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Individualizing Regimens to Optimize Outcomes in the Treatment of Chronic Hepatitis C With Peginterferon Alfa and Ribavirin

A Review of Selected Presentations
From the 58th Annual Meeting of the American Association for the Study of Liver Diseases
November 2–6, 2007
Boston, Massachusetts

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with chronic hepatitis C.

Statement of Need/Program Overview: Approximately 3.9 million Americans are currently infected with the hepatitis C virus (HCV), and an estimated 8,000–10,000 deaths each year result from HCV-associated chronic liver disease. Although public health measures instituted over the past two decades have resulted in changes in transmission rates, the major mode of HCV infection continues to be through injection drug use. Other modes of transmission account for a very low percentage of overall infections and include exposure through chronic hemodialysis treatment, accidental exposures in healthcare workers or between household contacts, and sexual activity with an infected partner. HCV infection affects persons of all ages, but most acute cases of hepatitis C and the highest seroprevalence of HCV infection are found among young adults, and the highest incidence and prevalence rates are among nonwhite racial/ethnic groups. Although the incidence of acute hepatitis C has declined in response to public health measures, there is a large reservoir of chronically infected Americans who can serve as a source of transmission to others and who are at risk of the severe consequences of chronic liver disease.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the unmet need in the treatment of chronic HCV with current standard-of-care regimens.
2. Discuss the latest evidence regarding the adjustment of current HCV regimens to optimize outcomes.
3. Define future research goals to further improve treatment of chronic HCV.

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and *Gastroenterology & Hepatology*. PIM is accredited by the ACCME to provide continuing medical education for physicians.

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Introduction

Epidemiology

Hepatitis C virus (HCV) is a major cause of liver disease in the United States, with an estimated 4.1 million people currently living with chronic HCV infection.[1] Rates of HCV-associated morbidity and mortality have been increasing in recent years; about 80% of persons with acute HCV infection develop chronic HCV, and up to 20% of these individuals develop liver cirrhosis over a 20- to 25-year period.[2] Cirrhosis is associated with an increased risk of end-stage liver disease and hepatocellular carcinoma.

Current Treatment Approaches

The goal in treating patients with chronic hepatitis C is to prevent HCV-related complications by achieving a sustained virologic response (SVR). SVR is defined as having no detectable HCV RNA both at the end of the treatment course and at follow-up, 6 months after treatment cessation.

According to the American Association for the Study of Liver Diseases (AASLD) treatment guidelines, it is widely accepted that adults with detectable HCV RNA who have abnormal alanine aminotransferase (ALT) values, liver biopsy showing significant fibrosis, compensated liver disease, and acceptable blood values should receive treatment.[3] Individual variables that should factor into the treatment decision include the severity of liver disease, potential for side effects, likelihood of treatment response, and presence of comorbidities.

The treatment of choice for chronic HCV is a combination of peginterferon and ribavirin.[3] Rates of SVR with this combination vary from approximately 45% among patients with genotype 1 infection to 75–80% among patients with genotype 2 or 3 infection.[4-5] Other predictors of response include baseline viral load, age, and weight.[4-5]

Early responses to therapy may predict future clinical outcomes. Most patients who achieve an SVR also show an early virologic response (EVR), defined as at least a 2 $\log_{10}$ decline in HCV RNA 12 weeks into therapy. As early responses to therapy can be an important tool for optimizing therapy, recent studies have investigated the predictive value of responses assessed as early as 4 weeks into treatment (ie, a rapid virologic response [RVR]). Other important unanswered questions being addressed in clinical trials include the optimal dosing and duration of peginterferon and ribavirin and the safe, effective treatment of patients with comorbidities, including hepatitis B virus (HBV) coinfection.

The following report highlights some of the most important data regarding HCV treatment presented at the 2007 AASLD annual meeting. The annual AASLD meeting is the largest meeting of its kind in North America, providing a forum for the exchange of groundbreaking research and clinical information in a variety of formats, including workshops, plenary and parallel sessions, poster sessions, scientific exhibits, and State-of-the-Art Lectures.

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Predictability of Response: Positive and Negative Predictive Values of Rapid and Early Virologic Responses to Peginterferon Alfa-2b and Ribavirin in the Treatment of Chronic Hepatitis C[1]

F Poordad, C Kambili

Another study evaluating the predictive value of early virologic kinetics was conducted by Poordad and Kambili, who evaluated the positive and negative predictive values of RVR and EVR in patients receiving peginterferon alfa-2b and ribavirin in multiple clinical trials. The analysis included data from 1,207 patients enrolled in 6 clinical trials and included patients with HCV/HIV coinfection. The investigators defined EVR as either undetectable HCV RNA or at least a 2 $\log_{10}$ reduction in HCV RNA level from baseline to week 12. Overall, the negative predictive value of RVR (which reflects the proportion of patients who do not attain an SVR among those who do not attain RVR) ranged from 44% to 84%, while the positive predictive value of RVR (which reflects the proportion of patients who attain SVR among those who attain RVR) ranged from 75% to 100%. The positive predictive value of RVR was lower among genotype 1 patients (75%) versus genotype 2 or 3 patients (81–91%). Failure to attain EVR was a consistent indicator of failure to attain SVR (negative predictive value 95–100%), whereas attaining EVR was a less reliable predictor of attaining SVR (positive predictive value 67–72%) for all genotypes (Figure 1). The positive predictive values reported for EVR varied

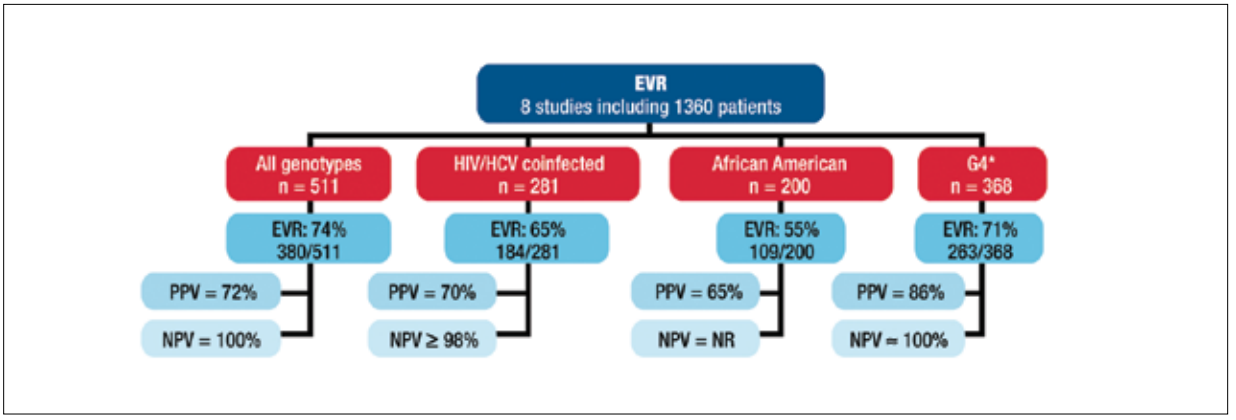

Figure 1. Data summary from all clinical trials combined.

G=genotype; NPV=negative predictive value; PPV=positive predictive value; RVR=rapid virologic response.

*24-Week regimens excluded from G4 analysis due to clear lack of efficacy.

Adapted from Poordad and Kambili.[10]

Table 1. Early Outcomes With High-Dose vs Low-Dose Peginterferon

Efficacy Outcome	Peg-IFN a-2a 360 µg/wk (n=423)	Peg-IFN a-2a 180 µg/wk (n=422)	*P* Value
HCV RNA <15 IU/mL			
• Week 4 (RVR)	35	26	<.001
• Week 8	61	26	<.001
• Week 12	74	49	<.001
EVR (HCV RNA <15 IU/mL or ≥2 $\log_{10}$ drop in HCV RNA)			
• Week 12	89	79	<.001

EVR=early virologic response; HCV=hepatitis C virus; Peg-INF=peginterferon; RVR=rapid virologic response.

Data from Roberts et al.[2]

across study populations, ranging from 48–83% among African American patients, 67–71% among HCV/HIV coinfected patients, 71% for genotype 1, 72% for mixed genotype, and 86–100% for genotype 4. Notably, the positive predictive value of EVR for SVR was significantly lower for patients who achieved EVR but had detectable viral loads at week 12 than for patients with undetectable viral loads (21% vs 83%; *P*<.001).

The investigators made several recommendations based the predictive value of RVR for SVR. First, they suggested that for genotype 2/3 patients, an RVR may identify patients in whom shorter treatment is feasible. Second, they encouraged clinicians to use RVR as a motivational tool to encourage continued treatment adherence. Third, they cautioned that the low negative predictive value of RVR means clinicians should not discontinue treatment based on a failure to attain an RVR.

Rapid and Early Virological Response Rates Are Increased with 12 Week 360 µg/wk Peginterferon Alfa-2a (40kd) and Standard Ribavirin in HCV Genotype 1 Treatment Naive Patients: Efficacy and Safety Analysis of the Induction Phase of the CHARIOT Study[2]

S Roberts, M Weltman, D Crawford, W Cheng, W Sievert, GW McCaughan, PV Desmond, M Yoshihara, JE Miller, J Depamphilis, P Marks, GJ Dore, on behalf of the CHARIOT Study Group

The international, multicenter, open-label CHARIOT study is evaluating a higher dose of peginterferon alfa-2a versus the standard dose in combination with ribavirin in treatment-naive patients with genotype 1 chronic hepatitis C. In the study, patients are randomized 1:1 to receive peginterferon alfa-2a at 360 µg/week or 180 µg/week for 12 weeks, followed by 180 µg/week for the next 36 weeks. All patients are receiving 48 weeks of ribavirin 1,000–1,200 mg/day.

A total of 845 patients were evaluable for safety and efficacy evaluation at the week 12 interim analysis. Baseline factors, including sex, age, weight, body mass index (BMI), ethnicity, serum HCV RNA levels, and fibrosis score, were similar between the two arms. Virologic responses were significantly superior in the higher-dose peginterferon arm at weeks 4, 8, and 12 (*P*<.001; Table 1). High-dose peginterferon was superior across multiple patient subgroups, including high versus low baseline HCV RNA, high versus low body weight, and older versus younger age (Figure 2).

The incidence of serious adverse events was similar with high- versus low-dose peginterferon (4% vs 3%), as was the proportion of patients discontinuing treatment (5% vs 4%). Rates of depression and fatigue were also similar between arms. Certain adverse effects were more common with the higher dose, including diarrhea (17% vs 12%), pyrexia (14% vs 8%), chills (14% vs 7%) and weight loss (10% vs 3%). Doses were modified in 22% of patients receiving high-dose peginterferon and 14% of patients in the low-dose arm. Hematologic toxicity rates were low, with less than 1% of patients in either arm requiring growth factor support: rates of neutropenia, thrombocytopenia, and anemia for the high- versus low-dose arms were 5% vs 2%, 4% vs <1%, and 10% vs 7%, respectively. The investigators concluded that induction dosing with peginterferon alfa-2a 360 µg/week provides

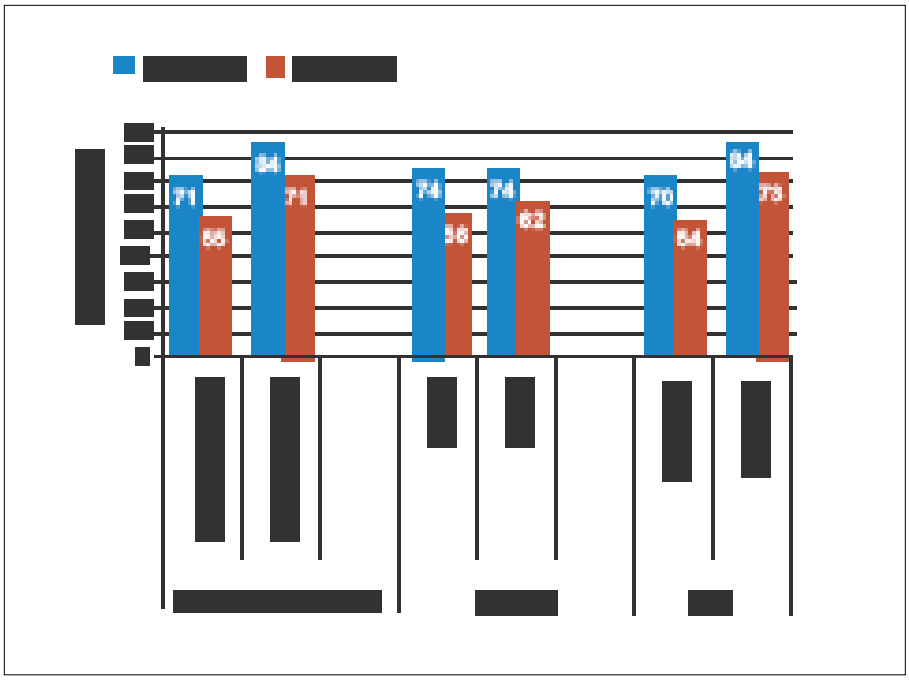

Figure 2. Responses to high-dose vs low-dose peginterferon in subgroup analysis.

Adapted from Roberts et al.[2]

more effective virologic responses than 180 µg/week with an acceptable safety profile.

An Open Label, Comparative, Multicenter Study of Peginterferon Alfa-2a Plus Ribavirin in the Treatment of Patients With Chronic Hepatitis C/Hepatitis B Co-Infection Versus Those With Chronic Hepatitis C Monoinfection[3]

CJ Liu, WL Chuang, CM Lee, SS Wu, LY Liao, HT Kuo, YC Chao, CL Chen, PJ Chen, DS Chen

Liu and colleagues conducted an open-label multicenter study in Taiwan evaluating the effect of HBV coinfection on responses to HCV treatment with peginterferon alfa-2a plus ribavirin. The study compared outcomes in patients with active HCV infection with HBV coinfection (n=161) or without coinfection (n=160). Patients with genotype 1 HCV received 48 weeks of peginterferon alfa-2a 180 µg/week and ribavirin 1,000–1,200 mg/day; patients with non–genotype 1 infection received 24 weeks of peginterferon alfa-2a 180 µg/week plus ribavirin 800 mg/day. Among patients with genotype 1 HCV, SVR was achieved in 66% of those with HBV coinfection and 75% of those with HCV monoinfection. SVR rates in patients with non–genotype 1 infection were 84% and 88%, respectively. Of 115 evaluable patients with HBV coinfection, 50% had serum HBV DNA levels greater than 1,000 copies/mL at baseline. HBV virologic responses (defined as HBV DNA <1,000 copies/mL) were seen in 55% of these patients at the end of treatment and 45% at the end of follow-up. Another 31% of dually infected patients had undetectable serum HBV DNA at baseline. By the end of follow-up, 38% of these patients (19 of 50) had HBV DNA rebounds, suggesting that reactivation strategies should be developed when treating patients with dual infection. Notably, 17 of the 19 patients with HBV DNA rebounds still had an HCV SVR and none had ALT elevations above 200 IU/L. Overall, 8.1% of patients discontinued treatment, most commonly due to noncompliance issues or the development of skin lesions. In conclusion, these data support combination therapy with peginterferon alfa-2a plus ribavirin in patients with HCV/HBV coinfection.

Early Discontinuation of Ribavirin in HCV-2 and HCV-3 Patients Responding to Peg-Interferon Alfa-2a and Ribavirin[4]

A Andriulli, C Cursaro, R Cozzolongo, A Iacobellis, MR Valvano, A Mangia, N Minerva, D Bacca, M Stanzione, A Scuteri, G Montalto, P Andreone

Although guidelines recommend a 24-week regimen of peginterferon alfa-2a and ribavirin in patients with HCV genotypes 2 and 3, half of these patients are known to

attain SVR with peginterferon monotherapy. Andriulli and colleagues conducted a multicenter trial to evaluate the feasibility of discontinuing ribavirin early in patients with genotype 2 and genotype 3 achieving an RVR at week 4. The investigators enrolled 144 patients with genotype 2 or genotype 3 to receive peginterferon alfa-2a 180 µg/week plus ribavirin 1000–1200 mg/day. Patients achieving RVR at week 4 were randomized to discontinue ribavirin and receive peginterferon alfa-2a monotherapy for the remaining 8 weeks (n=59) or to continue on combination therapy (n=61). Overall, 83% of patients achieved an RVR. Among those patients, SVR rates were significantly higher in patients randomized to continue ribavirin (82% vs 54% in patients stopping ribavirin; *P*<.001). At the end of treatment, 119 of the 120 patients with an RVR had achieved undetectable virus levels, although subsequent relapse rates were significantly higher among patients who discontinued ribavirin (46% vs 17%; *P*<.001). Five characteristics were significantly associated with SVR among patients who discontinued ribavirin: low body weight (*P*=.022), low BMI (*P*=.034), low HCV RNA level (*P*<.01), HCV genotype 3 (*P*=.031), and mild liver disease (*P*<.01). Two of these variables were significant in a multivariable analysis: low HCV RNA level (odds ratio [OR], 56.8; 95% confidence interval [CI], 4.3–745) and mild liver disease (OR, 27.3; 95% CI, 1.4–521). The investigators conducted subgroup analyses to further evaluate the impact of baseline HCV RNA level on response to an abbreviated ribavirin schedule. Among patients with a baseline HCV RNA level less than 300,000 IU/mL, SVR rates were similar whether stopping or continuing ribavirin (86% and 81%, respectively). Rates were also similar in patients with an intermediate HCV RNA level (70% and 71%). However, among patients with a baseline HCV RNA level greater than 700,000 IU/mL, SVR rates were significantly lower after stopping ribavirin versus continuing ribavirin (37% vs 88%; *P*=.004). Among the 24 patients (17%) who did not achieve an RVR, 63% responded by the end of treatment and 50% attained an SVR.

The investigators concluded that early discontinuation of ribavirin may be feasible in patients with HCV genotype 2 or 3 with a low baseline HCV RNA level who attain early viral clearance. This strategy deserves additional prospective evaluations, as it would lower the cost and quality-of-life burdens associated with HCV treatment.

Response to Peginterferon Alfa-2b + Ribavirin Combination Therapy in Genotype 2 and 3 Patients With Poor Baseline Prognostic Factors: Results of the Canadian POWeR Program[5]

RJ Bailey, DK Wong, C Cooper, N Hilzenrat, K Peltekian, J Daiter, N Abadir, P Marotta

Previous studies showed that up to 80% of patients with HCV genotype 2 or 3 can achieve an SVR following treatment with peginterferon alfa plus ribavirin for at least 24 weeks.[6,7] The current study is a subanalysis of the Canadian Peginterferon Alfa-2b Prospective Optimal Weight-Based Dosing Response (POWeR) study, an open-label, prospective, observational, noninterventional outcomes study conducted in treatment-naive patients with chronic hepatitis C. The POWeR study investigated whether the outcomes achieved with peginterferon plus ribavirin in clinical trials would be replicated in a wider arena of mixed academic and community settings. All patients received peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin administered using weight-based dosing (800–1200 mg/day), which is standard practice in Canada, regardless of HCV genotype. Bailey and colleagues presented a subanalysis evaluating the impact of fibrosis and baseline HCV RNA levels on SVR rates in patients with HCV genotype 2 (n=276) or genotype 3 (n=389), who comprised 37% of the study population. Fibrosis data were available for 41% of genotype 2 patients and 35% of genotype 3 patients; baseline viral load data were available for 73% and 72% of patients, respectively. Patients with HCV genotype 2 were more likely than those with genotype 3 to have a high baseline HCV RNA level (>600,000 IU/mL) (54% vs 49%), though they were less likely to have advanced fibrosis or cirrhosis (F3–F4) (33% vs 40%). The investigators reported greater efficacy in genotype 2 versus genotype 3 patients in terms of end-of-treatment response rates (86% vs 77%; *P*=.01) and SVR rates (79% vs 72%; *P*=.04). However, relapse rates were low in both groups (7.6% vs 6.4%).

The effects of baseline viral load and fibrosis score varied based on genotype: neither factor had a significant effect on response to therapy in patients with HCV genotype 2, but both factors affected outcomes in patients with genotype 3. SVR rates with high versus low baseline HCV RNA were 79% versus 83% in genotype 2 patients and 76% versus 64% (*P*=.03) in genotype 3 patients. Likewise, whereas METAVIR fibrosis score had little effect on SVR rates in genotype 2 patients, among genotype 3 patients SVR rates varied from 81% in those with F1 fibrosis to 47% in those

Table 2. Effect of Baseline Fibrosis on SVR Rates According to HCV Genotype

METAVIR Fibrosis Score	SVR Rate According to Genotype, %	
	Genotype 2 (n=113)	Genotype 3 (n=137)
F1	79	81*
F2	81	68
F3	80	71
F4	76	47*

*P<.02 for F1 vs F4 in genotype 3 patients.

Data from Bailey et al.[5]

with F4 fibrosis (P<.02; Table 2). These findings reveal important differences in responses between genotype 2 and genotype 3 patients. Patients with HCV genotype 3 might benefit from early therapeutic intervention, as they are more likely to have advanced fibrosis and less likely to attain an SVR with treatment. Moreover, investigators in future clinical trials could consider analyzing genotype 2 and 3 patients separately, given their potential for different outcomes.

Final Results of the Canadian POWeR (Pegetron Prospective Optimal Weight-Based Dosing Response) Program: Sustained Virologic Response to Weight-Based Peginterferon Alfa-2b + Ribavirin in a Large, Mixed, Community and Academic Observational Study[8]

P Marotta, SV Feinman, C Ghent, L Scully, M Varenbut, J Daiter, HB Witt-Sullivan, J Robert, B Romanowski, J Farley, N Abadir, RJ Bailey

Also presented at the 2007 AASLD meeting were the final results of the Canadian POWeR study, reporting outcomes in the total per-protocol patient population (N=1800). At baseline, 59.7% of patients weighed more than 75 kg, 60.4% had genotype 1 infection, 40.0% had advanced fibrosis (METAVIR score F3–F4), and 52.5% had a baseline viral load greater than 600,000 IU/mL. The overall end-of-treatment response rate was 61.7% and the SVR rate was 54.3%. SVR rates were higher in patients with non–genotype 1 HCV (Table 3, Figure 3). Efficacy also varied by degree of fibrosis, with SVR rates ranging from 60% in patients with minimal fibrosis (≤F2) to 35% in patients with F3–F4 fibrosis (P<.001). Relapses occurred in 11.9% of patients with an end-of-treatment response and were more common in patients with HCV genotype 1 (17.2%) versus genotypes 2, 3, and 4/5/6 (7.6%, 6.4%, and 6.9%, respectively).

The investigators noted that treatment outcomes in this study were similar to those observed in the large clinical trial by Manns and colleagues in terms of overall SVR rate (54.3% vs 54%), SVR rate in genotype 1 patients (41.6% vs 42%), SVR rate in genotype 2/3 patients (72–79% vs 82%), and overall relapse rate (11.2% vs 18%).[7] These findings suggest that the treatment outcomes observed in clinical trials can also be expected in clinical practice.

Clinical Relevance of Rapid Virological Response in Decompensated HCV-Related Cirrhosis Treated With Peg-Interferon and Ribavirin[9]

A Iacobellis, BE Annicchiarico, M Siciliano, G Niro, L Accadia, N Caruso, G Bombardieri, A Andriulli

The efficacy and safety of antiviral treatment in patients with HCV-related decompensated cirrhosis has not been well studied. Iacobellis and colleagues evaluated peginterferon alfa-2b and ribavirin in patients with HCV-related cirrhosis with hepatic decompensation. Results of the study were published in February 2007[10] and updated at AASLD 2007.[9] The study was limited to patients younger than 75 years of age who had not previously received antiviral combination therapy and who had evidence of previous decompensation such as ascites, bleeding, or encephalopathy. Exclusion criteria included insufficient blood counts, infection in the past month, hepatocellular carcinoma, autoimmune or metabolic liver disease, severe cardiopulmonary disease, and HIV or HBV coinfection. Treatment was initiated a month after hospital discharge and consisted of peginterferon alfa-2b 1.5 µg/kg/week plus weight-based ribavirin (800–1,200 mg/day) for 24 weeks (genotypes 2/3) or 48 weeks (genotypes 1/4).

Of the 94 patients enrolled, 66% were older than 60 years of age, 53% were male, 57% had a baseline HCV RNA level below 600,000 IU/mL, and 53% had HCV genotype 1 or 4 infection. In the overall population, 36.2% of patients achieved an RVR and 36.2% achieved

Table 3. Responses by Genotype in POWeR Study

Outcome	All Patients (N=1,800)	Genotype 1 (n=1,078)	Genotype 2 (n=276)	Genotype 3 (n=389)	Genotypes 4/5/6 (n=41)
EOTR, %	61.7	58.2	85.5	76.9	70.7
SVR, %	54.3	41.6	79.0	72.0	65.9

EOTR=end-of-treatment response; SVR=sustained virologic response.

Data from Marotta et al.[8]

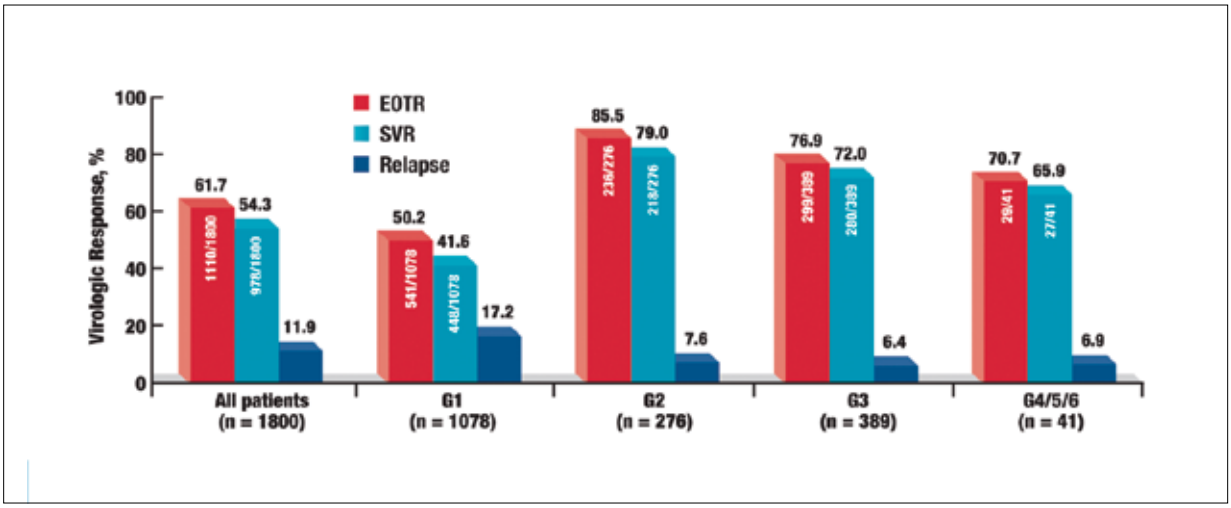

Figure 3. Response rates according to genotype (genotype was not available for 16 patients).

EOTR=end-of-treatment response; G=genotype; SVR=sustained virologic response.

Adapted from Marotta et al.[8]

an SVR. Patients with genotype 1 or 4 infection were significantly less likely to attain an SVR than patients with genotype 2 or 3 infection (16.0% vs 59.0%; *P*<.01). RVR was highly predictive of SVR, with a positive predictive value of 73.5%. The positive predictive value of EVR for SVR was 34.8%. Both RVR and EVR were more predictive of SVR in genotype 2 or 3 infection than in genotype 1 or 4 infection. Patients with a baseline HCV RNA level of 600,000 IU/mL or less were significantly more likely to achieve an RVR than were patients with a baseline HCV RNA level above 600,000 IU/mL (46.3% vs 20%). Overall, 3 factors were significant predictors of SVR in a multivariate analysis: baseline viral load of 600,000 IU/mL or less (OR, 3.41; 95% CI, 1.02–11.43; *P*=.0468), RVR (OR, 7.68; 95% CI, 2.52–23.36; *P*=.0003), and genotype 2 or 3 (OR, 3.71; 95% CI, 1.19–11.56; *P*=.0241).

The investigators concluded that there is a "clear indication" to treat patients with genotype 2 HCV and decompensated cirrhosis in Child-Turcotte-Pugh A and B classes, as more than half of these patients can be expected to attain an SVR. For patients with genotype 1 infection and decompensated cirrhosis, they suggested discontinuing treatment in those who do not attain an RVR, as the likelihood of an SVR in these patients is less than 20%. These findings support an individualized treatment strategy incorporating viral genotype and early responses to identify patients most likely to achieve SVRs.

Peginterferon Alfa-2b and Ribavirin Treatment of Patients With Chronic Hepatitis C and Normal Versus Elevated Aminotransferase Levels—Final Results of a Prospective Open Trial[11]

W Vogel, H Brunner, A Maieron, I Graziadei, M Rosenbeiger, K Jilek, RE Stauber, D Wolkersdorfer

Although responses to anti-HCV therapy appear to be similar in patients with elevated versus persistently normal aminotransferase levels, the impact of aminotransferase levels on treatment outcomes is not fully understood. In a prospective, open-label, multicenter trial, Vogel and colleagues evaluated the efficacy and safety of peginterferon alfa-2b plus ribavirin in 231 treatment-naive patients with persistently normal (n=110) or elevated (n=121) transaminases. Patients were stratified by baseline ALT level (based on the median of 3 measurements taken over at least 3 months), baseline viral load(<800,000 IU/mL vs ≥800,000 IU/mL), and genotype (1/4 vs 2/3). The median ALT level at baseline was 82.0±84.8 U/mL in the elevated ALT group and 27.0±7.9 U/mL in the normal ALT group. METAVIR fibrosis scores of F0–1 were more common among patients with persistently normal ALT levels versus elevated ALT (46.4% vs 31.4%; *P*=.0188). Other baseline variables, including age, body weight, BMI, sex, genotype, and viral load, were similar between the two arms.

Virologic response rates were similar in the two arms throughout the study, confirming the likelihood that SVR is independent of ALT level. The rates of HCV RNA undetectability at week 4 were 46.9% for patients with normal ALT and 43.6% for patients with elevated ALT; week 12 rates were 80.7% and 69%, respectively, and end-of-treatment rates were 73.6% and 67.8%, respectively. SVR rates were 50.9% and 47.9%, respectively.

Although ALT levels did not appear to affect virologic responses, HCV genotype and baseline viral load were predictive of response. Patients with genotype 2 or 3 were more likely to achieve a virologic response, with SVR rates of 64.0% for patients with normal ALT and 65.5% for patients with elevated ALT, compared with 47.1% and 42.4%, respectively, for patients with genotype 1 or 4. With regard to viral load, response rates were higher in patients with a baseline HCV RNA level below 800,000 IU/mL. This difference reached statistical significance in patients with persistently normal ATL, in whom response rates with low versus high baseline viral load were 58.3% versus 36.8%, respectively (*P*=.03).

Peg-IFN Alfa-2a Plus Ribavirin Is Superior Compared to High Dose Consensus Interferon and Ribavirin in the Treatment of Patients With Chronic Hepatitis C[12]

T Witthoeft

Dr. Thomas Witthoeft investigated the safety and efficacy of high-dose consensus interferon (CIFN) plus ribavirin for the treatment of patients with chronic hepatitis C. In this single-center study, 102 treatment-naive patients received either peginterferon alfa-2a 180 µg plus weight-based ribavirin (800–1,200 mg/day) (n=52) or CIFN (18 µg/day for 8 weeks followed by 9 µg/day subcutaneously) plus ribavirin 800 mg/day (n=50). Patients with detectable HCV RNA at week 24 discontinued treatment. Baseline characteristics were similar in the two arms. Efficacy was superior with peginterferon versus CIFN across genotypes. SVR rates in genotype 2/3 patients were 85% with peginterferon versus 73% with CIFN. SVR rates in genotype 1 and 4 patients were 58% and 48%, respectively. Although both regimens were well tolerated, adverse events including fever, muscle pain, weight loss, depression, and white blood cell count reductions, were more common with CIFN due to the increased interferon requirement. Whereas no patients in the peginterferon arm discontinued treatment, 4 patients (8%) discontinued CIFN. As has been observed in other studies, patients with a lower baseline viral load had better responses, and in this study greater responses were observed in women versus men in both arms. These findings support the superiority of peginterferon over CIFN for combination with ribavirin for the treatment of patients with chronic hepatitis C. The investigators suggested that CIFN might be favored in certain patients however, such as those with a high viral load or those who do not respond to standard therapy.

References

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Commentary

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The use of combination pegylated interferon and ribavirin represents the current standard of care in the treatment of hepatitis C. However, many positive and negative predictors of response have been elucidated since the landmark registration trials of the pegylated interferon molecules. Variables including host and viral factors and the dosing and duration of therapy have been assessed and found to significantly affect treatment outcomes. This wide array of treatment variables cannot be evaluated in a single study, and for this reason, multiple trials have been designed and conducted to answer a multitude of questions. It is an ongoing challenge to bring these data together and draw definite conclusions regarding the optimization of treatment outcomes for hepatitis C patients.

The concept of induction dosing with higher doses or more frequent dosing intervals is not a new one and was initially undertaken with nonpegylated formulations of interferon. Although on-treatment response appeared superior in several of those studies, it led to no significant improvement over standard dosing regimens in terms of intention-to-treat SVR. A major drawback to higher-dose regimens or more frequent dosing is the effect of these practices on the adverse event profile of interferon-based therapies. Resulting discontinuations and dose reductions often lead to suboptimal response rates. However, in those patients that are able to tolerate higher doses, there may indeed be an overall outcomes benefit.

In the CHARIOT study, the 12-week EVR rate favored the higher 360-µg weekly dose of peginterferon alfa-2a with a 10% differential over the standard 180-µg weekly dose. The ribavirin dose was 1,000–1,200 mg daily in both arms of the study. Interestingly, there were more dose reductions in the higher-dose arm, but the discontinuation rates were similar between the groups. The higher dose appeared to be relatively more effective in those with higher baseline viral loads, heavier patients (>85 kg), and those older than 40 years. This may indicate that the 180-µg dose is suboptimal for certain subsets of patients, particularly those who are heavier, but possibly also those with high viral loads as well as older patients who presumably have more fibrosis or may require more interferon-induced immune stimulation. Final results of the SVR analysis in this study will be of critical importance. If induction dosing does not prove significantly superior, a 48-week course of higher dosing will need to be tried to determine if it is superior to 180 µg weekly. If the induction dosing does prove superior, it will need to be fine-tuned in order to optimize outcomes in clinical practice. Eight weeks of induction may prove equally efficacious versus 12 weeks but will likely improve the incidence of adverse events. The difference in complete EVR between the regimens was 25% higher in the induction arm, which represents a profound difference. If this difference is maintained at 24 weeks, it seems likely that the induction regimen will prove superior overall. However, this will require further validation of higher doses of pegylated interferon alfa-2a, particularly for heavier individuals and those with baseline negative predictors of response such as advanced age, advanced fibrosis, and higher viral loads.

Liu and colleagues' study of HCV versus HCV/HBV co-infected individuals showed a very high SVR is achievable in Asian patients when compared to results from large, published registration trials, with no impact on outcomes engendered by HBV co-infection. Interestingly, 38% of patients had a flare of HBV when the suppressive effects of HCV were cleared with the virus. This suggests that frequent monitoring of HBV DNA is necessary in the co-infected patient and therapy with a nucleoside agent should be considered if HBV DNA levels increase.

The importance of cotherapy with ribavirin has been demonstrated in multiple studies, as has the validity of RVR and truncated therapy in all genotypes. Andriulli and coworkers conducted a multicenter study of 12-week therapy in genotype 2 and 3 patients who achieved RVR. Those with RVR were randomized to continue or stop ribavirin after 4 weeks for the remaining 8 weeks of therapy. Although the numbers in the study were small, SVR was comparable with or without ribavirin beyond 4 weeks in patients with viral loads less than 700,000 IU/mL. This is an interesting and important study in that it raises a question of the true role of ribavirin in rapid responders. Ribavirin cotherapy may be necessary for only the first few weeks, and consolidation following ribavirin treatment may only require interferon. This study may also indicate that patients achieving RVR have cleared the virus within the first 4 weeks of therapy and further treatment may be of little utility. Further exploration of this concept of eliminating ribavirin early in the course of rapid responders is warranted.

The Canadian POWeR study is a prospective, open-label, uncontrolled assessment of weight-based dosing in all HCV genotypes utilizing peginterferon alfa-2b at 1.5 µg/kg weekly and ribavirin at 800–1,400 mg daily. Overall, 1,800 patients were enrolled. Marotta and associates reported SVR rates comparable to those of randomized controlled trials, with 41.6% of genotype 1, 79% of genotype 2, and 72% of genotype 3 patients achieving SVR. An important finding in this study is the significant difference in SVR between those with fibrosis levels less than F2 and those with advanced fibrosis (60% vs 35%, $P<.001$). This may be an indication that minimal-fibrosis patients should receive treatment, given the much higher SVR rates achieved. Bailey and colleagues assessed the genotype 2 and genotype 3 patients in this study and found that although genotype 2 patients had higher viral loads, genotype 3 patients had more fibrosis, and SVR was higher in genotype 2 patients. Importantly, genotype 3 patients with fibrosis did very poorly with 24 weeks of therapy with an SVR of 47% compared to 76% in genotype 2 patients. These findings illustrate clear differences between genotypes 2 and 3 and indicate that they can no longer be considered similar, particularly in cases of advanced fibrosis or high viral load.

In a very unique and aggressive study of decompensated cirrhotics, patients were started on therapy with peginterferon alfa-2b and ribavirin within 1 month of hospital discharge for a decompensation-related event. A total of 94 patients were enrolled, with 36% achieving RVR and SVR (59% in genotype 2 and 3 patients). The positive predictive value for SVR in cases where RVR was achieved was 74%. This is comparable to other studies assessing the positive predictive value of RVR in noncirrhotic patients. The SVR in genotype 1 patients was 16%, indicating that lack of an RVR in this group rarely led to SVR. This group should discontinue therapy if RVR is not achieved. This study highlights the effectiveness of achieving SVR in advanced liver disease in those achieving RVR, particularly genotype 2 and 3 patients.

The importance of EVR as a predictor of response has been seen in multiple trials, ranging from 75% to 100% in its correlation to successful treatment. The lack of an EVR is a strong predictor of lack of subsequent SVR and should be adopted as a definite indicator for treatment discontinuation. Poordad and Kambili summarized the RVR/EVR data from multiple studies and found these rules to be applicable to HIV co-infected patients as well as African Americans and genotype 4 patients. An important caveat to the EVR rule is the distinction of complete EVR (no detectable virus) from partial EVR (2 log drop in viral DNA levels but detectable virus remaining). Patients with partial EVR have a significantly lower chance of achieving SVR compared to those with complete EVR (21% vs 83%).

Normal ALT measures are not associated with a lower rate of SVR when compared to patients with elevated ALT. This was confirmed in a study by Vogel and colleagues, who showed that viral load does affect SVR, even in the normal ALT group. The results were significantly better for viral loads below 800,000 IU/mL, which is consistent with several other lines of evidence that viral load is a strong predictor of response.

The current treatment paradigm of hepatitis C using pegylated interferon and ribavirin has been modified over the past few years with treatment truncation, extension, and most recently higher doses being evaluated. Evaluations of response and predictive assessments using polymerase chain reaction assay at 4-week, 12-week, and 24-week time points are now becoming standard of practice. Further refinement will continue as clinicians eagerly anticipate the arrival of oral protease- and polymerase-inhibiting compounds in the next several years. It is now clear that the development of these small molecules is more complex and arduous than initially anticipated. Indeed, current research shows pegylated interferon and ribavirin as the continuing backbone of future regimens. Thus, continued evaluation to optimize the use of these compounds remains a worthy endeavor. This is particularly relevant in challenging patient populations, such as those with advanced fibrosis, African Americans, and genotype-1 patients with high viral load. For at least the next several years, barring unforeseen issues with the development of protease compounds, optimization of the current standard treatment will continue.

Suggested Reading

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Notes

Individualizing Regimens to Optimize Outcomes in the Treatment of Chronic Hepatitis C With Peginterferon Alfa and Ribavirin

CME Post-Test: *Circle the correct answer for each question below.*

1. In the CHARIOT study, which of the following adverse events was more common with high-dose vs low-dose peginterferon?

   a. Diarrhea
   b. Depression
   c. Fatigue
   d. Hematologic toxicity requiring growth factor support

2. In the study of patients with HCV/HBV coinfection reported by Liu and colleagues, what proportion of patients with undetectable serum HBV DNA at baseline had HBV DNA rebound by the end of follow-up?

   a. 10%
   b. 38%
   c. 68%
   d. 81%

3. Andriulli and colleagues reported that which of the following factors were predictive of attaining an SVR after discontinuing ribavirin at week 4?

   a. Low baseline viral load and low body weight
   b. Low baseline viral load and HCV genotype 3
   c. Low baseline viral load and mild liver disease
   d. Mild liver disease and HCV genotype 3

4. In the Canadian POWeR program, which factor(s) were significantly predictive of responses to peginterferon alfa-2b plus ribavirin in genotype 2 patients?

   a. Baseline viral load
   b. Fibrosis score
   c. Baseline viral load and fibrosis score
   d. None of the above

5. In the same study, which factor(s) were significantly predictive of responses to peginterferon alfa-2b plus ribavirin in genotype 3 patients?

   a. Baseline viral load
   b. Fibrosis score
   c. Baseline viral load and fibrosis score
   d. None of the above

6. TRUE or FALSE: The Canadian POWeR program showed that the efficacy of anti-HCV therapy achieved in controlled clinical trials cannot be expected in clinical practice.

   a. True
   b. False

7. Approximately what proportion of patients with HCV genotype 2 or 3 and decompensated cirrhosis attained an SVR with peginterferon and ribavirin in the study by Iacobellis and colleagues?

   a. 20%
   b. 40%
   c. 60%
   d. 80%

8. Poordad and Kambili reported that the positive predictive value of EVR for SVR was highest in which population of patients?

   a. Genotype 1 patients
   b. Genotype 4 patients
   c. HCV/HIV co-infected patients
   d. African Americans

9. Vogel and colleagues reported that having an elevated ALT level at baseline (vs persistently normal ALT) had what effect on virologic responses to peginterferon plus ribavirin?

   a. Response rate higher in patients with elevated ALT at week 4; response rates similar by week 12
   b. Response rate higher in patients with elevated ALT at week 4; SVR rates similar
   c. Response rate higher in patients with persistently normal ALT at all time points
   d. Response rates similar in both groups at all time points

10. What proportion of patients with HCV genotype 1 or 4 had an SVR following treatment with CIFN plus ribavirin in a report by Witthoeft?

    a. 48%
    b. 62%
    c. 73%
    d. 78%

Evaluation Form: Individualizing Regimens to Optimize Outcomes in the Treatment of Chronic Hepatitis C With Peginterferon Alfa and Ribavirin

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the unmet need in the treatment of chronic HCV with current standard-of-care regimens.	1	2	3	4	5
2. Discuss the latest evidence regarding the adjustment of current HCV regimens to optimize outcomes.	1	2	3	4	5
3. Define future research goals to further improve treatment of chronic HCV.	1	2	3	4	5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1	2	3	4	5
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Provided new ideas or information I expect to use	1	2	3	4	5
Addressed competencies identified by my specialty	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

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Please list any topics you would like to see addressed in future educational activities.

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