction rules of RBV across all the treatment arms and studies might have provided a fairer comparison of the different performance of the two peg-IFNs without a confounding effect of various RBV regimens. In the two studies where RBV dosing was identical between the two arms (one RCT and one cohort-matched pair analysis), the difference in favor of peg-IFN-2a was maintained. Interestingly, the safety and adverse-event profiles were similar among the treatment arms in the above studies, irrespective of the RBV regimen.

A recent Cochrane systematic review of randomized trials that compared both peg-IFNs identified 12 studies (5008 participants). Meta-analysis using intention-to-treat analysis for SVR included 8 trials (4335 participants), and yielded an estimated effect in favor of peg-IFN-2a [47% vs 41% with peg-IFN-2b; risk ratio = 1.11; 95% confidence interval (CI): 1.04-1.19, P = 0.004]. Subgroup analyses with regard to HCV genotype yielded similar results for all subgroups. The meta-analysis of adverse effects leading to discontinuation of treatment included 11 trials and showed no significant differences between the two peg-IFNs. However, the study did not reach a definitive conclusion as to which of the two peg-IFN formulations in combination with RBV is superior across populations based on more appropriate RBV dosing.

Taken together, all these studies involve several relevant methodological flaws (such as mixed genotypes, inclusion of prior non-responders and co-infected patients, small samples, insufficient power, and different RBV doses and dose reduction rules) that preclude, at least for the time being, any firm conclusions about differences in efficacy between the two peg-IFNα formulations.

### Treatment of Difficult-to-Treat Patients

Advances in IFN-based treatment for chronic hepatitis C, such as the development of peg-IFNα and RBV and treatment modifications, have improved the SVR rates in patients with difficult-to-treat characteristics, such as genotype 1/4, high baseline viral load, previous non-response, overweight, and the presence of cirrhosis. However, the outcomes of treatments in such patients are still inadequate. Further treatment development for this difficult-to-treat population is necessary.

#### Re-treatment of non-responders

For the increasing number of non-responders to IFN-based treatment or patients with multiple difficult-to-treat features, retreatment with current standard combination or alternative options, such as maintenance therapy with peg-IFNα or the use of higher dose and/or extended duration of treatment, have been explored vigorously. Most retreatment options for non-responders have provided a limited chance of SVR and in fact have been associated with increased side effects. In contrast, treatment-naïve patients with several difficult-to-treat predictors of poor response are reported to gain from aggressive modification of the treatment regimens and show higher SVR rates.

The SVR rate with retreatment consisting of standard peg-IFN-2b plus RBV regimen was 12% in non-responders to prior treatment with conventional IFNα/RBV or peg-IFNα/RBV who had detectable HCV RNA at retreatment week 12. The SVR rate with standard peg-IFN-2a plus RBV regimen was 18% in non-responders (with advanced fibrosis/cirrhosis) to prior conventional IFN-based treatment who had undetectable HCV RNA at retreatment week 20. A randomized retreatment study for non-responders to prior peg-IFN-2b plus RBV compared 48-wk vs 72-wk treatment duration using higher induction dose (360 µg weekly for 12 wk) or standard dose peg-IFN-2a (180 µg weekly) plus RBV. Although the extended treatment duration rather than higher induction dose significantly increased SVR rates (16% for 72 wk vs 8% for 48 wk, P < 0.001), the SVR rate was unsatisfactorily low: 16% for the 72-wk/higher induction dose group, 14% for the 72-wk/standard dose group, 7% for the 48-wk/higher induction dose group, and 9% for the 48-wk/standard group. However, the study showed that SVR rates were higher in patients with undetectable HCV RNA at re-treatment week 12 (49%) compared to those with detectable HCV RNA at re-
treatment week 12 (4%). Despite differences in the study population and design among these retreatment trials, most of them have produced modest SVR rates ranging from 7% to 18%. A recent meta-analysis indicated that the pooled estimate of SVR rate was 16.3% with a 95% CI of 8.3%-29.6%, although there was a significant heterogeneity among the studies (P < 0.0001)\(^\text{[86]}\).

**Difficult-to-treat naïve patients**

In contrast, treatment-naïve patients, even with multiple unfavorable factors, may show a favorable treatment outcome with aggressive treatment regimens. A pilot study of peg-IFN\(\alpha\)-2b administered twice weekly in combination with RBV showed a significantly higher SVR rate among treatment-naïve patients with genotype 1/4 and high baseline viral load (55% vs 17% with the standard regimen)\(^\text{[80]}\). In another study, a very high dose of RBV based on an individualized schedule yielded a very high SVR rate with the combination of peg-IFN\(\alpha\)-2a for treatment-naïve patients with genotype 1 and high baseline viral load, although this was a very small pilot study\(^\text{[83]}\). A pilot, double-blind, RCT for treatment-naïve patients with multiple predictors of poor treatment response (genotype 1, high baseline viral loads of > 800 000 IU/mL, and body weight > 85 kg) showed that high fixed doses of peg-IFN\(\alpha\)-2a (270 \(\mu\)g/wk) and RBV (1600 mg/d) increased SVR rates compared with lower, conventional doses of both agents (180 \(\mu\)g/wk and 1200 mg/d, respectively)\(^\text{[84]}\). Week 48 end-of-treatment virologic response and SVR rates were 55% vs 46% and 47% vs 28%, respectively, suggesting that a more aggressive treatment approach could improve the virologic response and suppress relapse, although increasing the dose of RBV alone did not reduce relapse or substantially improve the SVR rates. However, the initial 12-wk induction with high dose of peg-IFN\(\alpha\)-2b (3.0 \(\mu\)g/kg per day) failed to produce a positively favorable treatment outcome in treatment-naïve genotype 1 patients, compared to standard regimen\(^\text{[84]}\).

Taken together, non-responders to a prior 48-wk course of standard peg-IFN\(\alpha\) plus RBV combination who have no virologic response at retreatment week 12 are the most difficult-to-treat population. Such non-responders may have a cluster of difficult-to-treat characteristics or yet undiscovered resistant factors. The overall modest efficacy in non-responders argues against an indiscriminate retreatment with peg-IFN\(\alpha\) and RBV. Restricting retreatment to patients with favorable factors or less unfavorable conditions, using a 12-wk treatment stopping rule, would optimize the potential benefit with little likelihood of missing a curative response. For instance, relapsers with earlier virologic response to the prior treatment, and patients infected with genotype 2 or 3, would be possible candidates for successful retreatment. For treatment-naïve patients even with multiple predictors of poor treatment response, aggressive treatment regimens using currently available medications could significantly improve the likelihood of achieving SVR.

### STAT-C AGENTS

A large number of STAT-C agents have been developed and are currently being tested in phase 1-3 trials\(^\text{[85,88]}\). Adding STAT-C agents to peg-IFN\(\alpha\) plus RBV should provide new treatment options for chronic hepatitis C.

Recently, the Protease Inhibition for Viral Evaluation (PROVE, evaluating telaprevir) and Serine Protease Inhibitor Therapy (SPRINT, evaluating boceprevir) clinical trials have suggested that protease inhibitors combined with peg-IFN\(\alpha\) plus RBV could produce SVR rates of 70%-75% in treatment-naïve genotype 1 patients\(^\text{[80,89,90]}\). Telaprevir and boceprevir, orally bioavailable inhibitors of the HCV NS3 protease, are two of several investigational agents that specifically and directly target HCV with increased likelihood of SVR. In the PROVE studies, discontinuation of treatment because of adverse events was more frequent in telaprevir-based groups, with rash the most common reason for discontinuation. The frequencies of pruritus, rash and anemia were increased in telaprevir-based groups\(^\text{[86,87,91]}\). In the SPRINT-1 study, the most common adverse events leading to discontinuation in boceprevir regimens were fatigue, nausea, depression, neutropenia and anemia. Incidence of rash-related adverse events was similar in boceprevir regimens and control\(^\text{[86]}\).

More recently, the results of the PROVE-3 study showed that retreatment with telaprevir in combination with peg-IFN\(\alpha\)-2a plus RBV was more effective than retreatment with peg-IFN\(\alpha\)-2a plus RBV alone in patients who failed to show SVR to the initial full course of peg-IFN\(\alpha\) plus RBV\(^\text{[91]}\). The SVR rates of three telaprevir-treated groups: 51% in the T12PR24 group (telaprevir for 24 wk and peg-IFN\(\alpha\)-2a for 24 wk), 53% in the T24PR48 group (telaprevir for 24 wk and peg-IFN\(\alpha\)-2a for 48 wk), and 24% in the T24P24 group (telaprevir and peg-IFN\(\alpha\)-2a for 24 wk), were significantly higher than that of the PR48 (control) group (peg-IFN\(\alpha\)-2a and RBV for 48 wk; 14%; P < 0.001, P = 0.02, respectively). Patients with a previous relapse in the T12PR24 and T24PR48 groups had SVR rates of 69% and 76%, respectively. Of note, those with a previous non-response had SVR rates of 39% and 38%, respectively, which are the highest reported to date and more than four times the SVR in the control group (9%). The higher discontinuation rates and the lower relapse rates in the T24PR48 group compared with the T12PR24 group suggest that an optimal retreatment regimen may consist of a shorter period of treatment with telaprevir combined with a longer period of treatment with peg-IFN\(\alpha\) and RBV.

In the SPRINT-1 study, boceprevir in combination with peg-IFN\(\alpha\)-2a (P) plus RBV (R) was more effective than P/R for 48 wk (control)\(^\text{[90]}\). The SVR rates of four boceprevir-treated regimens: 56% or 75% after 4 wk of P/R lead-in followed by P/R/boceprevir for 24 or 44 wk, and 55% or 67% after P/R/boceprevir for 28 or 48 wk, were significantly higher than that of the control (38%; P
The addition of STAT-C agents, such as telaprevir, to current standard treatment adds promising antiviral activity and is one of the most powerful retreatment strategies, especially for the non-responder population.

LONG-TERM EFFECT OF IFN TREATMENT ON THE PROGRESSION OF LIVER DISEASES

Retrospective cohort studies and preliminary randomized controlled trials

There are few satisfactory medical treatments for patients who do not achieve SVR in response to IFN-based treatment. In such patients, the liver disease could progress to cirrhosis, hepatocellular carcinoma (HCC) and liver failure, culminating in liver disease-related death. Earlier retrospective cohort studies suggested that conventional IFN treatment reduces the risk of HCC even in patients who are treated with a single course as brief as 6 mo and who show transient biochemical response but fail to eradicate HCV. In these non-randomized analyses, the short- or long-term efficacy of conventional IFN or impact of the treatment outcome on the clinical end point were evaluated based on serum ALT levels, but not the degree of viral response because serum HCV RNA levels were not monitored. These studies included patients with various disease stages (degree of fibrosis) and perhaps those with SVR at a certain rate. The SVR induced by conventional IFN treatment apparently provides a long-term benefit by reducing liver-related death. As shown by other retrospective cohort studies, it is conceivable that achievement of SVR following IFN-based treatment would reduce the risk of adverse clinical outcomes (liver-related complications, HCC and liver-related mortality) even in patients with cirrhosis or advanced fibrosis, compared to non-SVR. Furthermore, a small, prospective RCT suggested that even a single, brief (24-wk) course of conventional IFN treatment for patients with compensated cirrhosis (grade A on the Child-Pugh scoring system) could slow liver disease progression and reduce the cumulative incidence of HCC and mortality in the very long-term clinical course. Another RCT of extended conventional IFN treatment to 30 mo showed suppression of HCV RNA levels and reduction in serum ALT levels and histologic findings (necroinflammation and fibrosis) in non-responders to 6-mo conventional IFN treatment but with a histologic response. In that preliminary study, the majority of patients did not have advanced fibrosis or cirrhosis, and the impact of maintenance treatment on morbidity and mortality was not assessed. These favorable results encouraged clinicians to prevent progressive liver disease, including development of HCC and progression to cirrhosis and liver failure, with IFN-based maintenance treatment even in patients with advanced fibrosis or cirrhosis. However, most of the following prospective RCTs did not recommend long-term maintenance treatment for such patients.

Randomized controlled trials for advanced fibrosis and cirrhosis

A large, prospective RCT [the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial] also showed that maintenance treatment of peg-IFNα-2a at a dosage of 90 µg weekly for 3.5 years correlated significantly with decreases in serum HCV RNA levels, serum ALT levels and histologic necroinflammatory scores, compared to no treatment (P < 0.001), in patients with advanced fibrosis who had not achieved SVR to a standard regimen of peg-IFNα-2a plus RBV. Nevertheless, the maintenance treatment failed to reduce the rate of disease progression, as indicated by death, HCC, hepatic decompensation, or increase in the fibrosis score, in those with or without cirrhosis: 34.1% in the treatment group versus 33.8% in the control group (P = 0.90). Among patients with bridging fibrosis at baseline, cirrhosis developed by year 3.5 at rates similar in the two groups (28.2% vs 31.9%, respectively). Conversely, the rate of at least one serious adverse event was higher in the treatment group (38.6%) than in the control group (31.8%, P = 0.07).

In a substudy of the HALT-C trial, profound viral suppression by ≥ 4 log10 with standard-dose peg-IFN plus RBV during the 24-wk lead-in phase was significantly related to fewer clinically critical events (P = 0.003) over the ensuing 3.5 years, regardless of whether randomized to maintenance therapy or no treatment. Unexpectedly, persistent viral suppression by ≥ 4 log10 with maintenance therapy did not lead to a further reduction in clinical events. Thus, there is no rationale for peg-IFNα maintenance therapy in patients without viral suppression to undetectable levels during the treatment. Strangely, profound viral suppression even for a relatively brief period during the lead-in phase may be associated with clinical benefits.

In a small RCT, patients with biopsy-proven compensated cirrhosis who had at least one risk factor of complications were randomized to either conventional IFNα-2a (3 MU three times weekly) or no treatment for 24 mo. In the Colchicine Versus Pegintron Long-term Therapy (COPILOT) trial, patients with advanced fibrosis or cirrhosis who were non-responders to either conventional IFN or peg-IFNα with or without RBV were randomized to receive either peg-IFNα-2b at a dose of 0.5 µg/kg per week or colchicine for 4 years. In the study design of the Evaluation of Pegintron in Control of Hepatitis C Cirrhosis (EPIC3) trial, non-responders to a lead-in treatment phase of peg-IFNα-2b plus RBV were randomized to receive either peg-IFNα-2b at a dose of 0.5 µg/kg per week or no treatment for up to 3 years. Despite differences in the study design, the results of these trials were similar to those observed in the HALT-C trial; maintenance therapy with conventional IFN or peg-IFNα has little or no impact on prevention of progressive liver disease or complication-free survival in patients with advanced fibrosis.
or cirrhosis. In the COPilot and EPIC3 trials, however, maintenance therapy reduced complications almost exclusively in patients with portal hypertension.

The results of these prospective RCTs contradict those of the majority of retrospective, non-randomized cohort studies and earlier preliminary prospective RCTs. There were some differences among studies: the end points of disease events, inclusion criteria for the study, patients’ background involving wide-ranging fibrosis stage or advanced fibrosis/cirrhosis, race, and lifestyle (high calorie, cigarette smoking, or alcohol intake), and evaluation on the basis of the degree of viral suppression or decline in serum ALT. It is not clear why control patients in previous retrospective studies did not receive IFN-based treatment for long-term periods. These uncertainties may tip the balance in favor of the IFN-treated patient group. At the least, maintenance treatment with low-dose peg-IFNα or conventional IFN for 2-3.5 years does not appear to prevent disease progression in patients with advanced fibrosis/cirrhosis and persistent viremia, and thus provides no overall benefit to such patients. If maintenance therapy leads to profound viral suppression, it can potentially prevent progressive disease and liver-related complications.

**NEW INTERFERON AND ALTERNATIVE FORMS OF RIBAVIRIN**

The clinical trials of STAT-C agents, PROVE and SPRINT[40,90], suggest that peg-IFNα-2a or -2b and standard-dose RBV are required as indispensable components even in new combination regimens with the first-generation protease inhibitors, because treatment arms without ribavirin in the PROVE2 trial and with low-dose RBV in the SPRINT-1 trial showed increased viral breakthrough, higher relapse, and lower SVR. However, the addition of telaprevir or boceprevir resulted in higher rates of treatment discontinuation because of adverse events (rash, pruritus, and anemia), compared with the control arm. Furthermore, pre-existing resistant variants and naturally occurring resistance-related mutations against STAT-C agents would disturb the efficacy of “add-on” triple combination therapy[41,103]. To overcome these disadvantages resulting from the addition of STAT-C agents, alternative approaches to new treatment strategies are needed to increase the SVR rates and reduce adverse events by altering formulations of IFN and RBV.

**Albinterferon**

Recombinant human albumin-interferon α-2b (albinterferon, alb-IFN), a novel formulation of IFNα, is an 85.7-kDa protein consisting of IFNα-2b genetically fused to human albumin. In an in vitro study using liver cell-based and non-liver cell-based HCV replicon cell lines, alb-IFN preserved the antiviral properties of IFNα with significant suppression of HCV RNA at clinically relevant serum concentrations[104]. In a study of monkeys, alb-IFN had a prolonged elimination half-life, and consequently provided greater exposure relative to IFNα[105]. In dose-ranging phase 1/2 studies involving IFN-experienced and naïve patients, alb-IFN administration of up to 1200 µg at 14-d intervals demonstrated a favorable safety profile, the half-life was extended to approximate 144 h, and antiviral activity increased in a dose-dependent manner[106,107]. Alb-IFN was detectable throughout the entire dosing interval, corresponding to viral dynamic changes observed at doses of 900-1200 µg.

A phase 2b trial randomized naïve genotype 1 patients to four treatment arms: peg-IFNα-2a (180 µg once weekly), alb-IFN [900 or 1200 µg once every two weeks (q2wk), or 1200 µg once every four weeks (q4wk)] plus weight-based RBV (1000 or 1200 mg/d) for 48 wk[108]. The SVR rates in the 900-µg q2wk- and 1200-µg q2wk-alb-IFN groups (59% and 56%, respectively) were comparable to that in the peg-IFNα-2a group (58%), while SVR rate in the 1200-µg q4wk-alb-IFN group was lower (51%, P = 0.28). The discontinuation rates due to adverse events were comparable among the 900-µg q2wk- and 1200-µg q2wk-alb-IFN and peg-IFNα-2a groups (9%, 12%, and 6%, respectively), and higher for 1200-µg q2wk-alb-IFN (18%, P = 0.04). Another trial compared five alb-IFN-based regimens for non-responders to prior IFN-based treatment: 1200-µg q4wk and 900-, 1200-, 1500-, and 1800-µg q2wk plus RBV for 48 wk[109]. Although the overall SVR rate was only 11% for previous genotype 1 non-responders to peg-IFNα plus RBV, the trial suggested the potential advantage of higher doses of alb-IFN (1800 µg q2wk) and its promising antiviral activity. Taken together, alb-IFN is likely to have overall efficacy and safety profiles comparable to those of peg-IFNα-2a, with the convenience of a 2-wk to 4-wk interval dosing schedule. Interestingly, alb-IFN improves patients’ psychological condition and reduces missed workdays, and could further reduce the immunogenicity of IFN, compared to peg-IFNα.

**Taribavirin (Viramidine)**

Hemolytic anemia induced by RBV can cause fatigue, affect quality of life, and consequently result in dose reductions, which could lower the chance of SVR[2,3,45,49,110,111]. Erythropoietin preparations used to alleviate anemia and maintain RBV dose substantially increase medical expenses and may induce adverse effects[10,12]. Some protease and polymerase inhibitors exacerbate anemia observed with peg-IFNα plus RBV combination treatment[46,109]. Such cases strongly emphasize the need for an RBV analogue to alleviate hemolytic anemia.

Taribavirin (TBV, previously known as viramidine) is a prodrug of RBV being developed for combination treatment with peg-IFNα, in expectation of a lower incidence of anemia. The agent is a guanosine analogue that is primarily taken up by the liver and is rapidly converted to RBV by adenosine deaminase[113,114]. TBV-derived RBV is concentrated in the liver at three-fold the rate of native RBV[115]. Furthermore, TBV containing a positively charged 3-carboxamide group accumulates poorly in red blood cells (RBCs) and reduces RBV concentration in RBCs by half[104-110].
A phase 2 dose-ranging comparison of TBV vs RBV combined with peg-IFNα-2a (180 μg/week) evaluated TBV doses of 800, 1200 and 1600 mg/d and RBV at a weight-based dose of 1000 or 1200 mg/d. The SVR rates were lower in the TBV groups than in the RBV group (23%, 37%, 29% vs 44%), although anemia was significantly less in the TBV groups. The phase 3, double-blind, Viramidine's Safety and Efficacy versus Ribavirin 1 (ViSER1) study for naïve patients compared the safety and efficacy of flat-dose TBV (1200 mg/d) vs weight-based RBV (1000 or 1200 mg/d) in combination with peg-IFNα-2b (1.5 μg/kg per week). The SVR rates were 38% and 52%, respectively. The VR rate at every time point during the study was lower, and the relapse rate was higher in the TBV group. Thus, flat-dose TBV failed to show non-inferiority efficacy compared to weight-based RBV, suggesting that the dosage of TBV (1200 mg/d) is suboptimal or insufficient at least for a proportion of patients. However, the incidence of hemoglobin (Hb) events (Hb < 10 g/dL or a decrease of ≥ 2.5 g/dL from baseline) was significantly lower with TBV (55%) than with RBV (84%; P < 0.001). More patients were encountered in the TBV arm with diarrhea (30%) compared to the RBV arm (20%). The incidence of moderate or severe diarrhea in the former group was double that in the latter (10% vs 5%, respectively).

The ViSER2 study showed similar results of efficacy and safety. It was performed with the same study design, except for the usage of peg-IFNα-2a (180 μg once weekly, instead of peg-IFNα-2b). The SVR rate was 40% in the flat-dose TBV group and 55% in the weight-based RBV group. TBV was significantly superior to RBV in Hb event rates (54% vs 80%, P < 0.001). The rates of adverse events were similar between the groups except for diarrhea (TBV 30%; RBV 16%, P < 0.0001).

Similar to RBV, TBV appears to improve the SVR rate with higher TBV exposure based on body weight (mg/kg), and a dosage of > 18 mg/kg may be needed to produce SVR rates comparable to those of weight-based RBV. Therefore, further studies of TBV administered on a weight-based dosing schedule are required to determine the optimal dosage that would yield superior efficacy to, or at least comparable to, RBV, with preservation of the safety profile.

CONCLUSION
In summary, more optimal and highly individualized therapeutic strategies for HCV-infected individual patients are currently being investigated and developed, such as response-guided therapy, modified regimens with currently available medications, novel modified IFNα and RBV or combinations with STAT-C agents. In the foreseeable future, these ceaseless efforts will relieve a large number of HCV-infected patients all over the world.

REFERENCES
1. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49: 1335-1374
2. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrect JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958-965
3. Fried MW, Shiffman ML, Reddy KR, Smith C, Marininos G, Goesnel FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982
4. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzotto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140: 346-355
5. Jacobson IM, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, Becker S, Wakil AE, Pourd F, Godofsky E, Strauss R, Bernstein D, Flamm S, Pauly MP, Mukhopadhyay P, Griffin LH, Bras CA. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology 2007; 46: 971-981
6. Yoshioka K, Kakumu S, Wakita T, Ishikawa T, Itoh Y, Takayanagi M, Higashi Y, Shibata M, Morishima T. Detection of hepatitis C virus by polymerase chain reaction and response to interferon-alpha therapy: relationship to genotypes of hepatitis C virus. Hepatology 1992; 16: 293-299
7. Tsubota A, Chayama K, Iket K, Yasuji A, Koida I, Saitoh S, Hashimoto I, Iwasaki S, Kobayashi M, Hiromitsu K. Factors predictive of response to interferon-alpha therapy in hepatitis C virus infection. Hepatology 1994; 19: 1088-1094
8. Tsubota A, Kumada H, Chayama K, Arase Y, Saitoh S, Koida I, Murashima N, Suzuk Y, Kobayashi M, Takagi K, Kobayashi M, Ikeda K. Relationship between pretreatment viremia level and response to interferon-alpha therapy in chronic hepatitis C differs in viral type 1 and 2 infections. Dig Dis Sci 1996; 41: 1925-1932
9. Davis GL, Esteban-Mur R, Rusty V, Hoefs J, Gordon SC, Trepo C, Shiffman ML, Zeuzem S, Craxi A, Ling MH, Albrecht J. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N Engl J Med 1998; 339: 1493-1499
10. Poyart T, Marcellin P, Lee SS, Niederau C, Minuk GS, Igoe G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (HIT). Lancet 1998; 352: 1426-1432
11. Lee WM, Reddy KR, Tong MJ, Black M, van Leeuwen D, Hollinger FB, Mullen KD, Finstone N, Albert D, Gardner S. Early hepatitis C virus–RNA responses predict interferon treatment outcomes in chronic hepatitis C. The Consensus Interferon Study Group. Hepatology 1998; 28: 1411-1415
12. Neumann AU, Lam NP, Dahari H, Gretch DR, Wiley TE, Layden TJ, Perelson AS. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 1998; 282: 103-107
13. Yassu K, Okanooue T, Murakami Y, Itoh Y, Minami M, Sakamoto S, Sakamoto M, Nishioji K. Dynamics of hepatitis C viremia following interferon-alpha administration. J Infect Dis 1998; 177: 1475-1479
14. Zeuzem S, Lee JH, Franke A, Rüster B, Prümmer O, Herrmann G, Roth WK. Quantification of the initial decline of serum hepatitis C virus RNA and response to interferon alfa. Hepatology 1998; 27: 1149-1156
15. Neumann AU, Lam NP, Dahari H, Davidian M, Wiley TE, Mika BP, Perelson AS, Layden TJ. Differences in viral dynamics between genotypes 1 and 2 of hepatitis C virus. J
Effect of combined interferon-alpha induction therapy and ribavirin on chronic hepatitis C virus infection: a randomized multicentre study. *Scand J Gastroenterol* 2002; 37: 226-232

Tsubota A, Arase Y, Someya T, Suzuki Y, Saitoh S, Ikeda K, Akuta N, Hosaka T, Kobayashi M, Kumada H. Early viral kinetics and treatment outcome in combination of high-dose interferon induction vs. pegylated interferon plus ribavirin for naive patients infected with hepatitis C virus of genotype 1b and high viral load. *J Med Virol* 2005; 77: 24-38

Ferri P, Fried MW, Shiffman ML, Smith CI, Marinatos G, Gonçalves FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Chanac M, Reddy KR. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol* 2005; 43: 425-433

Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallaee M, Heaton S, Conrad A, Pockros PJ, McG Hutchison JG. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. *J Hepatol* 2004; 40: 484-490

Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT, Lok AS, Morgan TR, Bonkovsky HL, Lee WM, Dienstag JL, Ghany MG, Goodman ZD, Everhart JE. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Hepatology* 2004; 39: 1261-1269; discussion 947

Zeuzem S, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Ferenci P, Zacks S, Afdhal NH, Wahed AS. Race, insulin resistance and genotype 1b and high viral load. *Hepatology* 2005; 41: 108-115

Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ. Telaprevir with peginterferon and ribavirin for naive patients infected with hepatitis C virus of genotype 1b in high viral loads. *Dig Dis Sci* 2009; 54: 1317-1324

Okanoue T, Itto Y, Hashimoto H, Yasui K, Minami M, Takehara T, Tanaka E, Onji M, Toyota J, Chayama K, Yoshioka I, Izumi N, Akuta N, Kumada H. Predictive values of amino acid sequences of the core and NS5A regions in antiviral therapy for hepatitis C: A Japanese multi-center study. *J Gastroenterol* 2004; 39: 952-963

Tsubota A, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugach H, Izumi N, Tokunaga K, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; 41: 1105-1109

Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinez EL, Qui P, Bertsch AH, Muir AJ, Sulkowski M, Mc Hutchison JG, Goldstein DB. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461: 399-401

Suppia V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore CJ, Powell E, Riornd S, Sheridan D, Smedley A, Fragomelli V, Muller T, Bahlo M, Stewart GJ, Booth DR, George J. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; 41: 1100-1104

Lau JY, Simmonds P, Urdea MS. Implications of variations of “conserved” regions of hepatitis C virus genome. *Lancet* 1995; 346: 425-426

Dalgard O, Bjørkø, Hellum KB, Myrvang B, Ritland S, Skaug K, Raknerud N, Bell H. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology* 2004; 40: 1260-1265

von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, Bergk A, Bernsmeier C, Häussinger D, Herrmann E, Zeuzem S. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005; 129: 522-527

Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY, Chiu CF, Lin ZY, Chen SC, Hsieh MY, Wang LY, Chang WY, Chuang WL. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut* 2007; 56: 553-559

Dalgard O, Bjørkø, Ring-Larsen H, Bjørnsson E, Holberg-Petersen M, Skovlund E, Reichard O, Myrvang B, Sundelof R, Ritland S, Hellum K, Frydén A, Florholmen J, Verbaan P. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008; 47: 35-42

Mc Hutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffmann R, McNair L, Alam J, Muir AJ, Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; 360: 1827-1838

Kieffer TL, Sarrazin C, Miller JS, Welker MW, Forestier N, Reesink HW, Kwong AD, Zeuzem S. Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant hepatitis C virus replication in patients. *Hepatology* 2007; 46: 631-639

Sarrazin C, Kieffer TL, Bartels D, Hanzelka B, Müh U, Welker M, Wincheringer D, Zhou Y, Chu HM, Lin C, Weegink C, Reesink H, Zeuzem S, Kwong AD. Dynamic hepatitis C virus genotype and phenotypic changes in patients treated with the protease inhibitor telaprevir. *Gastroenterology* 2007; 132: 1767-1777

Sussen S, Welsch C, Wang Y, Zettler M, Domingues FS, Karrey U, Hughes E, Ralston R, Tong X, Herrmann E, Zeuzem
S, Sarrazin C. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. *Hepatology* 2009; 50: 1709-1718

44 Hayashi K, Kadoyo Y, Ishigami M, Itoh A, Hirooka Y, Nakano I, Uramo F, Yoshiduka K, Toyoda H, Kumada T, Goto H. Mutations in the core and NS5A region of hepatitis C virus genotype 1b and correlation with response to pegylated-interferon-alpha 2b and ribavirin combination therapy. *J Viral Hepat* 2010; Epub ahead of print

45 Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrect J. Early virologic response to treatment with peginterferon alpha-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2005; 38: 645-652

46 Afshald NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sułkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, Bowers PJ. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004; 126: 1302-1311

47 Bronowicki JP, Ouzan D, Asselah T, Desmotar H, Zarski JP, Foucher J, Bouriére M, Renou C, Tran A, Melin P, Hézode C, Chevaller M, Bouvier- Alias M, Chevallès S, Montestruc F, Lonjon-Domance J, Pawlotsky JM. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alpha-2a plus ribavirin. *Gastroenterology* 2006; 131: 1040-1048

48 Reddy KR, Shiffman ML, Morgan TR, Zeuzem S, Hadziyannis S, Hamzeh FM, Wright TL, Fried M. Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin Gastroenterol Hepatol* 2007; 5: 124-129

49 McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J, Lee WM, Mak C, Garaud J, Albrect JK. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002; 123: 1061-1069

50 Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, Ferenci P, Ackell AM, Willemis B. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006; 43: 954-960

51 Martinez-Bauer E, Crespo J, Romero-Gómez M, Moreno-Otero R, Solà R, Tesei N, Pons F, Forns X, Sánchez-Tapias JM. Development and validation of two models for early prediction of response to therapy in genotype 1 chronic hepatitis C. *Hepatology* 2006; 43: 72-80

52 Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara M, Ibrayni E, Weiland O, Noviello S, Brass C, Albrect J. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. *J Hepatology* 2006; 44: 97-103

53 Bárquez R, Moreno A, del Campo S, Muriel A, Mateos ML, Garrido E, García M, Quereda C, Moreno S, Moreno A. The magnitude of week 4 HCV RNA decay on pegylated interferon/ribavirin accurately predicts virological failure in patients with genotype 1. *Antivir Ther* 2007; 12: 401-406

54 Fried MW, Jensen DM, Rodriguez-Torres M, Nyberg LM, Di Bisceglie AM, Morgan TR, Pockros PJ, Lin A, Cupelli L, Duff F, Wang K, Nelson DR. Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon alpha-2a and ribavirin. *Hepatology* 2008; 48: 1033-1043

55 Ferenci P, Laffer H, Scherzer TM, Gschwantler M, Maieron A, Brunner H, Staubler R, Bischof M, Bauer B, Datz C, Löshenberger K, Formann E, Staufer K, Steindl-Munda P. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C genotype 1 and 4 patients with rapid virologic response. *Gastroenterology* 2008; 135: 451-458

56 Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, Buggisch P, Goesaert T, Rasenack J, Pape CR, Schmidt WE, Kallinowski B, Klinker H, Spengler U, Martin P, Alshuth U, Zeuzem S. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; 130: 1086-1097

57 Sánchez-Tapias JM, Diago M, Escartín P, Enríquez J, Romeño-Gómez M, Bárcena R, Crespo J, Andrade R, Martinez-Bauer E, Pérez R, Testillano M, Planas R, Solà R, García-Bengochea M, García-Samaniego J, Muñoz-Sánchez M, Moreno-Otero R. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006; 131: 451-460

58 Pearlman BL, Echleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. *Hepatology* 2007; 46: 1688-1694

59 Poynard T, McHutchison J, Goodman Z, Ling MH, Albrect J. Is an “a la carte” combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOCVIR Project Group. *Hepatology* 2000; 31: 211-218

60 Kamal SM, El Kamaray SS, Shardell MD, Hashem M, Ahmed IN, Muhammad M, Sayed K, Moustaafa A, Hakem SA, Ibrahim A, Moniem M, Mansour H, Abdelaziz M. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response. *Hepatology* 2007; 46: 1732-1740

61 Ferenci P, Laffer H, Scherzer TM, Maieron A, Hofer H, Stauber R, Gschwantler M, Brunner H, Weinisch C, Bischof M, Strasser M, Datz C, Vogel W, Löshenberger K, Steindl-Munda P. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C, genotype 1 and 4 patients with slow virologic response. *Gastroenterology* 2010; 138: 503-512, 512.e1

62 Lagging M, Langeland N, Pedersen C, Färkkilä M, Buhl MR, March K, Dhillon AP, Alsiö A, Hellstrand K, Westin J, Norkrans G. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. *Hepatology* 2008; 47: 1837-1845

63 Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annesi M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005; 352: 2609-2617

64 Mangia A, Minerva N, Bacca D, Cozzolongo R, Agostinacchino E, Sogari F, Scotto G, Vinelli F, Ricci GL, Romano M, Carretta V, Petruzellis D, Andriulli A. Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2009; 49: 358-363

65 Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Solà R, Shafraan SD, Barange K, Lin A, Somar A, Zeuzem S. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007; 357: 2609-2617

66 Tsubota A, Satoh K, Aizawa M, Takamatsu S, Namiki Y, Ohkusa T, Fujise K, Taji H. Four-week pegylated interferon alpha-2a monotherapy for chronic hepatitis C with genotype 2 and low viral load: a pilot, randomized study. *World J Gastroenterol* 2010; 16: 7220-7224

67 Bailon P, Palleroni A, Schaffer CA, Spence CL, Fung WJ, Porter JE, Ehrlich GK, Pan W, Xu ZX, Modi MW, Farid A, Berthold W, Graves M. Rational design of a potent, long-lasting form of interferon: a 40 kDa branched polyethylene glycol-conjugated interferon alpha-2a for the treatment of hepatitis C. *Bioconjug Chem* 2001; 12: 195-202

68 Youngster S, Wang YS, Grace M, Bausch J, Bordens R, Wyss DF. Structure, biology, and therapeutic implications of pegylated interferon alpha-2b. *Curr Pharm Des* 2002; 8: 2139-2157

69 Zeuzem S, Welsch C, Herrmann E. Pharmacokinetics of peginterferons. *Semin Liver Dis* 2003; 23 Suppl 1: 23-28

70 Foster GR. Review article: pegylated interferons: chemical and clinical differences. *Aliment Pharmacol Ther* 2004; 20.
825-830
71 Bruno R, Sacchi P, Ciappina V, Zochetti C, Patruno S, Maiocchi L, Filice G. Viral dynamics and pharmacokinetics of peginterferon alpha-2a and peginterferon alpha-2b in naive patients with chronic hepatitis C: a randomized, controlled study. *Antivir Ther* 2004; 9: 491-497
72 Silvia M, Poo J, Wagner F, Jackson M, Cutler D, Grace M, Bordin R, Cullen C, Harvey J, Laughlin M. A randomised trial to compare the pharmacokinetic, pharmacodynamic, and antiviral effects of peginterferon alfa-2b and peginterferon alfa-2a in patients with chronic hepatitis C (COMPARÉ). *J Hepatol* 2006; 45: 231-239
73 Di Bisceglie AM, Ghahri RH, Hammond FM, Rustgi VK. Early virologic response after peginterferon alfa-2b plus ribavirin or peginterferon alfa-2b plus ribavirin treatment in patients with chronic hepatitis C. *J Viral Hepat* 2007; 14: 712-729
74 Bruno R, Sacchi P, Scagnolari C, Torrionni F, Maiocchi L, Patruno S, Belloni F, Filice G, Antonelli G. Pharmacodynamics of peginterferon alpha-2a and peginterferon alpha-2b in interferon-naive patients with chronic hepatitis C: a randomized, controlled study. *Aliment Pharmacol Ther* 2007; 26: 369-376
75 Witthoeft T, Hueppe D, John C, Goetz J, Meyer U, Heyne R, Moeller b, Link R, Teuber G, Sworsitz S, Herrmann A, Wollsslaeger A, Baumgarten A, Simon KG, Cordes H-J, Moog G, Dikopoulos N, Mauss S. Efficacy and safety of peginterferon alfa-2a or -2b plus ribavirin in the routine daily treatment of chronic hepatitis C patients in Germany: the PRACTICE study. *J Hepatol* 2008; 48 (Suppl 2): S519
76 Awad T, Thorlund K, Hauser G, Stima D, Mabrouk M, Glud C. Peginterferon alfa-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. *Hepatology* 2010; 51: 1176-1184
77 Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, Moreno-Otero R, Carrilho F, Schmidt W, Berg T, McGarry T, Heathcote EJ, Gonçalves F, Di Bisceglie AM, Bonkovsky HL, Ghany MG. Effect of prolonged therapy of advanced chronic hepatitis C patients who failed to respond to interferon/ribavirin therapy: final results of the EPIC3 cirrhosis maintenance trial. *J Hepatol* 2010; 52: 213-219
78 Afdhal NH, Levine R, Brown R, Freilich B, O’Brien M, Brass C. Colchicine versus peginterferon alfa 2b long term therapy: results of the 4-year COPilot trial. *J Hepatol* 2008; 48 (Suppl 2): S46
79 Bruix J, Poynard T, Colombo M, Schiff E, Reichen J, Burak K, Heathcote EJL, Berg T, Po-Pamirez J-L, Brandao Mello CE, Reddy KR, Martin AO, Brandes A, Albrecht J. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology* 2009; 136: 1618-1628.e2
80 Bihl AM, Dukic M, Moreo F, Onorati R, Bartoli C, Versaci C, Ricci S, Forloni M, Cassoni P, Iannini C, La Rana G, Mattioli E, Puddu P, Nobile-Orazio E, Ponz de Leon M, Parenti S, Zavaglia R, Labarthe D, Ponzetto S, Hézode C, Saccucci M, Bismuth CH, Di Bisceglie AM, Bonkovsky HL, Ghany MG, Fattovich G, Santoro G, Yoshikawa H, Yamamoto Y, Iwakiri A, Ikeda T, Shioda K, Shiozaki K, Moriyama Y, Koyama S, Nakamura Y, Chisato M, Endo M, Ohashi T, Sato T, Saitoh K, Kuroki T, Yoshino S, Ikeda M, Hino K, Oka K. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. *J Hepatol* 2010; 53: 719-729
81 Camar D, Marcellin P, Muir AJ, Terrault NA, Jadavji A, Marcellin P, Freilich B, Andreone P, Di Bisceglie AM, Brandão-Mello CE, Reddy KR, Craxi A, Martin AO, Teuber G, Messinger D, Thommes JA, Tietz A. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2a: a randomized trial. *Ann Intern Med* 2009; 150: 528-540
82 Camma C, Cabibbo G, Bronte F, Enea M, Licata A, Attanasio M, Andriulli A, Craxi A. Retreatment with pegylated interferon plus ribavirin of chronic hepatitis C non-responders to interferon plus ribavirin: a meta-analysis. *J Hepatol* 2009; 51: 675-681
83 Soriano V, Peters MG, Zeuzem S. New therapies for hepatitis C virus infection. *Clin Infect Dis* 2009; 48: 313-320
84 Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology* 2010; 138: 447-462
85 Hézode C, Forestier N, Dusheiko G, Ferenci P, Sol S, Goesen T, Bronwicki J, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pavlovsky JM, Zeuzem S. Telaprevir and peginteron or with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; 360: 1839-1850
86 Kwo P, Lawitz E, McConie J, Schiff E, Vierling J, Pound D, Davis M, Galati J, Gordon S, Rabendran H, Rossaro L, Anderson F, Jacobson I, Rubin R, Koury K, Brass C, Chaudhri E, Albrecht J. HCV SPRINT-1: final results: SVR 24 from a phase 2 study of boceprevir plus peginterferon(peginterferon alfa-2b)/ribavirin in treatment-naive subjects with genotype-1 chronic hepatitis C. *J Hepatol* 2009; 50 (Suppl 1): 54
87 McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, Bsharat M, George S, Kauffman RS, Adda N, Di Bisceglie AM. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; 362: 1292-1303
88 Imai Y, Kawata S, Tamura S, Yabuchi I, Noda S, Inada M, Maeda Y, Shirai Y, Fukuizuki T, Kaji I, Ishikawa H, Matsuda Y, Nishikawa M, Seki K, Matsuayama Y. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. *Osaka Hepatocellular Carcinoma Prevention Study Group. Ann Intern Med* 1998; 129: 94-99
89 Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioa K, Kukumoto S, Iijima A, Urushihara A, Kiyosawa K, Okuda M, Hino K, Oka K. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. *Osaka Liver Disease Study Group. Hepatology* 1998; 27: 1394-1402
90 Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi H, Tsubota A, Nomura N, Nakamura I, Marusawa N, Kumada H, Kawanishi M. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis C type C: A long-term observation study of 1,643 patients using statistical analysis. *J Hepatol* 1999; 30: 491-497
91 Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinozama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan.
IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999; 131: 174-181

Imazeki F, Yokosuka O, Fukai K, Saisho H. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. *Hepatology* 2003; 38: 495-502

Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnu L, Mazzella G, Ascione A, Santantonio T, Piccinino F, Andreone P, Mangia A, Gaeta GB, Persico M, Fagioli S, Almasio PL. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007; 45: 579-587

Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007; 147: 677-684

Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, Beyer N, Asselah T, Martinot-Peignoux M, Maylin S, Carvalho-Filho RJ, Valla D, Bedossa P, Marcellin P. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol* 2010; 52: 652-657

Nishiguchi S, Shiomi S, Nakatani S, Takeda F, Fukuda K, Tamori A, Habu D, Tanaka T. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet* 2003; 357: 196-197

Shiffman ML, Hofmann CM, Contos MJ, Luketich VA, San-yal AJ, Sterling RK, Ferreira-Gonzalez A, Mills AS, Garrett C. A randomized, controlled trial of maintenance interferon therapy for patients with chronic hepatitis C virus and persistent viremia. *Gastroenterology* 1999; 117: 1164-1172

Farouk L, Degos F, Trepo C, Goria O, Cales P, Tran A, Bufe t C, Poynard T, Capron D, Raabe J, Roulot D, Naveau S, Grange JD, Poupon RE, Poupon R, Serfaty L. Effect of prolonged interferon therapy on the outcome of hepatitis C virus-related cirrhosis: a randomized trial. *Clin Gastroenterol Hepatol* 2007; 5: 502-507

Kuntzen T, Timm J, Berical A, Lennon N, Berlin AM, Young SK, Lee B, Heckerman D, Carlson J, Reyor LL, Kleyman M, McMahon CM, Birch C, Schulze Zur Wiesch J, Ledlie T, Koehrsen M, Kodira C, Roberts AD, Lauer GM, Rosen HR, Bihl F, Cerny A, Spengler U, Liu Z, Kim AY, Xing Y, Schneidewind A, Madey MA, Fleckenstein JF, Park VM, Galagan J, Nusbaum C, Walker BD, Lake-Bakaar GV, Daar ES, Jacobson IM, Gomperts ED, Edlin BR, Donfield SM, Chung RT, Talal AH, Marion T, Birren BW, Henn MR, Allen TM. Naturally occurring dominant resistance mutations to hepatitis C virus protease and polymerase inhibitors in treatment-naive patients. *Hepatology* 2008; 48: 1769-1778

Liu C, Zhu H, Subramanian GM, Moore PA, Xu Y, Nelson DR. Anti-hepatitis C virus activity of albinferon alfa-2b in cell culture. *Hepatol Res* 2007; 37: 941-947

Osborn BL, Olsen HS, Nardelli B, Murray JH, Zhou JX, Garncia A, Moody G, Zaritskaya LS, Sun C. Pharmacokinetic and pharmacodynamic studies of a human serum albumin-interferon-alpha fusion protein in cynomolgus monkeys. *J Pharmacol Exp Ther* 2002; 303: 540-548

Bain VG, Kaiya KD, Yoshida EM, Swain MG, Heathcote EJ, Neumann AU, Fiscella M, Yu R, Osborn BL, Cronin PW, Freimuth WW, McHutchison JG, Subramanian GM. A phase 2 study to evaluate the antiviral activity, safety, and pharmacokinetics of recombinant human albumin-interferon alpha fusion protein in genotype 1 chronic hepatitis C patients. *J Hepatol* 2006; 44: 671-678

Balan V, Nelson DR, Sulkowski MS, Everson GT, Lambiase LR, Wiesner RH, Dickson RC, Post AB, Redfield RR, Davis GL, Neumann AU, Osborn BL, Freimuth WW, Subramanian GM. A Phase 1/II study evaluating escalating doses of recombinant human albumin-interferon-alpha fusion protein in chronic hepatitis C patients who have failed previous interferon-alpha-based therapy. *Antivir Ther* 2006; 11: 35-45

Zeuzem S, Yoshida EM, Benhamou Y, Panico S, Bain VG, Shouval D, Fliksiak R, Rehak V, Grigorescu M, Kaita K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchion JC. Albinterferon alfa-2b dosed every two or four weeks in interferon-naive patients with genotype 1 chronic hepatitis C. *Hepatology* 2008; 48: 407-417

Nelson DR, Rustgi V, Balan V, Sulkowski MS, Davis GL, Muir AJ, Lambiase LR, Dickson RC, Weisner RH, Fiscella M, Cronin PW, Pulkstenis E, McHutchion JC, Subramanian GM. Safety and antiviral activity of albinterferon alfa-2b in prior interferon nonresponders with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2009; 7: 212-218

Gaeta GB, Precone DF, Felaco FM, Bruno R, Spadaro A, Stornaiuolo G, Stancione M, Ascione T, De Sena R, Campa none A, Fichler G, Piccinino F. Premature discontinuation of interferon plus ribavirin for adverse effects: a multicentre survey in ‘real world’ patients with chronic hepatitis C. *Al i ment Pharmacol Ther* 2002; 16: 1633-1639

Takaki S, Tsunoba A, Hosaka T, Akuta N, Soweta T, Kobayashi M, Sufuki H, Saiito S, Saitho S, Arase Y, Ikeda K, Kumada H. Factors contributing to ribavirin dose reduction due to anemia during interferon alfa-2b and ribavirin combination therapy for chronic hepatitis C. *J Gastroenterol* 2004; 39: 668-673

Dieterich DT, Wasserman R, Bräun N, Hassanein TI, Bini EJ, Bowers PJ, Sulkowski MS. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *Am J Gastroenterol* 2003; 98: 2491-2499

Wu JZ, Walker H, Lau JY, Hong Z. Activation and deactivation of a broad-spectrum antiviral drug by a single enzyme: adenosine deaminase catalyzes two consecutive deamination reactions. *Antimicrob Agents Chemother* 2003; 47: 426-431

Wu JZ, Lin CC, Hong Z. Ribavirin, viramidine and adenos ine-deaminase-catalysed drug activation: implication for nucleoside prodrug design. *Antimicrob Chemother* 2003; 52: 543-546

Lin CC, Yeh LT, Vitarella D, Hong Z. Viramidine, a prodrug of ribavirin, shows better liver-targeting properties and safety profiles than ribavirin in animals. *Antivir Chem Chemother* 2003; 14: 145-152

Lin CC, Lourenco D, Xu G, Yeh LT. Disposition and metabolic profiles of [14C]viramidine and [14C]ribavirin in rat and monkey red blood cells and liver. *Antimicrob Agents Chemother* 2004; 48: 1872-1875

Gish RG, Arora S, Rajender Reddy K, Nelson DR, O’Brien C, Xu Y, Murphy B. Virological response and safety outcomes in therapy-naïve patients treated for chronic hepatitis C with ribavirin and ribavirin in combination with pegylated interferon alfa-2a: a randomized, phase 2 study. *J Hepatol* 2007; 47: 51-59

Benhamou Y, Afndahl NH, Nelson DR, Shiffman ML, Hal liman DG, Heise J, Chun E, Pockros PJ. A phase III study of the safety and efficacy of viramidine versus ribavirin in treatment-naive patients with chronic hepatitis C: VIsERI results. *Hepatology* 2009; 50: 717-726

Marcellin P, Gish RG, Gitlin N, Heise J, Halliman DG, Chun E, Rodriguez-Torres M. Safety and efficacy of viramidine versus ribavirin in VisER2: randomized, double-blind study in therapy-naïve hepatitis C patients. *J Hepatol* 2010; 52: 32-38

Yennie N, Mehtap O, Gümrah M, Arican N. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. *Turk J Gastroenterol* 2006; 17: 94-98

S-Editor Wang JL, L-Editor Logan SN, E-Editor Lin YP