

HEPATOLOGY

Treatment of chronic hepatitis C in Asia: When East meets WestMing-Lung Yu*[†] and Wan-Long Chuang*[†]*Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, and [†]Hepatobiliary Division, Faculty of Internal Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan**Key words**

HCV, individualized therapy, interferon, peginterferon, ribavirin, roadmap.

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Abstract

The issue of best treatment for chronic hepatitis C virus (HCV) infection is in constant flux, not only in Western countries but also in Asia. Currently, pegylated-interferon plus ribavirin is the standard of care. Studies from Asia provide evidence to support the same broad treatment strategies for Asian patients as recommended in Western countries. Nevertheless, there is increasing evidence that Asians have a higher likelihood of achieving a sustained virological response (SVR) than their Caucasians counterparts when treated with the corresponding regimen. With the recommended 'standard dose and duration treatment regimens', SVR is achieved in Asia for around 70% of HCV genotype 1 (HCV-1) infected cases, ~ 90% of HCV-2/3, ~ 65% of HCV-4, and ~ 80% of HCV-6 patients. Difference of body weight in race might contribute the superior response in Asian patients. HCV genotype distribution in Asia also differs from North-America/Europe. HCV-6 and its variants, previously mistyped as HCV-1, needs accurate genotyping. Increasing data support the proposal that HCV genotype, baseline viral load and on-treatment virological response provide information for decision-making so that treatment can be individualized. Beyond the older recommendations, an abbreviated 24-week regimen could be suggested for HCV-1/4 patients with baseline viral loads < 400 000 IU/mL and a rapid virological response (RVR, HCV RNA undetectable at week 4), and an abbreviated 12–16 weeks of pegylated-interferon with weight-based doses of ribavirin could be suggested for HCV-2/3 patients with a RVR. Such tailored treatment regimens can reduce the costs of treatment and incidence of adverse events without compromising efficacy.

Hepatitis C virus (HCV) infection is one of the most important causes of cirrhosis worldwide, and particularly in some countries

of Asia (notably Japan) where it is now more prevalent than chronic hepatitis B virus infection. Hepatitis C virus infection can also lead to hepatocellular carcinoma (HCC). It is estimated that there are more than 170 million people chronically infected with HCV, and 3 to 4 million persons are newly infected each year.¹ The risk for developing cirrhosis 20 years after initial HCV infection among those chronically infected varies between studies, but is estimated at around 10%–15% for men and 1–5% for women.² Once cirrhosis is established, the rate of developing HCC is at 1%–4% per year. Approximately 280 000 deaths per year are related to HCV infection.¹ Hepatitis C virus-related end-stage liver disease and HCC have become the leading cause for liver transplantation worldwide.³ In the Asia-Pacific area, the estimated prevalence of antibodies to HCV (anti-HCV) range from 0.3% in New Zealand to 5.6% in Thailand.^{3–5} In Japan, Middle East, Vietnam and Taiwan, several HCV hyper-endemic areas have been reported with an anti-HCV prevalence rate of 12% to as high as 58%.^{3,6} In addition to the well-known endemic status of HBV infection in most countries of the Asia-Pacific region, HCV infection presents another critical scenario of public health issue in this region, as outlined in Guidelines by the Asia-Pacific Association for Study of the Liver (APASL).³ Given the lack of an effective vaccine, optimal treatment of chronic HCV infection is now perceived as a 'must' in terms of public health strategies, as well as of the clinical setting for individual patients.

Distribution of HCV genotypes in the Asia-Pacific region

Understanding the distribution of HCV genotypes, which are now classified into 6 major genotypes and more than 50 subtypes, is very important as part of a molecular clue for spread of HCV,⁷ and

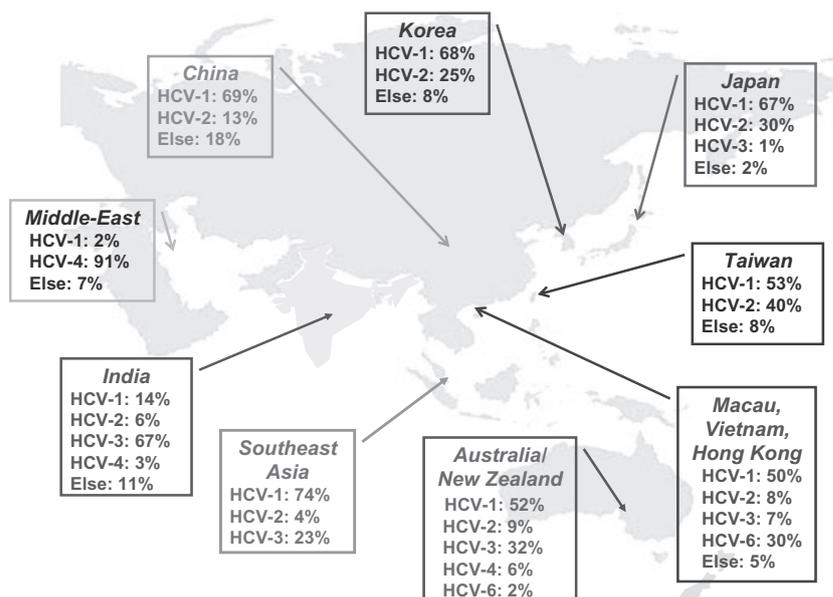


Figure 1 Distribution of HCV genotypes in Asia-Pacific region. HCV, hepatitis C virus.

an algorithm for individualization of therapy.^{1,3} Genotypes 1a (HCV-1a), 1b, 2a, 2b, and 3a are distributed globally and account for the majority of HCV infections worldwide. HCV-1b, the most common genotype worldwide, is also the dominant genotype in Asia-Pacific, particularly in Japan, South Korea, China and Taiwan. HCV-2a and 2b are also commonly distributed, in particular in Japan South Korea and southern Taiwan.⁶⁻⁸ HCV-3 is highly prevalent on the Indian subcontinent, Southeast Asia, Australian and New Zealand.^{9,10} Recent evidence indicates that HCV-3a is currently the most prevalent genotype in intravenous drug abusers (IDU) patients with an increasing trend of dissemination globally.^{7,11} Other HCV genotypes are more geographically restricted. HCV-4 is predominantly found in the Middle East and North Africa.^{12,13} HCV-5 was limited to South Africa,¹⁴ and HCV-6 was predominantly found in South-East Asia.¹⁵ Recently, genotypes 7 to 11 have been identified in South-East Asia; they appear to be the variants of HCV-3 (genotype 10a) and HCV-6a (genotypes 7, 8, 9, 11) and have been re-classified as subtypes of genotypes 3 and 6.⁷ The most used target region for genotype determination is the 5' untranslated region (5'UTR) of the viral genome. However, a limitation of the method is that HCV-6c-1, highly prevalent in the Asia-Pacific region, can be incorrectly classified as HCV-1b because they share similar nucleotide homology in the 5'UTR.³ The inability to distinguish HCV-6 subtypes might impact on predicted SVR to interferon (IFN)-based therapies in patients with apparent HCV-1 infection.¹⁶ Addition of Core motifs could improve the discrimination between HCV-1 and HCV-6.¹⁷ Epidemiological studies have disclosed that the prevalence of HCV genotypes has evolved with time due to independent HCV outbreaks or changes in the predominant route of transmission (Fig. 1).⁶ The HCV-1b has been associated with disease progression and risk of HCC development.^{6,18,19} Nevertheless, whether there exists intrinsic pathogenicity of HCV genotypes remains controversial. Chronic HCV-3 infection is associated with cytopathic steatosis due to blockade of lipoprotein secretion during

viral replication;²⁰ while metabolic steatosis in non-HCV-3 infected patients is predominantly due to virus induced insulin resistance.²¹ The importance of the HCV genotype for response to IFN-based treatments will be discussed later.

Evolution of treatment for chronic Hepatitis C

The primary goal of treatment for chronic hepatitis C is a sustained virological response (SVR), defined as HCV RNA levels less than 50 IU/mL at the end of 24 weeks follow-up after cessation of therapy.¹ SVR has been shown to be durable up to 18 years after treatment cessation; only 1.7% patients had residual HCV RNA in liver tissue, strongly suggesting that SVR may be considered to show eradication of HCV infection.²² Achieving the endpoint of SVR have been associated with persistent regression of hepatic fibrosis, reduced incidence of cirrhosis, HCC and liver-related mortality.^{19,22-26}

Definition of virological responses for treatment of Hepatitis C

Four on-treatment, and three off-treatment virological responses to antiviral therapy for hepatitis C have emerged over the past decade (Fig. 2).²⁷⁻²⁹ They include the following:

- 1 Rapid virological response (RVR):** polymerase chain reaction (PCR)-seronegative (≤ 50 IU/mL) of HCV RNA after 4 weeks of therapy.
- 2 Early virological response (EVR):** PCR-seronegative of HCV RNA or at least a two logs decrease of HCV RNA from baseline after 12 weeks of therapy. Recently, EVR has been suggested to be subdivided into RVR, complete EVR [cEVR] (no RVR, but HCV RNA < 50 IU/mL at week 12) and partial EVR [pEVR] (HCV RNA > 2 log drop in HCV RNA but still detectable [> 50 IU/mL] at week 12) to further

In a multicenter, randomized controlled study in Taiwan, 24 weeks of PegIFN/ribavirin achieved an SVR rate of 67%.⁴⁵ However, the response was not better than that with 24 weeks of conventional IFN/ribavirin (64%) in intention-to-treat analysis because of high rate of treatment discontinuation in the PegIFN/ribavirin arm. The superiority of PegIFN/ribavirin became significant when including patients who completed 48 weeks of treatment and follow-up periods (82% vs 68%, $P = 0.03$, per-protocol analysis). The Bureau of National Health Insurance in Taiwan is therefore reimbursing HCV treatment using 24-week combination therapy for all genotypes. In a Japanese study, an SVR was attained among significantly more HCV-1b patients receiving PegIFN plus ribavirin 600–1000 mg/day than PegIFN monotherapy (61% vs 26%, $P < 0.001$).⁴⁶

Current treatment strategies for chronic hepatitis C—roadmap of individualized therapy

Genotype-guided therapy

The optimal treatment duration and ribavirin dose were investigated in an international multicenter randomized clinical trial in which all CHC patients received PegIFN- α -2a at a dose of 180 μ g plus ribavirin at a dose of 800 mg or standard 1000–1200 mg daily, for either 24 or 48 weeks.⁴⁷ In HCV-1 patients, 48 weeks regimen with standard dose of ribavirin had the highest SVR rate at 52%; whereas in HCV non-1 patients, neither the duration of treatment nor the dose of ribavirin had an impact on treatment results, with an average SVR rate of 81% (79%–84%). This study supports the current recommendations that patients with HCV-1 or 4 require 48 weeks of PegIFN- α therapy with standard doses of ribavirin, while a 24-week regimen with lower dose of ribavirin, 800 mg/day, is recommended for HCV-2 or -3 patients.^{1,3,48–50} It is noted, however, that this study actually enrolled very few HCV-4 cases, and subsequent studies have found some evidence that response with this genotype, so common in North Africa and the middle east, may actually be somewhere between HCV-1 and HCV-2/3.^{51–53}

With the recommended regimens, SVR was around 50% (42%–52%) among HCV-1 patients and 80% (76%–84%) among HCV-2/3 patients in white people-predominant clinical trials.^{43,44,47,54,55} In Asia, similar SVR rates of HCV-1 and HCV-2/3 patients were observed in China (44% and 75%, respectively). However, the response to the recommended regimens has been observed to be substantial higher in other Asian countries. For example, the average SVR for HCV-1 was 61% in Japanese patients,⁴⁶ 65% (55%–70%) in Koreans,^{56–58} and around 77% (76%–80%) in Taiwanese.^{59–62} For HCV-2/3, SVR has been reported as 84% in Taiwanese,⁵⁹ and 87% (80%–94%) in Koreans.^{56–58} The SVR rate for HCV-2/3 Taiwanese patients could reach 95% when using a 24-week regimen with standard dose of ribavirin, 1000–1200 mg/day.^{4,63}

It is now important to tailor optimal treatment options for HCV-4 and 6 patients with comparable treatment approaches as for HCV-1, 2, and 3 patients. Data for HCV-4 are mainly from the Middle East and Egypt. Treatment with a 48-week regimen plus standard dose of ribavirin results in SVR rates of 55%–69%,^{51–53} compared to only 29%–49% with a 24-week regimen.^{51,52} Published data for HCV genotypes other than 1–4 are very limited and geographically

restricted. Therefore, a standard 48-week regimen is recommended for these groups. Recently, a retrospective study in Canada found that SVR in HCV-6 Asian American patients was 75% with a 48-week regimen of PegIFN plus RBV ($n = 12$), compared to 39% with a 24-week regimen ($n = 23$, $P = 0.044$).⁶⁴ Another small scale study in Hong Kong demonstrated that HCV-6 patients had a significantly higher SVR rate than did HCV-1 patients with standard 48 weeks regimen (86% vs 52%, $P = 0.019$).¹⁵ Larger prospective studies for HCV-6 patients are needed to confirm the optimal treatment duration with PegIFN/RBV.

No data are available for the treatment response to PegIFN/ribavirin in HCV-6 variants, HCV-7, 8 and 9. Dev *et al.* observed that 79% of HCV-7, 8 or 9 Southeast Asians, which were initially misclassified by line probe assay as HCV-1b, could achieve an SVR; while 59% of true HCV-1b Southeast Asians achieved an SVR with 48–52 weeks of conventional IFN plus ribavirin.¹⁶ The results imply that a standard 48-week PegIFN/ribavirin might be optimal for the subgroups of HCV-6 variants. The current available data indicate that standard 48-week regimen is an appropriate approach for HCV-4, 6, 7, 8 and 9 patients, whose response to treatment is at an intermediate level compared to those for HCV-1 and HCV-2/3 cases.

Response-guided Therapy

Week 4 virological response and abbreviated treatment duration

Although the recommended treatment is 48 weeks of PegIFN plus standard dose of ribavirin for HCV-1 patients, 42%–49% of HCV-1 patients could achieve an SVR with an abbreviated 24 weeks of PegIFN/ribavirin.^{47,62} Moreover, an earlier study in Taiwan demonstrated that 78% of HCV-1 patients who had a RVR could attain an SVR with IFN/ribavirin for 24 weeks.⁶⁵ Yu *et al.* followed 32 patients who required early termination from PegIFN/ribavirin among 617 CHC patients.⁶⁶ None of the 16 HCV-1 patients who received less than 20 weeks of treatment achieved an SVR. By contrast, five of the 13 (38.5%) HCV-2 patients, including two of four patients with 8–15 weeks of treatment and all of the three patients with 16 weeks of treatment, attained an SVR. Notably, all the five sustained responders achieved a RVR. These observations raise the question of whether it is possible to tailor the treatment regimen to a shorter duration to reduce the treatment cost and the incidence of adverse events while not compromising on the efficacy.

A 4 week RVR has been the single best predictor of an SVR for anti-HCV treatment with convention IFN or PegIFN plus ribavirin combination therapy, irrespective of HCV genotype.^{61,63,65,67} Thus, several studies have investigated the role of RVR as a marker for shorter treatment duration for CHC patients. This matter will be discussed in a later review in this JGH miniseries by Teoh *et al.*; data here will emphasise the relevance to Asian patients.

HCV-1/4 patients with a RVR. Several European and North American studies have provided data to support the concept that HCV-1/4 infected patients who have a RVR during PegIFN/ribavirin have high rates of SVR when the treatment course is shortened to 24 weeks, in particular among patients with lower

baseline viral loads.^{68–72} One proviso of these studies is that doses of ribavirin were the full weight-based ones.

Yu *et al.* conducted the first randomized, controlled study to evaluate the utility of a RVR in determining a shorter treatment duration for HCV-1 infected Asian patients.⁶¹ Two hundred Taiwanese HCV-1 patients were randomly assigned to receive either 24 or 48 weeks of PegIFN- α -2a (180 μ g/w) plus ribavirin 1000–1200 mg/day. The overall SVR rates were significantly lower in the 24-week arm (59%) than the 48-week arm (79%, $P = 0.002$), due to the higher relapse rate after shorter treatment (37% vs 12%, $P < 0.0001$). Although the results were better when looking at the group of patients achieving RVR, SVR appeared to remain lower in the 24-week arm than in the 48-week arm (89% vs 100%, $P = 0.056$). Nevertheless, for patients with low viremia (< 400 000 IU/mL) and RVR, the 24-week group had a comparable SVR rate (96%) with the 48-week group (100%). By contrast, for patients with high viremia and RVR, the SVR rate was significantly lower in the 24-week group than in the 48-week group (77% vs 100%, $P = 0.045$).⁶¹ Liu *et al.* accumulated additional evidence to support the abbreviated 24-week regimen in HCV-1 Taiwanese patients with low viral load and RVR.⁶⁰

HCV-2/3 patients with a RVR. Studies investigating shorter treatment duration for HCV-2 or 3 patients have been conducted since 2001. The hypothesis was first tested in three European studies.^{55,73,74} The results observed that HCV-2/3 infected patients who have a RVR during PegIFN plus weight-based dose of ribavirin have high rates of SVR when the treatment course is shortened to 12–16 weeks.^{55,73,74}

Yu *et al.* evaluated the utility of a RVR in determining an abbreviated treatment for HCV-2 patients in Asia.⁶³ HCV-2 patients were randomly allocated to receive either 16 ($n = 50$) or 24 ($n = 100$) weeks of PegIFN- α -2a (180 μ g/week) plus a weight-based dose of ribavirin 1000–1200 mg/day. Overall SVR rates were similar between the 16-week arm (94%) and the 24-week arm (95%). Both 16 and 24 weeks of treatment could achieve a high SVR, respectively 100% and 98%, among patients with RVR. However, SVR for patients without a RVR was substantially lower in the 16-week arm (57%) than in the 24-week arm (77%). Thus, these findings are in broad agreement with the European studies.^{55,73,74} These data provide evidence to support an abbreviated 12 to 16 weeks of PegIFN treatment with weight-based, standard dose of ribavirin, 800–1400 mg/day for HCV-2/3 patients provided that RVR is observed, without compromising treatment efficacy.

Notably, other studies in North America and Europe have failed to find treatment equivalence of short course PegIFN/ribavirin for HCV-2/3 patients when the dose of ribavirin is not weight based, i.e. when only a fixed (low) daily dose of 800 mg is used.^{75,76} Further studies to explore the optimal dose of ribavirin in Asians, who are typically 10–25 kg less in weight than their North American counterparts, are required, as well as to define the precise duration of shorter treatment necessary for optimal treatment efficacy HCV-2/3 patients with a RVR.

Week 12 virological response and treatment duration

Patients without an EVR. HCV-1 patients without an EVR have little chance of achieving an SVR (only 1.6%).⁷⁷ Asian studies have also observed this consistently; no patient without an EVR

achieved an SVR in several studies.^{60–62} Therefore, the current treatment guidelines recommend the 12-week stopping rule for HCV-1 patients without an EVR.^{1,3,48,50,78} Measurement of HCV RNA at week 12 is not currently recommended for HCV-2/3 patients, because of almost all HCV-2/3 patients achieved an EVR. Nevertheless, in the subgroup analysis in HCV-2 study by Yu *et al.*,⁶³ all of the HCV-2 patients who achieve a cEVR at week 12 attained an SVR; while among those without an EVR, none attained an SVR (unpublished data). The findings provide evidence suggesting the measurement of HCV RNA at week 12 for HCV-2/3 patients without a RVR.

Patients without a RVR, but with an EVR. Several studies have investigated the benefits of extending treatment duration to 72 weeks for subgroup of HCV-1/4 and patients without an EVR.^{71,79–81} As will be discussed in a later review by Teoh *et al.*, study design, patient selection criteria, RBV dose and subgroups for outcome analysis have varied across these trials. For these reasons, it is difficult to obtain conclusive information about outcomes across the published data. More recently, data from conference abstracts suggested that extending the treatment duration from 48 weeks to 72 weeks in HCV-1 patients could improve the SVR rate among patients with a pEVR but not among those with a cEVR.⁸² However, whether extending the treatment duration to 72 weeks have benefits in HCV-1 slow responders of Asian populations remains to be studied. Since only 50%–70% of HCV-1 cases have SVR with current regimens, this is an important topic for future collaborative research in the Asia-Pacific region.

According to the published literature, a treatment roadmap of individualized therapy for chronic hepatitis C can be constructed (Fig. 3). Beyond the current recommendation,⁴⁸ the Taiwan Association for the Study of the Liver Disease suggests an abbreviated 24-week regimen for HCV-1/4 patients with baseline viral loads < 400 000 IU/mL and a RVR, and an abbreviated of 12 to 16-week regimen with standard dose of ribavirin, 1000–1200 mg/day for HCV-2/3 patients with a RVR.^{49,50} Using the treatment strategy, there is an estimated cost saving of 11.8% per SVR for HCV-1/4 patients and 29% per SVR for HCV-2/3 patients based on the response rates in Taiwan.

Racial differences in response to IFN-based therapy: better results in Asian patients

Reviewing all the published data, it is becoming evident that, overall, Asian patients appear to have a considerably better response than Caucasians for corresponding HCV genotype and IFN-based regimens (Table 1). Inferior response to antiviral therapy is well documented in Afro-Americans compared with Caucasian patients.^{83,84} It is therefore now accepted that racial and ethnic differences might play a role in the treatment response to IFN-based therapy in CHC.

Four studies have directly compared the responses to IFN-based therapy between Asian and Caucasian patients with CHC. Dev *et al.* observed that treatment with 48–52 weeks of IFN- α plus ribavirin, Southeast Asian HCV-1b patients were more likely to achieve an SVR than European Australian HCV-1b patients (59% vs 15%).¹⁶ Hepburn *et al.* also demonstrated that SVRs were

Figure 3 Roadmap for individualized therapy for chronic hepatitis C. BL, baseline; W4, treatment week 4; W12, treatment week 12; LVL, low viral loads, HCV RNA < 400 000 IU/mL at baseline; HVL, high viral loads, HCV RNA \geq 400 000 IU/mL at baseline; RVR, rapid virological response, HCV RNA < 50 IU/ml at week 4; EVR, early virological response, seronegative of HCV RNA or decrease of HCV RNA by 2 logs from baseline values after 12 weeks of therapy; PegIFN, peginterferon; SD RBV, standard dose of ribavirin, 1000–1200 mg/day.

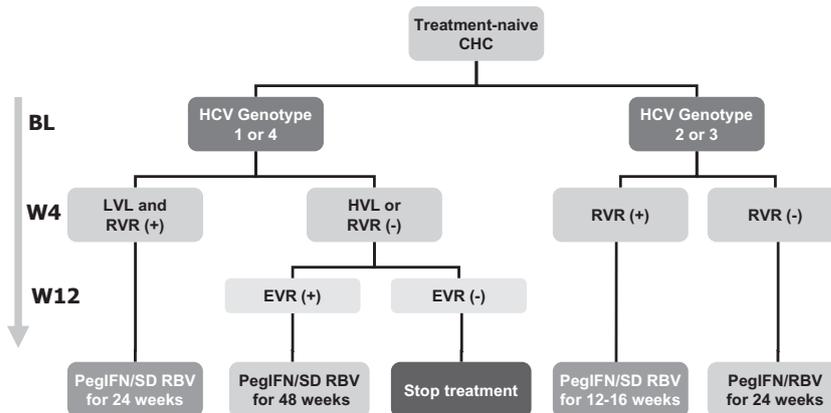


Table 1 Summary of treatment response to peginterferon plus ribavirin combination therapy for chronic hepatitis C in Asia

Patient population	Treatment regimen	Asian studies		
		Country	Reference	SVR rate
Genotype 1:	PegIFN plus SD RBV for 48 weeks	China	Yu <i>et al.</i> ⁶⁷	44%
		Japan	Kuboki <i>et al.</i> ⁴⁶	61%
		Korea	Lee <i>et al.</i> ⁵⁶	70%
		Taiwan	Liu <i>et al.</i> ⁶⁰	76%
		Taiwan	Liu <i>et al.</i> ⁵⁹	77%
		Taiwan	Yu <i>et al.</i> ⁶¹	79%
Genotype 1, LVL, and RVR	PegIFN plus SD RBV for 24 weeks	Taiwan	Liu <i>et al.</i> ⁶⁰	94%
		Taiwan	Yu <i>et al.</i> ⁶¹	96%
Genotype 2/3	PegIFN plus LD RBV for 24 weeks	China	Yu <i>et al.</i> ⁶⁷	75%
		Taiwan	Liu <i>et al.</i> ¹⁰⁷	84%
		Korea	Lee <i>et al.</i> ⁵⁶	94%
		Taiwan	Yu <i>et al.</i> ⁶³	95%
Genotype 2/3 and RVR	PegIFN plus SD RBV for 24 weeks	Taiwan	Yu <i>et al.</i> ⁶³	100%
Genotype 4	PegIFN plus SD RBV for 48 weeks	Kuwait	Hasan <i>et al.</i> ⁵³	68%
Genotype 6	PegIFN plus SD RBV for 48 weeks	Hong Kong	Fung <i>et al.</i> ¹⁵	86%

LD RBV, lower dose of ribavirin, 800 mg/day; LVL, low baseline viral loads; PegIFN, peginterferon; RVR, rapid virological response; SD RBV, standard dose of ribavirin, 1000–1200 mg/day; SVR, sustained virological response.

highest among Asians (61%), followed by Caucasians (39%), Hispanics (23%), and Afro-Americans (14%) with a 48-week regimen of daily or three times weekly IFN- α plus ribavirin. The odds ratio (OR) (95% CI) was 2.9 (1.3–6.2) in achieving an SVR for Asian versus Caucasian patients.⁸⁵

Recently, a retrospective analysis from a large multicenter Canadian study with PegIFN- α -2a plus ribavirin at a fixed dose of 800 mg/day showed that SVR occurred in 65% Asians and 45% Caucasians ($P = 0.0047$). The ethnic differences were independent of viral genotype and titer, pharmacological regimen, treatment adherence, BMI, age, and hepatic fibrosis.⁸⁶ The benefit of Asian ethnicity on treatment response was mainly observed in HCV-1 patients (Asian, 65% vs white, 36%, $P < 0.05$); it was not seen in HCV-2 or 3 (HCV-2: 77% vs 75%; HCV-3, 57% vs 64%, respectively). Similar results were also observed in previously IFN-resistant CHC patients using IFN- β , as mentioned earlier.³⁹ Recently, a retrospective study for 242 HCV-4 patients in France observed that the SVR rates to a standard 48-week regimen were

higher in patients infected in Egypt, compared with those infected in France or sub-Saharan Africa (55%, 40% and 32%, respectively, $P < 0.05$).⁸⁷

The explanation(s) for the superior response to IFN-based therapies in Asian patients remain unclear. Several factors might contribute. First of all, host genetic variations among different races are probably involved in the efficacy of IFN-based therapies for CHC.⁸⁸ Genetic polymorphisms of human leukocyte antigen, TNF- α -308 promoter gene, CC chemokine receptor 5, cytotoxic T lymphocyte antigen-4, interleukin-10, low molecular mass polypeptide 7, MxA, transforming growth factor- β 1, and suppressor of cytokine signalling 3 gene have been reported to have significant associations with responsiveness.^{29,89–92} These results reflect the important role of unique host genetic predisposition, at least in part, in the response to IFN-based therapy for CHC.

Second, geographic variations of HCV by emergence of quasi-species may have influenced the virological response.⁹³ HCV mutant type, defined by four or more amino acid substitutions in

the interferon sensitivity-determining region, has been associated with a more favourable response toward PegIFN/ribavirin combination therapy in Japanese and Taiwanese HCV-1 patients.^{94,95} However, these findings were not observed in European patients.⁹⁶ Further studies are necessary to explore the seeming discrepancy.

The third potential factor responsible for the discrepancy is the substantial 5–10 kg less of mean body weight in Asian patients compared with Caucasian patients. Obesity with a BMI greater than 30 kg/m² has been an independent negative predictor (OR 0.23) of response to CHC treatment.⁹⁷ Lower body weight means that patients have a considerably higher exposure dose of ribavirin by body weight, which is associated with a lower relapse and higher SVR rates.^{61,63,98,99} The dose-dependent increase in SVR rate was mainly observed among HCV-1 patients with weight-based exposure of ribavirin dose > 10 mg/kg/day.¹⁰⁰ Reddy *et al.* observed that SVR was not affected adversely by ribavirin reductions when the cumulative ribavirin exposure was greater than 60%, but was reduced significantly ($P = 0.0006$) in HCV-1 patients with less than the 60% cumulative ribavirin dose.⁹⁹ Furthermore, lower body weight,⁷² and the weight-based dose of ribavirin during first 4 weeks of treatment with a cut-off point of 13 mg/kg/day,¹⁰¹ have been associated with the achievement of an RVR. The RVR rate was 44%–66% for HCV-1 and 88% for HCV-2 patients in Taiwan, compared to 15%–27% for HCV-1 and 65%–75% in Western countries.^{102,103} Since RVR is the single best predictor of treatment response, factors predisposing to RVR, such as lower body weight and higher dose of ribavirin, would ensure the achievement of SVR.^{102,103}

Alternatively, SVR is dependent not only on pharmacological efficacy of PegIFN/ribavirin, but also on completion rates. Discontinuation due to adverse effects or a suboptimal treatment environment will erode treatment effectiveness; this matter will be reviewed in the later article by Teoh *et al.* in this series. Although the rate of withdrawal from treatment and dose reduction of PegIFN/ribavirin did not differ between Asian and Caucasian patients, the Asians achieved a significantly higher weight-adjusted dose of both PegIFN and ribavirin, and higher proportion of patients taking > 80% of ideal dose of ribavirin, because of their lower body weight.⁸⁶ More needs to be learnt about treatment adverse effects, and the settings of hepatitis C treatment clinics in Asian countries so as to best appreciate how to maximise treatment responses and minimise treatment side effects and discontinuation. To fully understanding the discrepancy of treatment response between Asian patients and other ethnic groups, further studies that use optimal doses of PegIFN and ribavirin, control the confounding parameter, such as body weight and age, are warranted.

In Asia, lower responses to IFN or PegIFN plus ribavirin combination therapy have been reported in China than in other Asian countries, including regions where the predominant ethnicity is Chinese (such as in Taiwan). It is difficult to discuss the discrepancy due to limited data available from China. The results from Japan also do not appear to be as impressive as those in Korea and Taiwan. This might be due to the use of lower dose of ribavirin and older patients in Japan. About three quarters of Japanese patients are older than 50 years and 40% older than 60 years.⁴² Old age is associated with not only poor adherence to treatment but also higher rate of treatment discontinuation, even with lower dose of ribavirin (< 60-year-old, 17% vs > 60-year-old, 30%).⁴²

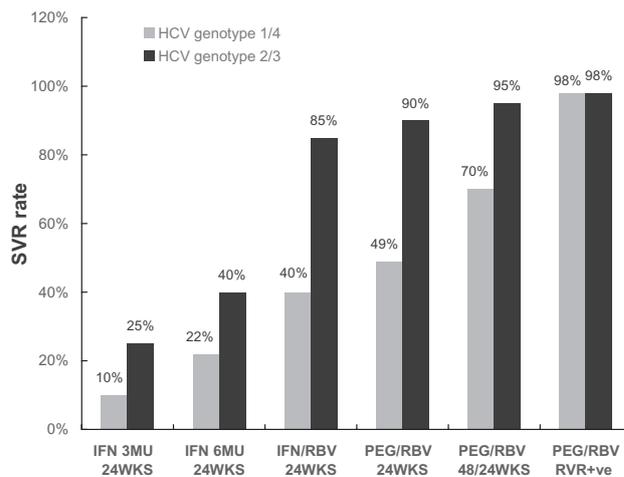


Figure 4 Milestones in therapy of chronic hepatitis C in Asia. Over the past 18 years there has been a dramatic improvement in treatment results for chronic hepatitis C in Asia. SVR, sustained virological response; IFN, interferon; MU, million units; WKS, weeks; RBV, ribavirin; PEG, peginterferon; RVR + ve, subgroup of patients who achieved a rapid virological response, defined as PCR-seronegative of HCV RNA after 4 weeks of therapy.

Conclusions and future directions

Figure 4 summarizes the progress in treatment of CHC over the past 18 years in Asia. Currently, PegIFN plus RBV is the standard of care. Studies from Asia provide evidence supporting the same treatment strategies for Asian patients as recommended in Western countries. However, increasing evidence supports that the Asian patients have a higher likelihood to achieve an SVR than Caucasians with corresponding regimen. HCV genotype, baseline viral load and on-treatment virological response could provide information for decision-making of individualized treatment. The tailored treatment regimen can reduce the cost of treatment and the incidence of adverse events without compromising on efficacy. However, a number of patients remain refractory to the current treatment regimens. Higher fixed doses of PegIFN- α -2a (270 μ g/week) and ribavirin (1600 mg/day) may increase SVR rates in the 'difficult-to-treat' patients.¹⁰⁴ Recent progress in the development of novel recombinant interferon, albinferon,¹⁰⁵ and specifically targeted antiviral therapy for HCV, such as protease, polymerase and cyclophilin inhibitors,¹⁰⁶ might further optimize the antiviral treatment for CHC.

Reference

- 1 National Institutes of Health Consensus Development Conference Statement. Management of hepatitis C: 2002–June 10–12, 2002. *Hepatology* 2002; **36**: S3–20.
- 2 Freeman AJ, Dore GJ, Law MG *et al.* Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001; **34**: 809–16.
- 3 McCaughan GW, Omata M, Amarapurkar D *et al.* Asian Pacific Association for the Study of the Liver consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. *J. Gastroenterol. Hepatol.* 2007; **22**: 615–33.

- 4 Chuang WL, Yu ML, Dai CY, Chang WY. Treatment of chronic hepatitis C in southern Taiwan. *Intervirology* 2006; **49**: 99–106.
- 5 Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J. Viral Hepat.* 1999; **6**: 35–47.
- 6 Yu ML, Chuang WL, Chen SC *et al.* Changing prevalence of hepatitis C virus genotypes: molecular epidemiology and clinical implications in the hepatitis C virus hyperendemic areas and a tertiary referral center in Taiwan. *J. Med. Virol.* 2001; **65**: 58–65.
- 7 Simmonds P, Bukh J, Combet C *et al.* Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. *Hepatology* 2005; **42**: 962–73.
- 8 Suh DJ, Jeong SH. Current status of hepatitis C virus infection in Korea. *Intervirology* 2006; **49**: 70–5.
- 9 Valliammai T, Thyagarajan SP, Zuckerman AJ, Harrison TJ. Diversity of genotypes of hepatitis C virus in southern India. *J. Gen. Virol.* 1995; **76**: 711–16.
- 10 Nakai K, Win KM, Oo SS, Arakawa Y, Abe K. Molecular characteristic-based epidemiology of hepatitis B, C, and E viruses and GB virus C/hepatitis G virus in Myanmar. *J. Clin. Microbiol.* 2001; **39**: 1536–9.
- 11 Farrell GC. New hepatitis C guidelines for the Asia-Pacific region: APASL consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. *J. Gastroenterol. Hepatol.* 2007; **22**: 607–10.
- 12 Kamal SM, Fouly AE, Kamel RR *et al.* Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. *Gastroenterology* 2006; **130**: 632–8.
- 13 Bdour S. Hepatitis C virus infection in Jordanian haemodialysis units: serological diagnosis and genotyping. *J. Med. Microbiol.* 2002; **51**: 700–4.
- 14 Smuts HE, Kannemeyer J. Genotyping of hepatitis C virus in South Africa. *J. Clin. Microbiol.* 1995; **33**: 1679–81.
- 15 Fung J, Lai CL, Hung I *et al.* Chronic hepatitis C virus genotype 6 infection: response to pegylated interferon and ribavirin. *J. Infect. Dis.* 2008; **198**: 808–12.
- 16 Dev AT, McCaw R, Sundararajan V, Bowden S, Sievert W. Southeast Asian patients with chronic hepatitis C: the impact of novel genotypes and race on treatment outcome. *Hepatology* 2002; **36**: 1259–65.
- 17 Bouchardeau F, Cantaloube JF, Chevaliez S *et al.* Improvement of hepatitis C virus (HCV) genotype determination with the new version of the INNO-LiPA HCV assay. *J. Clin. Microbiol.* 2007; **45**: 1140–5.
- 18 Lee CM, Lu SN, Hung CH *et al.* Hepatitis C virus genotypes in southern Taiwan: prevalence and clinical implications. *Trans. R. Soc. Trop. Med. Hyg.* 2006; **100**: 767–74.
- 19 Yu ML, Lin SM, Chuang WL *et al.* A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. *Antivir. Ther.* 2006; **11**: 985–94.
- 20 Hui JM, Kench J, Farrell GC *et al.* Genotype-specific mechanisms for hepatic steatosis in chronic hepatitis C infection. *J. Gastroenterol. Hepatol.* 2002; **17**: 873–81.
- 21 Sheikh MY, Choi J, Qadri I, Friedman JE, Sanyal AJ. Hepatitis C virus infection: molecular pathways to metabolic syndrome. *Hepatology* 2008; **47**: 2127–33.
- 22 Maylin S, Martinot-Peignoux M, Moucari R *et al.* Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. *Gastroenterology* 2008; **135**: 821–9.
- 23 Huang JF, Yu ML, Lee CM *et al.* Sustained virological response to interferon reduces cirrhosis in chronic hepatitis C: a 1,386-patient study from Taiwan. *Aliment. Pharmacol. Ther.* 2007; **25**: 1029–37.
- 24 Yu ML, Lin SM, Lee CM *et al.* A simple noninvasive index for predicting long-term outcome of chronic hepatitis C after interferon-based therapy. *Hepatology* 2006; **44**: 1086–97.
- 25 Shiratori Y, Ito Y, Yokosuka O *et al.* Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann. Intern. Med.* 2005; **142**: 105–14.
- 26 Yu ML, Huang CF, Dai CY, Huang JF, Chuang WL. Long-term effects of interferon-based therapy for chronic hepatitis C. *Oncology* 2007; **72** (Suppl. 1): 16–23.
- 27 Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003; **38**: 645–52.
- 28 Lee SS, Ferenci P. Optimizing outcomes in patients with hepatitis C virus genotype 1 or 4. *Antivir. Ther.* 2008; **13** (Suppl. 1): 9–16.
- 29 Yu M-L, Chuang W-L. Interferon-Based therapy for Hepatitis c infections. In: Jirillo E, ed. *Hepatitis C Virus Disease: Immunobiology and Clinical Applications*. New York: Springer, 2007; 168–91.
- 30 Hoofnagle JH, Mullen KD, Jones DB *et al.* Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N. Engl. J. Med.* 1986; **315**: 1575–8.
- 31 Di Bisceglie AM, Martin P, Kassianides C *et al.* Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. *N. Engl. J. Med.* 1989; **321**: 1506–10.
- 32 Poynard T, Leroy V, Cohard M *et al.* Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology* 1996; **24**: 778–89.
- 33 McHutchison JG, Gordon SC, Schiff ER *et al.* Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N. Engl. J. Med.* 1998; **339**: 1485–92.
- 34 Poynard T, Marcellin P, Lee SS *et al.* 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 (IHIT). *Lancet* 1998; **352**: 1426–32.
- 35 Lai MY, Kao JH, Yang PM *et al.* Long-term efficacy of ribavirin plus interferon alfa in the treatment of chronic hepatitis C. *Gastroenterology* 1996; **111**: 1307–12.
- 36 Yu ML, Dai CY, Chen SC *et al.* High versus standard doses of interferon-alpha in the treatment of naive chronic hepatitis C patients in Taiwan: a 10-year cohort study. *BMC Infect. Dis.* 2005; **5**: 27.
- 37 Shiratori Y, Kato N, Yokosuka O *et al.* Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Tokyo-Chiba Hepatitis Research Group. *Gastroenterology* 1997; **113**: 558–66.
- 38 Yu ML, Dai CY, Chen SC *et al.* A prospective study on treatment of chronic hepatitis C with tailored and extended interferon-alpha regimens according to pretreatment virological factors. *Antivir. Res.* 2004; **63**: 25–32.
- 39 Cheng PN, Marcellin P, Bacon B *et al.* Racial differences in responses to interferon-beta-1a in chronic hepatitis C unresponsive to interferon-alpha: a better response in Chinese patients. *J. Viral Hepat.* 2004; **11**: 418–26.
- 40 Chan HL, Ren H, Chow WC, Wee T. Randomized trial of interferon beta-1a with or without ribavirin in Asian patients with chronic hepatitis C. *Hepatology* 2007; **46**: 315–23.

- 41 Koike K. Antiviral treatment of hepatitis C: present status and future prospects. *J. Infect. Chemother.* 2006; **12**: 227–32.
- 42 Iwasaki Y, Ikeda H, Araki Y *et al.* Limitation of combination therapy of interferon and ribavirin for older patients with chronic hepatitis C. *Hepatology* 2006; **43**: 54–63.
- 43 Manns MP, McHutchison JG, Gordon SC *et al.* 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**: 958–65.
- 44 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.* 2002; **347**: 975–82.
- 45 Lee SD, Yu ML, Cheng PN *et al.* Comparison of a 6-month course peginterferon alpha-2b plus ribavirin and interferon alpha-2b plus ribavirin in treating Chinese patients with chronic hepatitis C in Taiwan. *J. Viral Hepat.* 2005; **12**: 283–91.
- 46 Kuboki M, Iino S, Okuno T *et al.* Peginterferon alpha-2a (40 KD) plus ribavirin for the treatment of chronic hepatitis C in Japanese patients. *J. Gastroenterol. Hepatol.* 2007; **22**: 645–52.
- 47 Hadziyannis SJ, Sette H Jr, Morgan TR *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann. Intern. Med.* 2004; **140**: 346–55.
- 48 Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology.* 2004; **39**: 1147–71.
- 49 Yu ML. Treatment of chronic hepatitis C genotype 2 or 3. *Gastroenterol. J. Taiwan* 2008; **25** (Suppl. 1): 40–5.
- 50 Hung CH, Lee CM. Treatment of Chronic Hepatitis C Genotype 1 or 4. *Gastroenterol J. Taiwan* 2008; **25** (Suppl. 1): 34–9.
- 51 Kamal SM, El Tawil AA, Nakano T *et al.* Peginterferon {alpha}-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. *Gut* 2005; **54**: 858–66.
- 52 El-Zayadi AR, Attia M, Barakat EM *et al.* Response of hepatitis C genotype-4 naive patients to 24 weeks of Peg-interferon-alpha2b/ribavirin or induction-dose interferon-alpha2b/ribavirin/amantadine: a non-randomized controlled study. *Am. J. Gastroenterol.* 2005; **100**: 2447–52.
- 53 Hasan F, Asker H, Al-Khaldi J *et al.* Peginterferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4. *Am. J. Gastroenterol.* 2004; **99**: 1733–7.
- 54 Zeuzem S, Hultcrantz R, Bourliere M *et al.* Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J. Hepatol.* 2004; **40**: 993–9.
- 55 Wagner M, Huber M, Berg T *et al.* Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005; **129**: 522–7.
- 56 Lee HJ, Eun JR, Choi JW, Kim KO, Moon HJ. [Comparison of therapeutic results between combination therapy of peginterferon alpha-2a plus ribavirin and interferon alpha-2b plus ribavirin according to treatment duration in patients with chronic hepatitis C]. *Korean J. Hepatol.* 2008; **14**: 46–57.
- 57 Lee H, Choi MS, Paik SW *et al.* [Peginterferon alfa-2a plus ribavirin for initial treatment of chronic hepatitis C in Korea]. *Korean J. Hepatol.* 2006; **12**: 31–40.
- 58 Kim KT, Han SY, Kim JH *et al.* [Clinical outcome of pegylated interferon and ribavirin therapy for chronic hepatitis C]. *Korean J. Hepatol.* 2008; **14**: 36–45.
- 59 Liu CJ, Chuang WL, Lee CM *et al.* Peginterferon Alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology* 2009; **136**: 496–504.
- 60 Liu CH, Liu CJ, Lin CL *et al.* Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clin. Infect. Dis.* 2008; **47**: 1260–9.
- 61 Yu ML, Dai CY, Huang JF *et al.* Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology* 2008; **47**: 1884–93.
- 62 Yu ML, Dai CY, Lin ZY *et al.* A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan. *Liver Int.* 2006; **26**: 73–81.
- 63 Yu ML, Dai CY, Huang JF *et al.* A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut* 2007; **56**: 553–9.
- 64 Nguyen MH, Trinh HN, Garcia R, Nguyen G, Lam KD, Keeffe EB. Higher rate of sustained virologic response in chronic hepatitis C genotype 6 treated with 48 weeks versus 24 weeks of peginterferon plus ribavirin. *Am. J. Gastroenterol.* 2008; **103**: 1131–5.
- 65 Yu ML, Chuang WL, Dai CY *et al.* Different viral kinetics between hepatitis C virus genotype 1 and 2 as on-treatment predictors of response to a 24-week course of high-dose interferon-alpha plus ribavirin combination therapy. *Transl. Res.* 2006; **148**: 120–7.
- 66 Yu ML, Dai CY, Lee LP *et al.* Outcome of chronic hepatitis C patients who required early termination of peginterferon-alpha plus ribavirin combination therapy. *Antivir. Ther.* 2006; **11**: 1015–19.
- 67 Yu JW, Wang GQ, Sun LJ, Li XG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. *J. Gastroenterol. Hepatol.* 2007; **22**: 832–6.
- 68 Zeuzem S, Buti M, Ferenci P *et al.* 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. Hepatol.* 2006; **44**: 97–103.
- 69 Jensen DM, Morgan TR, Marcellin P *et al.* Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006; **43**: 954–60.
- 70 Kamal SM, El Kamary SS, Shardell MD *et al.* 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**: 1732–40.
- 71 Mangia A, Minerva N, Bacca D *et al.* Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology* 2008; **47**: 43–50.
- 72 Ferenci P, Laferl H, Scherzer TM *et al.* Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterology* 2008; **135**: 451–8.
- 73 Dalgard O, Bjoro K, Hellum KB *et al.* Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology* 2004; **40**: 1260–5.
- 74 Mangia A, Santoro R, Minerva N *et al.* Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N. Engl. J. Med.* 2005; **352**: 2609–17.
- 75 Shiffman ML, Suter F, Bacon BR *et al.* Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N. Engl. J. Med.* 2007; **357**: 124–34.
- 76 Lagging M, Langeland N, Pedersen C *et al.* 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**: 1837–45.
- 77 Davis GL. Monitoring of viral levels during therapy of hepatitis C. *Hepatology* 2002; **36**: S145–51.
- 78 Yee HS, Currie SL, Darling JM, Wright TL. Management and treatment of hepatitis C viral infection: recommendations from the

- Department of Veterans Affairs Hepatitis C Resource Center program and the National Hepatitis C Program office. *Am. J. Gastroenterol.* 2006; **101**: 2360–78.
- 79 Berg T, von Wagner M, Nasser S *et al.* Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; **130**: 1086–97.
 - 80 Sanchez-Tapias JM, Diago M, Escartin P *et al.* 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**: 451–60.
 - 81 Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatology* 2007; **46**: 1688–94.
 - 82 Berg T, Carosi G. Optimizing outcomes in patients with hepatitis C virus genotype 2 or 3. *Antivir Ther.* 2008; **13** (Suppl. 1): 17–22.
 - 83 Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N. Engl. J. Med.* 2004; **350**: 2265–71.
 - 84 Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. Peginterferon alfa-2a (40 kd) and ribavirin for black American patients with chronic HCV genotype 1. *Hepatology* 2004; **39**: 1702–8.
 - 85 Hepburn MJ, Hepburn LM, Cantu NS, Lapeer MG, Lawitz EJ. Differences in treatment outcome for hepatitis C among ethnic groups. *Am. J. Med.* 2004; **117**: 163–8.
 - 86 Missiha S, Heathcote J, Arenovich T, Khan K. Impact of asian race on response to combination therapy with peginterferon alfa-2a and ribavirin in chronic hepatitis C. *Am. J. Gastroenterol.* 2007; **102**: 2181–8.
 - 87 Roulot D, Bourcier V, Grando V *et al.* Epidemiological characteristics and response to peginterferon plus ribavirin treatment of hepatitis C virus genotype 4 infection. *J. Viral Hepat.* 2007; **14**: 460–7.
 - 88 Tang J, Kaslow RA. Pharmacogenomic perspectives of chronic hepatitis C virus (HCV) infection. *Pharmacogenomics J.* 2004; **4**: 171–4.
 - 89 Persico M, Capasso M, Persico E *et al.* Suppressor of cytokine signaling 3 (SOCS3) expression and hepatitis C virus-related chronic hepatitis: Insulin resistance and response to antiviral therapy. *Hepatology* 2007; **46**: 1009–15.
 - 90 Yu ML, Dai CY, Chen SC *et al.* Human leukocyte antigen class I and II alleles and response to interferon-alpha treatment, in Taiwanese patients with chronic hepatitis C virus infection. *J. Infect. Dis.* 2003; **188**: 62–5.
 - 91 Dai CY, Chuang WL, Chang WY *et al.* Tumor Necrosis Factor-alpha Promoter Polymorphism at Position -308 Predicts Response to Combination Therapy in Hepatitis C Virus Infection. *J. Infect. Dis.* 2006; **193**: 98–101.
 - 92 Persico M, Capasso M, Russo R *et al.* Elevated expression and polymorphisms of SOCS3 influence patient response to antiviral therapy in chronic hepatitis C. *Gut* 2008; **57**: 507–15.
 - 93 Lam NP. Hepatitis C: natural history, diagnosis, and management. *Am. J. Health Syst. Pharm.* 1999; **56**: 961–73.
 - 94 Shirakawa H, Matsumoto A, Joshita S *et al.* Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients using viral and host factors. *Hepatology* 2008; **48**: 1753–60.
 - 95 Yen YH, Hung CH, Hu TH *et al.* Mutations in the interferon sensitivity-determining region (nonstructural 5A amino acid 2209–2248) in patients with hepatitis C-1b infection and correlating response to combined therapy of pegylated interferon and ribavirin. *Aliment. Pharmacol. Ther.* 2008; **27**: 72–9.
 - 96 Pascu M, Martus P, Hohne M *et al.* Sustained virological response in hepatitis C virus type 1b infected patients is predicted by the number of mutations within the NS5A-ISDR: a meta-analysis focused on geographical differences. *Gut* 2004; **53**: 1345–51.
 - 97 Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. *Hepatology* 2003; **38**: 639–44.
 - 98 Shiffman ML, Salvatore J, Hubbard S *et al.* Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. *Hepatology* 2007; **46**: 371–9.
 - 99 Reddy KR, Shiffman ML, Morgan TR *et al.* Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin. Gastroenterol. Hepatol.* 2007; **5**: 124–9.
 - 100 Snoeck E, Wade JR, Duff F, Lamb M, Jorga K. Predicting sustained virological response and anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) plus ribavirin. *Br. J. Clin. Pharmacol.* 2006; **62**: 699–709.
 - 101 Rodriguez-Torres M, Sulkowski M, Chung RT, Hamzeh FM, Jensen D. Association of pretreatment and on-treatment factors with rapid virological response in HCV genotype 1-infected patients with peginterferon alfa-2a/ribavirin. *Hepatology* 2007; **46**: 817A.
 - 102 Dai CY, Chuang WL, Huang JF, Hsieh MY, Yu ML. Possible determinants of rapid virological response suggesting shorter courses of combination therapy for hepatitis C virus genotype 2. *Hepatology* 2008; **48**: 342.
 - 103 Yu ML, Dai CY, Huang JF, Chuang WL. Rapid virological response to peginterferon and ribavirin for hepatitis C genotype 1: the role of weight-based ribavirin exposure. *Hepatology* 2008; **48**: 1019–20.
 - 104 Fried MW, Jensen DM, Rodriguez-Torres M *et al.* 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**: 1033–43.
 - 105 Zeuzem S, Yoshida EM, Benhamou Y *et al.* Albinterferon alfa-2b dosed every two or four weeks in interferon-naive patients with genotype 1 chronic hepatitis C. *Hepatology* 2008; **48**: 407–17.
 - 106 Kronenberger B, Welsch C, Forestier N, Zeuzem S. Novel hepatitis C drugs in current trials. *Clin. Liver Dis.* 2008; **12**: 529–55, viii.