MODERN MANAGEMENT OF HCV
A CASE-BASED APPROACH NEWSLETTER
ISSUE 3
Hepatitis C: Nonresponder Case Study

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Hepatitis C
NONRESPONDER CASE STUDY

NEWSLETTER ISSUE #3

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STATEMENT OF NEED

Recent review of data presented at annual conferences has identified multiple new challenges and approaches to management of patients infected with hepatitis C virus (HCV). Specifically, the substantial incidence of patients who do not respond to standard initial antiviral therapies for HCV has emerged as a growing problem.

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 options for management of patients who do not respond to or who relapse after receiving standard antiviral therapies for HCV.
- Tailor the treatment of nonresponder patients according to patient and disease characteristics.

PREREQUISITES

There are no prerequisites.

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INTRODUCTION

Hepatitis C virus (HCV) infects an estimated 170 million people 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] Apart from its epidemiological significance, HCV genotype has implications for the choice of and response to treatment; for example, it dictates the duration of interferon (IFN) and ribavirin (RBV) therapy and, for many clinicians, the dosage of the latter. Patients with genotype 2 or 3 are 2–3 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 virus eradication and clinical outcomes compared with the IFN monotherapy of the previous decade, the expected sustained response rate is still only about 50% across all genotypes. For patients with genotype 2 or 3, 24 weeks of PEG-IFN–RBV treatment, or possibly even less if HCV RNA clears by Week 4, is sufficient, whereas most patients with genotype 1 require 48 weeks of therapy.[6-8] Generally, with adequate doses and duration of PEG-IFN and 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).[9-12]

Despite recent advances in antiviral therapy, there remains a sizeable proportion of patients, particularly those with HCV genotype 1, who do not respond to current HCV antiviral regimens. Indeed, patients with HCV genotype 1 who do not respond to IFN and RBV have shown only a 8%–15% SVR rate with current standard-of-care treatments (PEG-IFN and RBV).[13,14]

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

CASE STUDY

A 31-year-old married woman with 2 young children underwent surgical repair of an atrial septal defect at 6 years of age and received blood transfusions. After delivery of her second child at the age of 29, she was found to have HCV genotype 1 infection with a viral level of 175,000 IU/mL. Physical examination revealed no signs of advanced liver disease or cirrhosis. Liver biopsy revealed grade 2-3, stage 3-4 fibrosis (bridging fibrosis with nodularity).

The patient began treatment with PEG-IFN α2b 1.5 μg/kg/wk and RBV 1000 mg/day. Pretreatment laboratory data included: alanine aminotransferase (ALT), 40 U/L; aspartate aminotransferase (AST), 28 U/L; albumin, 4.9 mg/dL (49 g/L); and total bilirubin, 0.8 mg/dL (13.7 μmol/L). After 24 weeks of treatment, without dose reductions, the HCV RNA level was 4170 IU/mL and the ALT was 17 U/L.

Several options were discussed with the patient, including: 1) continuing her regimen for another 12–24 weeks to maximize the histologic benefit of treatment; 2) discontinuing therapy, since the chance of SVR was extremely remote; or 3) switching to daily consensus interferon (cIFN, IFN alfacon-1) and ribavirin in light of preliminary reports suggesting that such a regimen can induce SVR in some patients who fail to respond to PEG-IFN and RBV therapy.[15,16]

The patient was switched to treatment with cIFN 9 μg daily and RBV 1000 mg/day. After 1 month, the HCV RNA level by polymerase chain reaction (PCR) assay was 2820 IU/mL; after 2 months, it was 87 IU/mL; and after 3 months, it became undetectable (<50 IU/mL), but a qualitative transcription-mediated amplification (TMA) assay with a lower limit of detection (5 IU/mL) was positive.

The patient's cIFN dose was increased to 15 μg/day, and RBV 1000 mg/day was continued. After 1 month of this increased dose (i.e., 4 months of cIFN in total), both the PCR and TMA assays for HCV RNA were negative. Over the next 8 months, HCV RNA remained undetectable. The patient had side effects common with IFN-based treatment, such as fatigue. She also developed 2 1-cm skin ulcers at injection sites on the abdominal wall. Cultures were positive for *Pseudomonas aeruginosa,* and antibiotics were given.

After 8 months of TMA negativity (12 months of cIFN and RBV treatment in total), treatment was stopped. HCV RNA was detected in serum 1 month later.

ANTIVIRAL TREATMENT FOR NONRESPONDERS

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 10%–15%.[17-19] The addition of RBV to IFN treatment in the late 1990s increased the overall SVR rates to about 40%.[20,21]

In recent years, 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 of 2 different sizes (40 kDa for PEG-IFN α2a, 12 kDa for PEG-IFN α2b) to the IFN molecule. This has led to significantly better pharmacokinetics of IFN and increased response rates.

The 2002 National Institutes of Health (NIH) Consensus Statement indicated 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 of RBV daily.[22] The SVR rate for such therapy in patients with genotype 1 is 42%–46% overall with 48 weeks of therapy. In patients with genotype 1 and a high HCV viral load, the SVR rate is between 30% and 40%, whereas for patients with genotype 1 and a low viral load, it varies between 55% and 70%. Patients with genotypes 2 or 3 have SVR rates between 75% and 84% with 24–48 weeks of therapy.[11-13]

Nonresponder Antiviral Treatment Options

Although SVR rates have risen dramatically in recent years, substantial numbers of patients do not respond to initial antiviral treatment regimens. Nonresponders fall into 3 categories: 1) nonresponders to IFN monotherapy, 2) nonresponders to IFN and RBV therapy, and 3) nonresponders to PEG-IFN and RBV therapy. There are more published data on retreatment of the first 2 groups with PEG-IFN and RBV, but, given the chronology of the development of therapeutic regimens, the third group is the one that has expanded most dramatically in recent years. Unfortunately, since PEG-IFN and RBV is still the standard of care, there is currently no generally accepted therapeutic strategy for this patient population. Clinical trials have focused on 3 approaches: switching to the other PEG-IFN therapy, cIFN-based therapies, and low-dose, maintenance IFN-based therapy (see Table).[13-16,23-31] There are also trials being performed of new agents such as specifically targeted antiviral therapies and immune modulators.

Table 1. Trials of Repeat Antiviral Treatment in HCV Nonresponders

STUDY	POPULATION	TREATMENT	DURATION	SVR RATE
Jacobson[14]	Nonresponse to IFN tx (n=47) Nonresponse to IFN+RBV tx (n=219) Relapse after IFN+RBV tx (n=55)	PEG-IFN α2b 1.5 μg/kg/wk + RBV 800 mg/d or PEG-IFN α2b 1.0 μg/kg/wk + RBV 1000–1200 mg/d	48 weeks	21% 8% 42%
HALT-C[13]	Nonresponse to IFN tx, with or without RBV (n=604)	PEG-IFN α2a 180 μg/wk + RBV 1000–1200 mg/d	48 weeks, if HCV RNA undetectable at Week 20	Monotherapy nonresponders: 28% Combination tx nonresponders: 12%
EPIC3[3,23]	Nonresponse to IFN– or PEG-IFN–RBV tx Relapse after any IFN– or PEG-IFN–RBV tx (total n=575)	PEG-IFN α2b 1.5 μg/kg/wk + RBV 800–1400 mg/d	48 weeks[1]	15% 39%
Krawitt[25a]	Nonresponse to IFN or IFN–RBV tx (n=116) Relapse after IFN or IFN–RBV tx (n=66)	PEG-IFN α2b 1.5 μg/kg/wk + RBV 1000–1200 mg/d	48 weeks	20% 55%
RENEW[25b]	Nonresponse to IFN+RBV tx (n=963)	PEG-IFN α2b 0.5, 1.5, or 3.0 μg/kg/wk + RBV 800–1400 mg/d	48 weeks (tx stopped at Week 24 if HCV RNA-negative)	3.0 μg/kg: 17% 1.5 μg/kg: 12%[2]
REPEAT[26]	Nonresponse to PEG-IFN α2b +RBV tx	PEG-IFN α2a 360 μg/wk (n=430) vs. 180 μg/wk (n=426); both + RBV 1000–1200 mg/d	12 weeks[3]	EVR: 43% EVR: 26%
Rustgi[27]	Nonresponse to PEG-IFN α2b+RBV tx (n=29)	PEG-IFN α2a+RBV (no doses given)	48 weeks	3%
Leevy[15]	Nonresponse to PEG-IFN α2b+RBV tx (n=137)	cIFN 15 μg/d + RBV 1000–1200 mg/d for 12 wks, then cIFN 15 μg 3 times/wk + RBV 1000–1200 mg/d for 36 wks	48 weeks	37%
Kaiser[16]	Nonresponse to PEG-IFN α2a or α2b+RBV tx (total n=95)	cIFN 27 μg/d for 4 wks, then 18 μg/d for 12 wks, then 9 μg/d + weight-based RBV vs. cIFN 9 μg/d for 16 wks, then + weight-based RBV	48–72 weeks, depending on when PCR result became negative	PEG-IFN α2b nonresponders: Induction cIFN: 25% Consistent cIFN: 18% PEG-IFN α2a nonresponders: Induction cIFN: 41% Consistent cIFN: 34%
Kaiser[28]	Relapse after PEG-IFN+RBV tx (n=81)	cIFN 9 μg/d vs. PEG-IFN α2a 180 μg/wk; both + weight-based RBV	72 weeks	69% 44%
Cornberg[29]	Nonresponse to non-PEG-IFN or IFN+RBV tx (n=77)	cIFN 18 μg/d for 8 wks, then 9 μg/d for 40 wks; vs. cIFN 9 μg/d for 48 wks; both + RBV 1000–1200 mg/d	48 weeks	30% (22% for nonresponders to IFN+RBV tx)
DIRECT[30]	Nonresponse to PEG-IFN +RBV tx (n=343)	cIFN 9 μg/d + RBV vs. cIFN 15 μg/d + RBV	48 weeks	EOT: 16% EOT: 19%
COPILOT[31]	Nonresponse to IFN+RBV or PEG-IFN+RBV tx (n=534)	PEG-IFN α2b 0.5 μg/kg/wk vs. colchicine 6 mg twice daily	≥2 years	NA; clinical, histological, and quality-of-life outcomes only

EOT = end of treatment; EVR = early virologic response (>2-log decrease or undetectable HCV RNA level at Week 12[26]), IFN = interferon; NA = not available; PEG-IFN = pegylated interferon, RBV = ribavirin; SVR = sustained virologic response.

[1] Interim data.

[2] Enrollment in the low-dose arm was stopped when the U.S. Food and Drug Administration (FDA) approved higher doses of PEG-IFN α2b.

[3] Induction phase data only.

Jacobson and colleagues assessed the efficacy of retreatment with combination PEG-IFN and RBV therapy in patients unresponsive to IFN monotherapy or combination IFN–RBV treatment or who relapsed despite combination therapy.[14] Patients (n=321) were randomized to receive either PEG-IFN α2b 1.5 μg/kg/wk plus RBV 800 mg/day or PEG-IFN α2b 1.0 μg/kg/wk plus RBV 1000–1200 mg/day. The SVR rate was 8% in the combination-therapy nonresponders, 21% in the IFN-monotherapy nonresponders, and 42% in the combination-therapy relapsers, without significant differences between treatment arms. Among nonresponders to prior combination therapy, an HCV RNA level <100,000 copies/mL at the end of the previous treatment course was associated with a significantly higher SVR rate compared with levels ≥100,000 copies/mL (21% vs. 5%; $P=0.002$). Thus, combination therapy with PEG-IFN α2b plus RBV appeared to be much more effective, as might have been expected, in patients who relapsed after combination standard IFN plus RBV therapy than in nonresponders to either combination therapy or IFN monotherapy.[14]

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial was a prospective, randomized, controlled study of maintenance PEG-IFN therapy versus no treatment for patients with HCV and advanced fibrosis or cirrhosis who failed to achieve an SVR after previous IFN treatment with or without RBV.[13] Patients were treated with a lead-in regimen of PEG-IFN α2a 180 μg/week and RBV 1000–1200 mg/day. Patients who had no detectable HCV RNA at Week 20 of the initial phase of the study remained on combination therapy for 48 weeks, and SVR was monitored.

In the lead-in study, 35% of patients had undetectable HCV RNA at treatment Week 20, and 18% achieved SVR. Factors associated with SVR included previous treatment with IFN monotherapy compared with combination therapy (28% versus 12%), infection with HCV genotype 2 or 3, a lower AST:ALT ratio, non-black race, and absence of cirrhosis. Reducing the dose of RBV from ≥80% to ≤60% of the starting dose during the first 20 weeks of treatment was associated with a significant decrease in SVR rate, from 21% to 11%, but SVR rate did not appear to be affected by reducing the dose of PEG-IFN or reducing RBV after Week 20, when HCV RNA had become undetectable. (Later analysis showed that ribavirin discontinuation had a much larger effect than did PEG-IFN dose reduction.) The authors concluded that selected nonresponders to previous IFN-based therapy can achieve SVR after retreatment with PEG-IFN α2a plus RBV.[13]

In the Evaluation of Peg-Intron in Control of Hepatitis C Cirrhosis (EPIC[3]) trial, Poynard and colleagues sought to determine the efficacy of PEG-IFN with RBV in patients who were unresponsive to IFN plus RBV-based therapies (relapsers were included).[23] Patients were treated with PEG-IFN α2b 1.5 μg/kg/wk and RBV 800–1400 mg/d for up to 48 weeks. If HCV RNA was reduced by >2 logs or undetectable at Week 12, patients continued treatment for another 36 weeks plus 24 weeks of follow-up. All patients had pretreatment biopsies scored by a single reviewer using METAVIR criteria. HCV RNA level was determined at treatment Weeks 12, 24, and 48 of therapy and at follow-up Weeks 12 and 24.

Of the first 575 patients enrolled in EPIC[3], 23% achieved SVR. The SVR rate was 54% among patients with genotype 2 or 3 versus 16% for genotype 1 patients and 39% for previous relapsers versus 15% in nonresponders. Notably, nonresponders and relapsers who were HCV RNA-negative at Week 12 were equally likely to achieve SVR, the rate of which was higher in F2/3 patients (27%) compared with F4 patients (14%). The SVR rate was higher in nonresponders with genotype 2 or 3 versus genotype 1 (47% vs. 12%) and relapsers (58% vs. 29%). In a subsequent analysis of 1354 EPIC[3] patients,[24] those with residual viremia at Week 12 seldom attained SVR (6%), whereas 56% of those with negative PCR at Week 12 did so. Given these outcomes, the investigators concluded that retreatment with PEG-IFN plus RBV-based therapies might lead to SVR in a substantial proportion of patients with previous treatment failure who are HCV RNA-negative at treatment Week 12.[24]

Krawitt et al. also assessed the efficacy of PEG-IFN α2b with RBV therapy in 182 patients who did not respond to or who relapsed after IFN-based treatment with or without RBV.[25a] The SVR rates were 20% (23/116) for previous IFN nonresponders and 55% (36/66) for previous relapsers ($P<0.001$).

The "RENEW" study assessed the efficacy of doubling the dose of PEG-IFN α2b and employing a weight-based RBV dosing model in patients who had not responded to treatment with IFN and RBV.[25b] Patients were randomized to receive 48 weeks of treatment with PEG-IFN α2b at 0.5, 1.5, or 3.0 μg/kg/wk with RBV 800–1400 mg/day. Treatment was discontinued at treatment Week 24 if the patient's serum was HCV RNA-negative. The primary endpoint was the absence of HCV RNA after 24 weeks of treatment. In all, 963 patients were enrolled, and 818 started treatment. Enrollment in the low-dose arm was stopped when the U.S. Food and Drug Administration (FDA) approved higher doses of PEG-IFN α2b. At that point, 704 treated patients remained in the study—352 in each of the other 2 treatment arms.[25b]

On an intent-to-treat basis, the rate of SVR was 17% for patients receiving PEG-IFN α2b 3.0 μg/kg/wk compared with 12% for those receiving 1.5 μg/kg/wk ($P<0.03$). SVR was less likely overall among patients with F3/4 fibrosis and those who were black, but such patients receiving PEG-IFN α2b 3.0 μg/kg had SVR rates equivalent to the rest of the patients. The authors concluded that, among patients who had never cleared HCV RNA with previous IFN and RBV therapy, PEG-IFN α2b 3.0 μg/kg weekly combined with RBV 800–1400 mg/day was more effective than PEG-IFN 1.5 μg/kg weekly with RBV therapy, especially among black patients and those with advanced fibrosis.[25b]

Data are limited regarding the efficacy of retreatment of patients who do not respond to standard doses of PEG-IFN and RBV who "cross over" to other pegylated interferons. The REPEAT trial investigated crossing over to PEG-IFN α2a with RBV therapy among patients unresponsive to treatment with PEG-IFN α2b and RBV. In an interim analysis of 12-week induction data, 43% of 430 patients randomized to receive high-dose PEG-IFN α2a (360 μg/wk) with RBV 1000–1200 mg/d achieved early virologic response (EVR, defined as a ≥2-log drop in or undetectable HCV RNA level at Week 12) compared with 26% of 426 patients randomized to receive standard-dose PEG-IFN α2a (180 μg/wk) with the same ribavirin dose.[26] Another small study noted an overall SVR rate of 3% when patients unresponsive to PEG-IFN α2b and RBV therapy were switched to PEG-IFN α2a and RBV therapy.[27] Conversely, in Europe, an ongoing trial is evaluating the retreatment of PEG-IFN α2a–RBV nonresponders with PEG-IFN α2b and RBV. Further data, especially SVR rates and delineation of how prior nonresponse is defined and reported (including doses of both PEG-IFN and RBV), are needed to explore the merits, if any, of crossing to an alternative PEG-IFN and/or retreating with increased doses of PEG-IFN.

In addition to PEG-IFN and RBV antiviral treatments, other classes of interferons, such as cIFN, also might benefit prior nonresponders. Leevy and colleagues retrospectively analyzed 137 patients treated for 12 weeks with PEG-IFN α2b 1.5 μg/wk and RBV 1000–1200 mg/day.[15] Patients with a lack of response at 12 weeks, defined as a decrease in HCV RNA level of $<2\ \log_{10}$), went on to receive cIFN 15 μg daily with RBV 1000–1200 mg daily for 12 weeks, and then cIFN 15 μg 3 times weekly with RBV 1000–1200 mg daily for 36 weeks. The SVR rate was 37%, with relatively few relapsers among the 43% of those with an end-of-treatment response, and cIFN was well tolerated (growth factors were permitted).

Similarly, Kaiser and colleagues treated 95 prior nonresponders to PEG-IFN and RBV therapy with either an induction dose of cIFN (27 μg daily for 4 weeks, followed by 12 weeks of cIFN 18 μg) or a consistent dosage of 9 μg daily for 16 weeks, with both regimens followed by treatment with cIFN 9 μg daily and weight-based RBV for another 34–56 weeks depending on when the HCV RNA level became undetectable. SVR rates were 25% and 41% among PEG-IFN α2b and α2a nonresponders, respectively, in the induction group and 18% and 34% for nonresponders in the consistent-dose group.[16]

Kaiser and colleagues also conducted a study of 72 weeks of treatment with cIFN 9 μg daily versus PEG-IFN α2a 180 μg weekly (both with weight-adjusted RBV) in 81 patients who had relapsed after 48 weeks of prior treatment with PEG-IFN and RBV therapy.[28] The end-of-treatment virologic response rates were 89% for the cIFN arm and 76% for the PEG-IFN arm; the SVR rates were 69% and 44%, respectively ($P<0.05$).

In the first peer-reviewed publication regarding cIFN and RBV therapy for patients unresponsive to IFN (but not PEG-IFN) and RBV therapy, Cornberg and colleagues investigated the effects of such therapy on viral kinetics, SVR rates, and histological responses in a randomized, open-label pilot study.[29] Patients were eligible if they were virologic nonresponders to previous nonpegylated IFN therapy, with or without RBV treatment. Seventy-seven patients were randomized to receive either an 8-week induction dosing regimen of 18 μg cIFN daily followed by 9 μg daily for 40 weeks, or 9 μg of cIFN daily for 48 weeks. Both groups received weight-based RBV at the standard dose of 1000 mg (<75 kg) or 1200 mg daily (>75 kg).

Overall, 82% of the patients showed EVR, 65% had an end-of-treatment response, and 30% had SVR. Patients who had been unresponsive to IFN and RBV had an SVR rate of 22%, whereas the rate among nonresponders to IFN monotherapy was 39%. Although first-phase HCV-RNA decay was increased with induction dosing, patients who received such dosing did not have a higher SVR rate. The incidence of SVR was related to higher ALT level, younger age, and second-phase viral kinetics. Liver histology was improved only among patients with SVR and those who relapsed.

A randomized, controlled trial, the Daily-dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy (DIRECT) trial, is comparing treatment with cIFN 9 μg daily versus 15 μg daily, each in combination with RBV, in 343 nonresponders to PEG-IFN and RBV therapy.[30] Preliminary data reported at the 2006 American Association for the Study of Liver Diseases (AASLD) annual meeting indicate 48-week rates of HCV RNA negativity defined by TMA (lower limit of detection, 5 IU/mL) of 16% and 19% in the 2 treatment arms, respectively.[30] Patients with F4 fibrosis had SVR rates of only 8% and 6% in the low- and high-dose arms, respectively, whereas patients with F0-2 fibrosis had rates of 19% and 28%, respectively. Further data are eagerly awaited.

There is enormous interest in maintenance therapy with low-dose PEG-IFN as a means to retard the progression of liver disease and improve clinical outcomes in nonresponders. Three multicenter studies are evaluating this concept. The only interim data available are from a randomized, controlled study comparing PEG-IFN α2b 0.5 μg/kg/week versus colchicine 6 mg twice daily in patients with advanced fibrosis (Ishak stage >3) who failed prior treatment with IFN and RBV or PEG-IFN and RBV.[31] The primary endpoints are death, liver transplantation, HCC, variceal or portal hypertensive bleeding, and liver failure, defined as an increase in Child-Turcotte-Pugh (CPT) score of ≥2 points with ascites, jaundice, or encephalopathy.

In an interim, intention-to-treat analysis of 534 patients, investigators found that 8.5% of the patients given colchicine versus 5.5% of those given PEG-IFN had reached a clinically verified endpoint at 24 months. Kaplan-Meier survival analysis showed improved efficacy for PEG-IFN over colchicine (log-rank $P=0.003$). With secondary stratification, there was also significant benefit in favor of PEG-IFN over colchicine for patients with cirrhosis (CPT score 5–7), albumin <3.5 mg/dL (35 g/L), and portal hypertension, with most of the benefit coming in the form of reduced variceal bleeding. Although encouraging, these data are preliminary. The full dataset from the completed study must be evaluated before any definitive conclusions can be reached.

DISCUSSION

The outlined clinical research on HCV nonresponder therapy provides additional insight into the presented case study. Patients who initially do not respond to current standard treatment with PEG-IFN and RBV have several clinical options. Specifically, the patient might: 1) continue PEG-IFN and RBV therapy, but change the dose; 2) switch to a different PEG-IFN and RBV-based therapy; 3) switch to cIFN and RBV treatment; 4) start maintenance therapy of low doses of IFN; or 5) stop therapy. The efficacy of switching pegylated interferons has not been proven, as only anecdotal or interim data are available. In the presented case study, cIFN proved effective in achieving PCR negativity after initial non-response. Unfortunately, the patient relapsed within a month of stopping treatment. It is speculative whether a more prolonged course of cIFN and RBV would have succeeded in inducing a sustained response.

In deciding which treatment approach to take, there are several factors to take into account. Principally, the clinician should factor in prior non-response versus relapse, degree of fibrosis of the patient, degree of viral load reduction with prior therapy, tolerance of prior therapy, and the patient's "mindset." A longer course of treatment may be effective for relapsers, and "watching and waiting" is an option that ought not to be ignored, particularly for patients with mild liver disease. In this regard, an updated liver biopsy, particularly in patients whose last biopsy was performed >3 years previously, may be quite helpful. The notion of longer treatment for relapsers is attractive because of 2 recently published trials in treatment-naïve patients showing that slow responders have higher rates of SVR and/or lower rates of relapse with 72 weeks versus 48 weeks of treatment.[32,33]

In summary, although SVR rates have increased significantly over the past 10 years, nonresponders continue to make up a significant proportion of HCV-infected patients treated with antiviral therapies. Currently, there is no generally accepted course of treatment for these patients, but several treatment options have been suggested to provide additional support beyond the standard of care. Ongoing research on longer-term PEG-IFN treatment, cIFN–RBV therapy, and maintenance IFN-based therapy will further clarify the best options for patients. In the long run, however, novel agents such as viral enzyme inhibitors, on which there is intense focus at present, will likely have the greatest effect for patients who do not respond to current standard therapies.

Hepatitis C: Nonresponder Case Study

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

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

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6. Any other comments/suggestions for future educational activities relating to Hepatitis C? _____

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POST-TEST

CME POST-TEST

Please select the single best answer.

1. 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

2. 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

3. 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

4. Approaches to the management of patients who do not respond to standard antiviral therapies for HCV might in the future include:

a. Longer-term PEG-IFN and RBV therapy
b. Consensus IFN therapy, alone or combined with other antiviral treatments
c. Low-dose "maintenance" IFN-based therapy
d. Immune modulators
e. All of the above

5. Factors associated with sustained virologic response (SVR) after repeat antiviral treatment of HCV appear to include all of the following except:

a. HCV genotype
b. Previous IV drug use
c. Race
d. Degree of fibrosis
e. Response to previous courses of antiviral treatment

Full Name _____ Phone _____

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