MODERN MANAGEMENT OF HCV
A CASE-BASED APPROACH NEWSLETTER
ISSUE 1
Hepatitis C: A Genotype 3 Case Report

845 Morningside Lane, Elm Grove, WI 53122

Hepatitis C

A GENOTYPE 3 CASE REPORT

NEWSLETTER ISSUE #1

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Hepatitis C:

A GENOTYPE 3 CASE REPORT

K. Rajender Reddy, MD
Elliott D. Kozin

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CONTENT CONTRIBUTORS

K. Rajender Reddy, MD
Professor of Medicine and Surgery
Director, Hepatology
Medical Director of Liver Transplantation
University of Pennsylvania
Philadelphia, Pennsylvania

Elliott Kozin
Division of Gastroenterology
Department of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

EDUCATIONAL REVIEWER

Adnan Said, MD
Assistant Professor of Medicine
Unit of Gastroenterology
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

STATEMENT OF NEED

Recent review of data presented at annual conferences has identified multiple new challenges and approaches to the patient with HCV. Specifically, changes in duration of therapy for all genotypes, individualization of dosing and the approaches to diagnosis of fibrosis have been highlighted.

INTENDED AUDIENCE

The target audience for this educational meeting includes gastroenterologists and infectious disease physicians involved in the care and management of patients with viral hepatitis

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Identify the patient and disease characteristics that can affect the efficacy and optimal duration of antiviral treatments for hepatitis C virus genotype 3 infection.
- Tailor the dosage and duration of antiviral treatments for individual patients with hepatitic C virus genotype 3 infection, according to the characteristics described in #1 and according to their early response to such treatment.

PREREQUISITES

There are no prerequisites.

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Dr. Reddy indicates that he has received honoraria from Gilead Sciences, Roche Pharmaceuticals, and Valeant Pharmaceuticals.

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No relevant financial relationships with any commercial interests to disclose.

Adnan Said, MD
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INTRODUCTION

Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide and nearly 4 million Americans.[1,2] HCV is a significant cause of chronic liver disease and is the leading indication for liver transplantation.[3,4] Complications from chronic HCV infection include cirrhosis, liver failure, and hepatocellular carcinoma (HCC). A major cause of morbidity and mortality, HCV represents a global pandemic.

Six distinct but related genotypes of HCV and at least 50 subtypes have been identified. The nucleotide sequences of the different genotypes differ by 30%–50% throughout the 9.6-kb genome.[5] The major genotypes have different geographic distributions. Types 1a and 1b, followed by types 2 and 3, are most common in the U.S. and Western Europe. Genotype 2 is more prevalent in countries such as Japan, where genotypes 2a and 2b make up 30% of the HCV distribution.[6] Genotype 3 is more prevalent in India and Pakistan, among other countries, and is more prevalent in intravenous drug users.[7] Apart from the epidemiological significance, HCV genotype has implications for choice of and response to treatment; for example, it dictates the duration of interferon (IFN) and ribavirin (RBV) therapy and the dosage of the latter. Indeed, patients with genotype 2 or 3 are almost 3 times more likely than are those with genotype 1 to respond to current therapies, and optimal treatment duration is variable.

The current standard of care for patients with HCV is weekly subcutaneous injections of pegylated-IFN (PEG-IFN) α2a or α2b combined with daily oral RBV for either 24 or 48 weeks, based on the genotype. Although current combination therapy has markedly improved clinical outcomes compared with the IFN monotherapy of 10 years ago, the expected treatment response rate is still only about 50%. For patients with genotype 2 or 3, 24 weeks of PEG-IFN–RBV treatment, or even less, likely is sufficient, whereas those with genotype 1 require 48 weeks of therapy.[8-10] Generally, with adequate doses and duration of PEG-IFN–RBV treatment, 60%–90% of patients with genotype 2 or 3, and about 30%–50% of those with genotype 1, can achieve a sustained viral response (SVR) irrespective of viral load and presence of cirrhosis.[11-14]

This newsletter presents a case study of a patient with HCV genotype 3 and discusses antiviral treatment options for such patients based on recent observations in clinical trials.

CASE STUDY: HCV GENOTYPE 3a PATIENT

A 44-year-old man was evaluated for chronic HCV infection. The patient worked as a respiratory therapist and was exposed to blood and multiple needle sticks throughout his career. He related no history of intravenous drug use, but he had multiple tattoos. He related a history of heavy drinking for about 5 years that had ended 8 years previously. He weighed 324 lbs (147 kg) and was 5'11" (180 cm), indicating obesity (body mass index, 47.2). The physical examination was unremarkable.

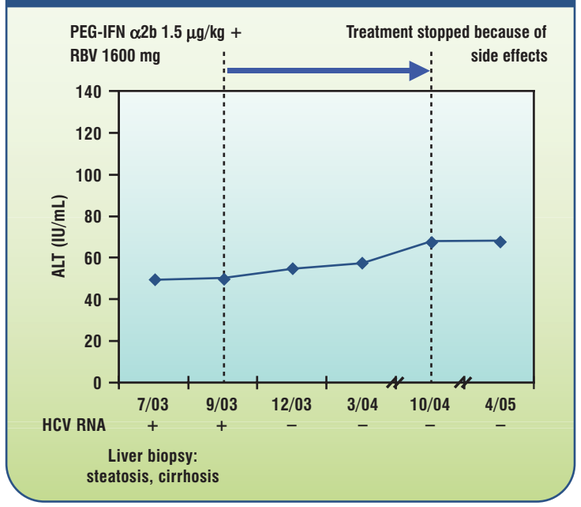
Hepatic biochemical laboratory values were normal except for an elevated alanine aminotransferase (ALT) of 124 U/L (normal, <40 U/L). His white blood cell count was 3.8×10^9/L; hemoglobin, 14 g/dL (8.7 mmol/L); and platelet count, 183×10^9/L. All other laboratory values were within normal ranges. He was anti-HCV–positive, had an HCV RNA level of 286,000 IU/mL, and was determined to be infected with HCV genotype 3a. Results were positive for anti-hepatitis B virus surface (HBs) antibodies but negative for hepatitis B surface antigen (HBs Ag), anti-hepatitis B core (HBc) antibodies, and anti-hepatitis A virus (HAV) antibodies.

Ultrasound revealed fatty liver with mild splenomegaly, and the patient declined liver biopsy at the time of initial evaluation.

He was started on a 24-week course of anti-HCV therapy, receiving subcutaneous PEG-IFN α2b 1.5 μg/kg weekly with oral, weight-based RBV 1200 mg daily (note: standard dosage is 800 mg daily; weight-based dosing of ribavirin is not approved by the FDA). After 3 months of antiviral therapy, he became HCV RNA-negative, and his ALT had decreased to 80 U/L. Over the next 3 months, he remained HCV RNA-negative and had a relatively consistent ALT value of 100 U/L.

However, 6 months after cessation of treatment, he again became HCV RNA-positive (344,000 IU/mL) and had an elevated ALT level of 50 U/L. He underwent a liver biopsy at this stage that revealed steatosis, chronic hepatitis, and cirrhosis. In response to these findings, he was placed on a planned 72 weeks of therapy with subcutaneous PEG-IFN α2b 1.5 μg/kg weekly and higher-dose oral RBV therapy (1600 mg daily). After 3 months of retreatment, he again became HCV RNA-negative and his ALT level was 50 U/L. After 65 weeks of treatment, he stopped therapy early due to side effects of the antiviral treatment. He has remained HCV RNA-negative but has an elevated ALT more than 2 years after discontinuing therapy.

Figure 1. Case Study: Response to Repeat Antiviral Therapy



ANTIVIRAL TREATMENT FOR HCV GENOTYPE 3

Standard-of-Care Treatment for HCV

The objective of HCV treatment is to eliminate the virus and prevent potential complications from chronic HCV infection, including necrosis, fibrosis/cirrhosis, hepatic decompensation, and HCC. Because complications of HCV evolve over an extended period and at varying rates in different patients, the primary, quantifiable goal of HCV treatment is SVR, defined as HCV RNA-negativity 6 months after cessation of therapy.

The past 15 years have witnessed steady improvement in HCV therapy. In the mid-1990s, type 1 IFNs (IFN-α2a and IFN-α2b) were considered treatments of choice and were given by injection 3 times weekly for 6–12 months. This therapy was associated with overall SVR rates of 6%–10%.[15-17] The addition of RBV to IFN treatment in the late 1990s increased the overall SVR rates to about 30%.[18,19] More recently, to realize the potential benefit of sustained IFN concentrations, the half-life of the IFN has been increased by attaching an inert polyethylene glycol (PEG) molecule to the IFN molecule. This has led to significantly better pharmacokinetics of interferon and response rates.

The 2002 National Institutes of Health (NIH) Consensus Statement indicates that the combination of PEG-IFN α2a or α2b and RBV (1000–1200 mg daily) for 48 weeks is appropriate for patients with HCV genotype 1, whereas those with genotype 2 or 3 should receive 24 weeks of combination therapy that includes 800 mg RBV daily.[20] The SVR rate for such therapy in patients with genotype 1 is 42%–56% overall with 48 weeks of therapy. In patients with genotype 1 and a high HCV viral load, the SVR rate is between 26% and 42%, whereas for patients with genotype 1 and a low viral load, it varies between 52% and 56%. Patients with genotypes 2 or 3 have SVR rates between 75% and 84% with 24 weeks of therapy.[11-13]

Genotype 2 and 3 Antiviral Treatment Options

Given the increased frequency of side effects with prolonged treatment, leading to premature treatment termination in many patients, and that HCV treatment is expensive (24-48 weeks of combination PEG-IFN α2a–RBV treatment averaged between $12,000 and $18,000 in 2001 dollars),[21] investigators have assessed the efficacy of shorter treatment durations for the available antiviral therapies.[22] Courses of 24 weeks of PEG-IFN–RBV treatment (or even less) may be sufficient for some patients with HCV genotype 2 or 3 (Table 1).[8,9,13,19,23,24]

In one of the first randomized, double-blind studies of shorter-duration therapy, Hadziyannis et al. assessed the efficacy and safety of 24 or 48 weeks of treatment with PEG-IFN α2a (180 μg/week) plus a standard (800 mg/d) or weight-based dose of RBV (1000 or 1200 mg/d) in 1311 patients with chronic HCV.[13] The SVR rates did not differ significantly by treatment for the 492 patients with HCV genotype 2 or 3. Thus, these patients might be adequately treated with PEG-IFN α2a and a low dose of RBV for 24 weeks.

Zeuzem et al. also investigated the efficacy of open-label PEG-IFN α2b (1.5 μg/kg/week) plus RBV (800–1400 mg/d, based on weight) given for 24 weeks in patients with chronic HCV genotype 2 (n=42) or 3 (n=182) infection.[23] Using historical data from a previous large study, the SVR rate was predicted to be 84.4% if the patients in the study had been treated for 48 weeks. The actual SVR rates were 93% and 79% for the genotype 2 and 3 patients, respectively. Baseline viremia, treatment duration >16 weeks, and steatosis were significant independent predictors of SVR. The investigators concluded that 24 weeks of PEG-IFN α2b–RBV treatment is sufficient in patients with HCV-2 or -3 infection. Further, the SVR rate was higher in patients infected with HCV-2 versus -3; thus, virologic response rates should be assessed and presented by individual genotype rather than being combined.

Table 1. Antiviral Trials in Patients with HCV Genotypes 2/3, by Treatment Duration

STUDY	DESIGN	POPULATION	DURATION	DRUG REGIMEN	SUSTAINED VIRAL RESPONSE
Hadziyannis et al.[13]	Randomized; double-blind	HCV-2 or -3 (n=492)	24 or 48 wks	PEG-IFN α2a 180 µg/wk + LD (800 mg/d) RBV or WB (1000 or 1200 mg/d) RBV	24 wks, LD: 84% 24 wks, WB: 81% 48 wks, LD: 79% 48 wks, WB: 80%
Zeuzem et al.[23]	Open-label	HCV-2 (n=42) HCV-3 (n=182)	24 wks	PEG-IFN α2b 1.5 µg/kg/wk + WB 800-1400 mg/d RBV	HCV-2: 93% HCV-3: 79%
Dalgard et al.[8]	Uncontrolled	HCV-2 (n=23) HCV-3 (n=99)	14 or 24 wks based on PCR negativity at 4 and 8 wks (EVR)	PEG-IFN α2b 1.5 µg/kg/wk + WB 800-1400 mg/d RBV	EVR 14 wks HCV-2: 91% HCV-3: 89% No EVR 24 wks HCV-2: 50% HCV-3: 56%
Mangia et al.[19]	Randomized	HCV-2 (n=213) HCV-3 (n=70)	24 wks (fixed) or 12/24 wks (variable) based on RVR	PEG-IFN α2b 1.0 µg/kg/wk + WB 1000-1200 mg/d RBV	24 wks (fixed) HCV-2: 76% HCV-3: 76% RVR 12 wks (variable) HCV-2: 87% HCV-3: 77% No RVR 24 wks (variable) HCV-2: 72% HCV-3: 41%
Von Wagner et al.[9]	Randomized	HCV-2 (n=39) HCV-2/-3 (n=1) HCV-3 (n=113)	16 or 24 wks based on RVR	PEG-IFN α2a 180 µg/wk + WB 800-1200 mg/d RBV	RVR 16 wks HCV-2 LVL: 100% HCV-2 HVL: 93% HCV-3 LVL: 93% HCV-3 HVL: 54% RVR 24 wks HCV-2 LVL: 100% HCV-2 HVL: 93% HCV-3 LVL: 84% HCV-3 HVL: 67% No RVR 24 wks HCV-2 or -3: 36%
Shiffman et al.[24]	Randomized; open-label	HCV-2 (n=728) HCV-3 (n=727)	16 or 24 wks	PEG-IFN α2a 180 µg/wk + 800 mg/d RBV	16 wks HCV-2: 65% HCV-3: 65% 24 wks HCV-2: 82% HCV-3: 71%

EVR = early virologic response (undetectable HCV RNA level at Weeks 4 and 8[8]), HVL = high pretreatment viral load (HCV RNA level >800,000 IU/mL), IFN = interferon, LD = low-dose, LVL = low pretreatment viral load (HCV RNA level <800,000 IU/mL), PEG-IFN = pegylated interferon, RBV = ribavirin, RVR = rapid virologic response (undetectable HCV RNA level at Week 4), WB = weight-based.

In a nonrandomized pilot study among 20 hospitals, Dalgard et al. assessed the efficacy of 14 weeks of combination antiviral treatment in treatment-naive patients with HCV genotype 2 (n=23) or 3 (n=99) infection.[8] Patients received 1.5 µg/kg PEG-IFN α2b subcutaneously once a week plus 800–1400 mg/d RBV based on weight. Treatment was stopped at Week 14 in patients with early virologic response (EVR), defined as undetectable HCV RNA levels at 4 and 8 weeks after treatment initiation. Patients without EVR were assigned to 24 weeks of treatment. In all, 95 patients (78%) had EVR and received 14 weeks of treatment. Of those with EVR, 85 patients (90%) achieved SVR compared with only 15 (56%) of the patients receiving 24 weeks of treatment after having no EVR. Among the genotype 3 patients, SVR was achieved after 14 weeks of treatment more often among those with low versus high viral load at baseline (98% vs. 79%; $P<0.019$). Absence of bridging fibrosis/cirrhosis was the only independent predictor of SVR. Although this was not a randomized controlled study, patients with genotype 2 or 3 and EVR did achieve a high SVR after only 14 weeks of treatment.

In a more recent study, Mangia et al. hypothesized that for patients infected with HCV genotype 2 or 3 who had rapid virologic responses (RVR), defined as undetectable HCV RNA levels 4 weeks after beginning therapy, 12 weeks of treatment might be as effective as 24 weeks.[19] Of the total 283 patients enrolled, 70 were randomized to receive a standard 24-week regimen of PEG-IFN α2b (1.0 µg/kg/week) plus RBV (1000 or 1200 mg daily, based on weight), and 213 were allocated to receive the same drug regimen for 12 or 24 weeks, depending on whether tests for HCV RNA were negative or positive at Week 4 (the variable-duration group).

In all, 45 patients (64%) in the standard-duration group had RVR compared with 133 patients (62%) in the variable-duration group; the rates of SVR were 76% and 77%, respectively. By genotype, the overall rates of SVR were 80% and 66% for genotypes 2 and 3, respectively ($P<0.001$). In this study, 12 weeks of therapy was as effective as 24 weeks of therapy for patients with HCV genotype 2 or 3 who had responded to treatment at 4 weeks.

This finding was supported by a similar study from von Wagner et al., which compared the efficacy and safety of combination antiviral therapy given for 16 or 24 weeks in patients with chronic HCV genotype 2 (n=39) or 3 (n=113) infection.[9] Patients received PEG-IFN α2a (180 µg/wk) and ribavirin (800–1200 mg/day), and HCV RNA was quantitatively assessed after 4 weeks. Patients with RVR (HCV RNA level <600 IU/mL) were then randomized for a total treatment duration of 16 or 24 weeks. Patients without RVR (HCV RNA ≥600 IU/mL at week 4, 7% of the cohort) were treated for 24 weeks. Overall, end-of-treatment virologic response rates were 94% for patients with RVR treated for 16 weeks, 85% for those with RVR treated for 24 weeks, and 73% for those without RVR. The corresponding SVR rates were 82%, 80%, and 36%, respectively. Genotype 3 patients with a high baseline viral load (HCV RNA >800,000 IU/mL) had a significantly lower SVR rate than did genotype 3 patients with a lesser baseline viral load (59% vs. 85%, respectively; $P=0.003$). Thus, for patients with genotype 2 or 3 and a low baseline viral load who have RVR, 16 weeks of treatment may be sufficient. Patients with genotype 3 infection and a higher baseline viral load may require longer treatment.

Preliminary results of the ACCELERATE trial, the largest randomized, controlled study in patients with HCV genotype 2 or 3, have recently been presented.[24] The study was designed to determine whether a 16-week course of PEG-IFN α2a and RBV (800 mg) could be as effective as the standard 24-week course. In this study, the SVR rate was higher with 24 weeks versus 16 of treatment regardless of HCV genotype or baseline serum HCV RNA level. Even patients who had become HCV RNA-negative by Week 4 had a higher SVR rate with 24 versus 16 weeks of treatment ($P=0.007$). The lower SVR in patients treated for 16 weeks was primarily due to a near-doubling in the relapse rate; genotype 2 or 3 patients without RVR had an SVR rate of only 49%. Since RBV is associated with lower relapse rates, the lower dosage of RBV used in ACCELERATE relative to other studies may partly explain this finding. The SVR rate after 24 weeks of therapy was similar to that seen in previous studies. Thus, 16 weeks of treatment appeared to be inferior to standard treatment in patients with HCV genotype 2 or 3 infection.

DISCUSSION

The outlined research on HCV genotype 3 and shorter-duration therapies provide greater insight into the presented case study. HCV genotype 3-infected patients, especially those with cirrhosis, have higher relapse rates compared with patients with genotype 2 infection; therefore, clinicians should take into account all of the various host and viral factors when deciding on a treatment regimen. As represented in the studies by Dalgard et al. and others, the case-study patient might have benefited from longer-duration therapy given the presence of cirrhosis. Dalgard et al. found that the absence of cirrhosis was an independent predictor of SVR; however, since the patient declined to undergo initial liver biopsy, cirrhosis could not be confirmed histologically. Liver biopsy may be more strongly suggested for HCV genotype 3-infected patients to ascertain the presence of cirrhosis, which can factor into decisions related to duration of therapy.

There is an evolving concept in current practice to assess for rapid virologic response while patients are receiving HCV therapy. The Week 4 virologic response has been suggested to dictate whether longer- or shorter-duration antiviral therapy is required. If an HCV genotype 2 or 3-infected patient has undetectable levels of virus after 4 weeks of treatment, then shorter-duration therapy can be considered, particularly if the patient has difficulty in tolerating treatment. Conversely, patients with persistent HCV RNA levels at Week 4 should receive treatment for at least 24 weeks and perhaps up to 48 weeks. Data to support a greater benefit with 48 weeks of therapy are lacking, but it would seem reasonable to consider prolonged therapy for HCV genotype 3-infected patients with high viral load and those with cirrhosis who fail to achieve RVR. The viral load of the case-study patient was not evaluated after the first month of treatment. Given the patient's relapse after initial treatment, virus might well have persisted after 4 weeks; thus, he perhaps should have been maintained on therapy beyond the initial 24 weeks.

Another issue of the HCV genotype 3-infected patient relates to weight and RBV dosage. Several recent studies have suggested a tailored RBV dosage based on patient weight. Given the patient's moderate obesity, he probably should have received a higher initial dose of RBV, which might have prevented his initial relapse.

In summary, although HCV genotype 3-infected patients have an SVR rate 2–3 times higher than that of patients with genotype 1 infection, their course of treatment must be individually tailored and monitored to achieve optimal results. Current clinical research suggests that HCV genotype 3-infected patients have higher relapse rates compared with genotype 2-infected patients, and therapy may need to continue longer for genotype 3 patients with high viral load and/or cirrhosis. Recent data also suggest that an assessment of RVR should probably occur shortly after treatment initiation, to help guide its duration. Finally, a patient's weight may play a role in achieving SVR; the dosage of RBV may require adjustment accordingly. This aspect again may be more applicable to HCV genotype 3-infected patients.

Hepatitis C: A Genotype 3 Case Report

EVALUATION

1. Did the material presented in this activity meet the learning objectives stated on page 2?

☐ Met the stated objectives.
☐ Did not meet the stated objectives.

2. Please rate the contents of this newsletter using the following scale: 5 = Excellent; 4 = Very good; 3 = Good; 2 = Fair; 1 = Poor (Circle one response for each question.)

Timely, up to date?	5	4	3	2	1
Practical?	5	4	3	2	1
Relevant to your practice?	5	4	3	2	1

3. Are there any other topics you would like to have seen addressed in this activity?

☐ Yes (Please specify): _____
☐ No

4. Please describe any changes you plan to make in your clinical practice based on the information presented in this newsletter: _____

5. Development and production of this newsletter were made possible with educational funding from a commercial sponsor. Did you detect any commercial bias in this newsletter?

☐ Yes (Please describe:) _____
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6. Any other comments/suggestions for future educational activities relating to Hepatitis C? _____

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In order to complete this activity successfully, you must:

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- Complete the evaluation section.
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POST-TEST

CME POST-TEST

Please select the single best answer.

1. **The most common genotype of hepatitis C virus in the U.S. is:**

   a. Genotype 1
   b. Genotype 2
   c. Genotype 3
   d. Combined genotypes 2 and 3
   e. Genotype 4

2. **The current standard of therapy for patients with HCV is:**

   a. Pegylated interferon (PEG-IFN) alone
   b. Ribavirin alone
   c. Combination PEG-IFN with ribavirin
   d. Immune globulins
   e. All of the above

3. **The response to combination anti-HCV treatment can be influenced by**

   a. The presence of steatosis
   b. The presence of cirrhosis
   c. The specific HCV genotype
   d. The pretreatment viral load
   e. All of the above

4. **The primary objective of HCV treatment is to:**

   a. Maintain serum levels of the virus at an acceptable level
   b. Eliminate virus and prevent complications of chronic HCV infection, such as fibrosis/cirrhosis, decompensated liver disease and hepatocellular carcinoma (HCC)
   c. Prevent coinfection with other hepatitis viruses or HIV
   d. Ameliorate the symptoms of hepatitis
   e. None of the above

5. **In general, which genotype tends to respond best to standard antiviral treatment for HCV infection?**

   a. Genotype 1
   b. Genotype 1 or 3
   c. Genotype 2 or 3
   d. Genotype 4
   e. All genotypes tend to respond similarly to antiviral treatment for HCV

6. **Shorter courses (12–16 weeks) of antiviral treatment for HCV might be appropriate for patients with:**

   a. A rapid viral response to therapy
   b. A low initial viral load
   c. HCV genotype 2 or 3
   d. No cirrhosis at baseline
   e. All of the above

7. **In appropriate patients with HCV, liver biopsy ideally:**

   a. Should be performed after antiviral therapy is completed
   b. Should be performed before antiviral treatment begins
   c. Should be performed both before and after antiviral therapy
   d. Should be performed every 6 months, regardless of treatment
   e. None of the above

8. **For patients with HCV genotype 3, the dosage of ribavirin:**

   a. Should be the same for all patients
   b. Should be tailored according to the patient's weight
   c. Should alternate between a high dose and a low dose
   d. Should be increased until a sustained viral response is achieved
   e. None of the above

Full Name _____ Phone _____

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