Time to Response Seen as Key to HCV Treatment

BY DOUG BRUNK

SAN DIEGO — Dr. Mitchell Shiffman views therapy for hepatitis C as an accordion in which treatment with pegylated interferon and ribavirin is compressed for early responders and extended for slow responders.

"The single best predictor for sustained viral response is the time at which the patient becomes HCV RNA undetectable," he said at a meeting on chronic liver disease sponsored by Scripps Clinic. "Time to response is everything."

Clinicians are starting to modify the duration of therapy with pegylated interferon and ribavirin based on time to respond. Five published studies have examined extending therapy to 72 weeks in patients who are slow to respond. The best-designed study found that the sustained virologic response (SVR) in these patients was 52% by week 48 and 69% by week 72. Other studies have shown that rapid responders may not require therapy beyond 24 weeks (Hepatology 2006;43:954-60).

"So if you have a complete early virologic responder who is negative for disease at 12 weeks, then the optimal duration of therapy appears to be 48 weeks. On the other hand, if you [have] a rapid responder who is negative for disease at 4 weeks, you can compress that therapy down to 24 weeks in most of these patients, with minimal risk of relapse. The worst that can happen is that if you do have a relapse, you can re-treat for 48 weeks. We've done that on occasion," said Dr. Shiffman, chief of the hepatology section at Virginia Commonwealth University, Richmond.

For patients who do not become virus negative until week 24, "you stretch out the duration of therapy to 72 weeks to limit relapse," he said.

Among patients treated with pegylated interferon and ribavirin, those with a virologic response by week 4 are referred to as rapid virologic responders and have the highest SVR and the lowest rates of relapse. Because of that, a shorter period of treatment may suffice, Dr. Shiffman said.

Complete early virologic responders have a virologic response by week 12. "You would not expect this group to have as high a cure rate as the rapid responders," he said.

Among slow responders, HCV becomes undetectable by week 24 and a log2 drop is reached by week 12. "Therefore, you continue therapy in these patients" and monitor viral load, he said. "It's important to differentiate the slow responder from the partial responder."

Patients with a partial response also have a log2 drop by week 12, he said, "but then the virus does not continue to fall; it plateaus. … They never become virus negative. It is irrational to treat this patient beyond week 24."

Recognizing response patterns enables clinicians to predict a patient's chances of achieving a virologic response. Among patients with genotype 1 disease, 15% achieve a virologic response by week 4, compared with 35% by week 12 and 15% by week 24 (J. Hepatol. 2005;43:453-71). The remainder has a null response (20%) or partial response (15%). The SVR rate is highest among those who achieve a virologic response by week 4 (91%), compared with those who achieve a virologic response by weeks 12 and 24 (66% and 45%, respectively).

"So if you have a patient who is slow to respond, they become virus negative at week 24, their chance of relapsing is higher than their chance of getting a sustained response," Dr. Shiffman said.

The single best predictor for sustained viral response is the time when HCV RNA becomes undetectable.

DR. SHIFFMAN

Among patients with genotypes 2 and 3 disease, 66% achieve a virologic response by week 4, 31% achieve virologic response by week 12, and 3% are nonresponders (N. Engl. J. Med. 2007;357:124-34). The SVR rate is highest among those who achieve a virologic response by week 4 (90%), compared with those who achieve a virologic response by week 12 (49%).

Poor prognostic features that are correlated with a low SVR rate include African American race, body mass index of greater than 27 kg/m^2, viral loads that exceed 400,000 IU/mL, and cirrhosis. "The reason this occurs is because these features are associated with slower responses," Dr. Shiffman explained. "But if a patient with a poor prognostic factor achieves a rapid response, their cure rate is just as good as anybody else with a rapid response," Dr. Shiffman said, citing data from a retrospective analysis of six studies that he and his associates conducted involving a total of 894 patients with HCV infection; the SVR rates were similar among patients who achieved a virologic response by week 4 "regardless of any of these poor prognostic factors" (75%, compared with 63% and 33% for those who achieved a virologic response by weeks 12 and 24, respectively).

Dr. Shiffman disclosed that he has received research grants from Hoffmann-La Roche Inc., Schering-Plough Corp., and Vertex Pharmaceuticals, and has received speaker fees from Roche and Schering-Plough. ■

THE EFFECTIVE PHYSICIAN

Hepatitis C

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Nearly 80% of the 4 million Americans positive for hepatitis C antibody have chronic viremia. The American Association for the Study of Liver Diseases recently issued an updated guideline for managing this long-term infection.

Conclusions

Hepatitis C virus (HCV) is the leading cause of death and liver transplantation in the United States.

Patients with chronic HCV have a 5%-25% chance of developing cirrhosis over 25-30 years. Patients with HCV-related cirrhosis have a 30% chance of hepatic failure over 10 years and a 1%-3% annual risk of hepatic carcinoma.

Although intravenous drug use is the leading cause of infection, individuals can be infected after sharing paraphernalia for intranasal drug use. Sexual transmission of the virus between monogamous partners is rare; prevalence is higher in those with multiple sexual partners.

Patients with HIV, undergoing hemodialysis, or presenting with persistent liver enzyme elevations should be tested for HCV. Of the six viral genotypes, subtypes 1a and 1b are the most common, followed by genotypes 2 and 3.

The goal of treatment is to prevent complications and death from HCV. White patients with genotype 1 have a 50% response to antiviral therapy, while black patients obtain only a 30% remission rate. Patients with genotypes 2 and 3 have an 80% chance of sustained remission. Patients coinfected with HIV have lower response rates to antiviral therapy because of higher baseline HCV viremia.

Sustained viral response (SVR) is the absence of HCV viral RNA 24 weeks after cessation of therapy. End of treatment response does not predict SVR. Early viral response (EVR) is the absence of or a more than log2 decrease in HCV RNA at 12 weeks of therapy. Failure to achieve EVR is a strong predictor of not achieving SVR.

Implementation

HCV RNA can be identified within 2 weeks of exposure, while anti-C is not detectable for 8-12 weeks.

Patients with chronic viremia should be considered for therapy, but those with normal enzyme levels are at low risk for progressive disease unless liver biopsy shows evidence of advanced fibrosis. Patients with associated nonhepatic conditions such as symptomatic mixed cryoglobulinemia should be considered for therapy regardless of hepatic status.

All patients should receive genotyping prior to initiation of antiviral therapy because of different prognoses and length of treatment for different viral presentations.

Pegylated interferon alpha plus ribavirin is the treatment of choice for appropriate candidates.

All patients should be tested after 12 weeks of therapy to verify EVR. Failure to achieve EVR after 12 weeks should result in cessation of therapy as it is unlikely that the patient will reach SVR with continued administration of antivirals. Patients with a log2 reduction at 12 weeks but with persistent viremia should be retested at 24 weeks of therapy and have their medication stopped if viremia persists at that time. Patients infected with genotype 1 who clear HCV during weeks 12-24 might benefit from extending antiviral therapy to 72 weeks.

Responsive patients with genotype 1 should receive 48 weeks of pegylated interferon alpha and weight-based dosing of ribavirin. Responsive patients with genotypes 2 and 3 should receive 24 weeks of peglylated interferon alpha and low-dose ribavirin.

Interferon can cause significant hematologic suppression. Dose reduction to greater than 60% of baseline therapy can result in successful treatment. Current evidence does not support use of growth factors to support hematologic status.

Interferon can cause neuropsychiatric side effects. Preexisting, uncontrolled mood disorders are a contraindication for initiation of antiviral therapy.

Nearly half of patients with symptomatic acute HCV will clear the virus. Evidence suggests that patients who do not clear HCV should be treated 8-12 weeks post acute presentation to reduce likelihood of chronic viremia. Treatment with interferon with or without ribavirin for 12 weeks is the current recommendation for therapy.

There are no data to support a second course of antiviral therapy with current medications for patients who fail to achieve SVR or who suffer a relapse of chronic viremia.

Infected patients should not share toothbrushes or shaving equipment with others.

Reference

Ghany M.G., et al. Diagnosis, management, and treatment of hepatitis C: An update. Hepatology 2009;49:1335-74.

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