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Challenging Cases in the Management of Hepatitis C Viral Infection

A Case Study Compendium

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Switching Regimens in a Nonresponder

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Chronic infection with the hepatitis C virus (HCV) is one of the most common causes of liver disease worldwide and is associated with significant morbidity and mortality. It is estimated that 4 million persons are chronically infected in the United States.[1] Interferon-based therapies are the mainstay of HCV treatment.

Currently, sustained virologic response (SVR) is achieved in about 50–60% of HCV infected patients treated with peginterferon (PegIFN) plus ribavirin (RBV),[2,3] with the implication that about half of HCV infected patients undergoing treatment will not successfully clear the virus. In order to treat these patients, many alternative regimens have been studied, including high-dose interferon-based therapy, induction therapy, maintenance therapy, and interferon alfacon-1 (consensus interferon, Infergen®, Three Rivers Pharmaceuticals)–based therapy.[4–7]

Recent data have also demonstrated that certain patient characteristics and virologic factors have significant impact on treatment success. Well-known factors include genotype, baseline viral load, race/ethnicity, and weight. Emerging factors include steatosis, insulin resistance, and viral kinetics during therapy.[8] Specifically regarding viral kinetics, emerging data suggest that early rapid response is a strong predictor of treatment success, and equally importantly, slow response is a predictor of treatment failure.[9,10]

Virally guided HCV treatment, based on viral kinetics, allows clinicians to tailor the treatment regimen to each patient, thus allowing improved chances for treatment success. We describe here a case of an HCV-infected patient with advanced liver disease with slow response to initial treatment with PegIFN and RBV where virally guided therapy was helpful.

Case Report

A 49-year-old man was referred to our hepatology clinic for consultation regarding management of his chronic genotype-1 HCV infection. Risk factors for liver disease include a remote history of injection drug use more than 30 years previously with longterm abstinence. He additionally reports a history of daily alcohol use during the same time period; currently he has not had any alcohol for many years. The medical history is otherwise unremarkable and he has previously completed vaccination against hepatitis A and B infection. A liver biopsy completed 2 years previously revealed grade 2 inflammation and stage 1 fibrosis. The biopsy results were discussed in detail and the patient elected to undergo treatment with interferon based therapy. The patient was uncomfortable with the possible risks associated with chronic infection. This discomfort was complicated by an HCV-related death in his family and he desired to eradicate the virus if possible.

Initial treatment with PegIFN alpha-2b (PegIntron®, Schering-Plough) 1.5 µg/kg/week and ribavirin 1,000 mg/day (wt, 163 lbs) was begun by his primary gastroenterologist and 48 weeks of treatment was anticipated. Therapy was tolerated well with the development of initial flu-like symptoms and mild anemia, which did not require dose modifications or other interventions; he reported excellent compliance with therapy. Following completion of 12 weeks of therapy, the patient's viral load had declined from 1.2 million to 85,000 IU/mL, an approximate 2-$\log_{10}$ decline. Further management options were discussed, including discontinuation of treatment with ongoing monitoring, continuation of current therapy with reassessment of viral load at 24 weeks of treatment, or conversion to daily interferon alfacon-1 and RBV with reassessment of viral load at 12 weeks of therapy.

Following discussion, interferon alfacon-1–based therapy was initiated at 15 µg daily and 1,200 mg of RBV daily, without washout of his current therapy. Treatment was well-tolerated, with a recurrence of flu-like symptoms during the initial few weeks of therapy, followed by improvement. The patient developed episodes of mild anxiety without associated depression or manic traits;

Table 1. Laboratory Results During Initial Standard Therapy and Interferon Alfacon-1 and Ribavirin Therapy

	ALT	AST	HGB	ANC	PLT	HCV
Baseline	60	52	14.6	5.2	238,000	1,190,000
12 weeks	34	27	11.1	3.1	190,000	85,000
Consensus	30	37	11.3	2.6	183,000	85,000
4 weeks	27	34	9.7	2.1	153,000	720
12 weeks	27	30	10.0	1.8	162,000	<25
24 weeks	26	22	9.8	1.6	164,000	<25
48 weeks	19	24	10.0	2.0	201,000	<25
24 weeks post-treatment	19	20	15.1	5.7	298,000	<25

these were managed with intermittent low-dose benzodiazepine therapy. He also continued to experience anemia with ongoing fatigue throughout the duration of his treatment but this was manageable and dose reduction or the addition of growth-factor support were not required. He continued to work his usual schedule throughout treatment, without interruption, and within 2–3 weeks of completion of therapy his side effects had returned to baseline. The viral response to therapy is shown in Table 1.

Discussion

Background and Pretreatment Predictors of Response to Therapy

Sustained virologic response following antiviral therapy for HCV is highly durable[11] and has been associated with reduced rates of liver-disease–related complications in retrospective studies.[12] Despite significant advances in the management of chronic HCV infection, approximately 50–60% of genotype 1 patients treated with currently approved treatment regimens will fail to achieve SVR following an initial course of therapy.[2,3] A variety of pre-treatment variables are predictive of viral response to treatment. The strongest of these is HCV genotype. Non-genotype–1 patients are significantly more likely to achieve SVR with currently available therapies (OR 4.11 [95% CI 2.90–5.86]) compared to genotype 1 patients.[13] Additional positive predictors of SVR have been identified and are reviewed in Table 2.

Table 2. Established Pre-treatment Predictors of Sustained Virologic Response to Interferon-based Therapy

Factor	Increased response	Decreased response
HCV Genotype	Genotype non-1	Genotype 1
Viral load	Less than 400,000 IU/mL	More than 400,000 IU/mL
Fibrosis	Non-cirrhotic	Cirrhotic
Gender	Female	Male
Age	<40 years	>40 years
Weight	<85 kg	>85 kg
Race	Non-African American	African American
Co-infection	HCV mono-infection	Co-infection with HBV and/or HIV

Management of Patients Not Achieving SVR on Initial Therapy Using Standard Interferons (Alpha 2a or 2b)

Declining incidence of new cases of HCV and success rates of available HCV therapies have led to an expanding pool of treatment-experienced patients who have failed to achieve SVR with their initial course of interferon therapy. These patients can be divided into two groups based on response to initial treatment: relapsers, who achieve undetectable HCV levels at the completion of their course of therapy but in whom HCV reemerges in the first 6 months following therapy, and nonresponders, who continue to have detectable HCV levels at the end of their course of treatment.

Re-treatment of HCV genotype-1 patients with prior nonresponse to interferon-based therapy with PegIFN and RBV has also been studied. Overall, the reported SVR rates are considerably lower than those for treatment-naïve and relapsing patients. A large study that included over 1,800 genotype-1 patients, who were non-responders

to previous combination interferon and RBV (62%) or PegIFN and RBV (37%) resulted in an SVR rate of 15%. The SVR rate among all genotypes in patients who were previously treated with PegIFN combination was a disappointing 4%.[14] During the lead-in phase of the HALT-C trial, 936 genotype-1 patients with advanced hepatic fibrosis, who were non-responders to previous interferon based treatment, 36% monotherapy and 64% standard combination therapy, were re-treated with PegIFN and RBV with an SVR rate of 14%.[15] In an additional study that examined 942 previous nonresponders to PegIFN and RBV, 91% were genotype 1. Pooled results combining induction dosing of increased doses of PegIFN alpha-2a (Pegasys®, Roche) and RBV 1,000–1,200 mg daily and standard dosing of PegIFN and RBV 1,000–1,200 mg daily for 48 weeks yielded an SVR rate of 8%.[5] Other arms of this study examined the impact of extending the duration of therapy to a total of 72 weeks. Pooled analysis of both induction and standard dosing arms resulted in an SVR rate of 16%. One limitation of this study was that out of the 847 evaluable patients that were re-treated, 537 had an unknown response to their previous PegIFN/RBV therapy. A number of recent trials of re-treatment of PegIFN and RBV non-responders as control arms of trials evaluating new HCV therapies have shown SVR rates of 2–4%.[16–18]

Another strategy that has been employed to reduce morbidity and mortality resulting from chronic HCV infection is maintenance therapy with the initiation of low-dose PegIFN monotherapy for an indefinite duration of treatment. The final results for over 1,000 patients with advanced hepatic fibrosis in the longterm arm of the HALT-C study have recently been published. Unfortunately, the use of maintenance dosing did not yield any significant difference in any of the primary outcomes, which included: increase in fibrosis, decompensated cirrhosis, primary liver cancer, or death.[6]

Predictors of SVR During Therapy

The concept of virally guided therapy is continually evolving in the management of HCV infection. In essence, virally guided therapy acknowledges the realization that each patient represents a unique set of pre-treatment and on-treatment variables, some fixed and others modifiable, which ultimately determine the chances of SVR to currently available therapies and, further, that the culmination of these variables is adjudicated by the slope of viral decline once a therapy is initiated.

It has previously been identified that the viral load following 12 weeks of initial therapy can predict the outcome of a course of treatment. Patients who fail to experience early virologic response (EVR), defined as a 100-fold or greater reduction (2 $\log_{10}$) in HCV viral count during the first 12 weeks of treatment, have poor chance (0–3%) of attaining SVR, even with a complete course of therapy.[19] This finding has led to what is known as the 12-week stopping rule. This principle has been expanded to incorporate viral response and outcomes at a variety of time points during treatment (Table 3). The earlier in the course of treatment that the HCV viral load becomes undetectable, the greater the chance of achieving SVR. Patients with an undetectable viral load at 4 weeks after beginning therapy, rapid virologic response (RVR), have been shown to have SVR rates of approximately 90%.[20] Reduced duration of treatment and dosing may be possible without reducing efficacy in patients with certain pretreatment variables. Patients experiencing RVR should be encouraged to continue therapy and maintain adherence to their dosing regimen.

Table 3. Response Level Definitions

On therapy response	Definition
Rapid viral response (RVR)	HCV RNA negative at treatment week 4, <50 IU/mL
Early viral response (EVR) • Complete EVR (cEVR) • Partial EVR (pEVR)	No RVR, HCV RNA negative or ≥2 log drop at week 12 • No RVR, HCV RNA negative at week 12 • No RVR, ≥2 log drop, HCV RNA positive at week 12
Sustained viral response	HCV RNA negative 24 weeks after stopping therapy
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued
Partial response	≥2 log drop, HCV RNA positive at week 24
Non-response (NR) Early null response (eNR)	<2 log drop at week 12 <1 log drop at week 4

Patients experiencing an undetectable viral load (<50 IU/mL) at 12 weeks of therapy are termed complete early virologic responders (cEVR). Patients who achieved cEVR in a recent analysis of 6 trials of PegIFN and RBV in genotype-1 patients by Marcellin and associates resulted in an SVR rate of 68% with 48 weeks of treatment.[21] Patients with a greater than 2 $\log_{10}$ reduction in viral load from baseline, who still have virus detected at 12 weeks but become undetectable by week 24, are said to have partial early virologic response (pEVR). These patients have an SVR rate of 27% with 48 weeks of treatment.[21]

In an effort to reduce the high rate of relapse, three studies of PegIFN and RBV therapy have evaluated the efficacy of increasing treatment duration from 48 to 72 weeks in genotype-1 patients with pEVR. Two of these studies have utilized PegIFN with fixed-dose RBV of 800 mg/day which resulted in SVR in 16–33% versus 44–46% of patients in the 48 and 72 week treatment arms, respectively.[22,23] In the third study, the dose of RBV was weight adjusted to 1,000–1,200 mg daily and the rates of SVR were 18% and 38%, respectively, for standard and extended duration of therapy.[24] Another recent paper by Mangia in 696 genotype-1 patients examined virally guided therapy and suggested that undetectable viral load at 8 weeks of therapy may be a better prognostic indicator of SVR and patients who do not have undetectable HCV until week 12 may also benefit from extending therapy to 72 weeks.[10] This study also demonstrated that patients not achieving a cEVR at Week 12 experienced poor response rates—0% SVR in the 48-week arm and 7.5% SVR in the variable arm (72 weeks).

Management of Patients Not Achieving SVR to Initial Therapy Using Daily Interferon Alfacon-1

Another approach to re-treatment of non-responders is treatment with daily interferon alfacon-1 and RBV. This approach is outlined in the Daily Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy (DIRECT) trial.[25] This study evaluated the efficacy of interferon alfacon-1 15 µg/day or 9 µg/day, both with RBV, 1,000–1,200 mg daily versus observation in over 500 patients with HCV genotype 1 and previous nonresponse to PegIFN and RBV, despite documented adherence to previous therapy. The demographics of this study revealed a high prevalence of several difficult to treat characteristics: More than 80% of patients had a less than 2 $\log_{10}$ decline in viral load during their previous course of treatment, 62% had advanced hepatic fibrosis (stage 3 or 4 fibrosis on biopsy), and the majority of patients were obese with a mean body mass index of 29.6 kg/m^2. In addition, over 85% of patients had a viral load over 400,000 IU/mL. Growth factors were not allowed to correct for neutropenia or hemolytic anemia. The results of the intention to treat analysis (ITT) indicated SVR rates of 6.9% and 10.7% in the 9 µg and 15 µg arms, both of which were statistically significant compared to the no treatment arm. In a per protocol analysis of approximately 200 patients who did not require dose reductions of either medication, the SVR rates were 7% and 17%. Additional stratification based on fibrosis stage and degree of response to previous therapy yielded ITT SVR rates of 8%, 17%, and 32% in noncirrhotic patients with previous response to therapy of less than 1 $\log_{10}$, 1–2 $\log_{10}$, and greater than 2 $\log_{10}$ drops in HCV RNA counts, respectively. Cirrhotic patients had SVR rates of 0–10%. In a per protocol analysis, the SVR rates were 13%, 31%, and 38% in noncirrhotics and 0%, 10%, and 25% in cirrhotic patients.

The DIRECT trial has shown that up to 38% of noncirrhotic nonresponders to pegylated interferon and ribavirin can achieve an SVR with daily interferon alfacon-1 and ribavirin if a nearly full dose of therapy is maintained. In addition, the DIRECT trial has contributed important knowledge to the selection of potential re-treatment candidates among non-responders to PegIFN and RBV. Patients with a greater than 1–2 $\log_{10}$ decline in viral load appear to be reasonable candidates for consideration for re-treatment. The concept of early identification of patients with a poor on-treatment response to therapy as a method of reducing patient risk and treatment expense was advanced by Reau and associates, who found that patients with early null response, (eNR) defined as a viral load reduction of less than 1 $\log_{10}$ at 4 weeks of treatment have a poor chance (5–8%) of achieving SVR (genotype 1 patients achieved only a 3% SVR). Consideration of treatment modification in these patients may be warranted.[26]

In summary we have reviewed the rationale for an individualized, virally guided approach to the management chronic HCV infection and presented the case of a patient with genotype-1 hepatitis C infection and high viral load with a slow response to PegIFN and RBV who has benefited from a virally guided approach to management of his HCV and has achieved an SVR to a 48-week course of daily interferon alfacon-1 and RBV therapy.

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Re-Treatment of a Partial Early Responder With Side Effects to Standard Therapy

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Chronic infection with HCV is the leading indication for liver transplantation[1] and the most common chronic blood borne pathogen in the United States.[2] Dire predictions of HCV-related disease burden are slowly being realized; HCV mortality rates have increased 123% between 1995 and 2004 and risen 376% in the 45–54-year-old age group in the same time period.[3]

Although the standard of care therapy, combination PegIFN and RBV, can achieve an overall SVR in over one half of patients treated, the SVR rate is significantly lower in patients with genotype 1 infections, particularly those with high viral loads, those of African-American descent, those with advanced fibrosis on pretreatment liver biopsy, those with HIV-HCV co-infection, and those who are obese and/or insulin-resistant. As an example, treatment-naïve, genotype 1 HCV-infected African-Americans only achieve SVR rates of 19–28%, compared to 39–52% among whites in the same clinical trials with similar pretreatment characteristics.[4-6]

Another difficult-to-treat group is that of patients who previously failed therapy, particularly those who were nonresponders to PegIFN and RBV; patients re-treated with a second PegIFN regimen attain SVR only 2–4% of the time.[7-9] The following case describes the successful re-treatment of an African-American, genotype-1–infected patient with high pretreatment viremia and advanced fibrosis on liver biopsy, with interferon alfacon-1 and RBV.

Patient History

A 43-year-old African American man with a history of chronic HCV infection was referred to our clinic from a local gastroenterology practice after unsuccessful treatment with standard PegIFN/RBV therapy. His past medical history was significant for essential hypertension diagnosed ten years previously, for which he takes daily amlodipine, and chronic HCV infection, which he likely acquired from intravenous cocaine use in the mid-1970s.

The patient had learned of his HCV status approximately 1 year previously through prerequisite laboratory testing when applying for life insurance. His primary care physician confirmed HCV viremia and referred him to the aforementioned gastroenterologist. The patient's only complaint is chronic fatigue, but a thorough workup reveals no other etiology beyond viral hepatitis. The patient is a local truck driver and is married with no children. He does not smoke tobacco and has not drunk alcohol since learning of his HCV status. Family history is negative for liver disease but positive for hypertension in multiple relatives.

Physical examination reveals a healthy, well-appearing man, 5 foot 10 inches tall, weighing 172 pounds. Vital signs are normal, including a blood pressure of 132/82. His liver is 9 cm to percussion at the mid-clavicular line, and he has no stigmata of chronic liver disease.

The patient's laboratory measures upon presentation to our clinic are shown in Table 1. His pretreatment liver biopsy was 2.6 cm in length, containing 16 portal tracts and showing chronic hepatitis with moderate activity and prominent portal fibrosis with multiple septae (A2F3, METAVIR; Figures 1–3).

A careful review of his medical record revealed the following therapeutic history. The patient had received 12 weeks of treatment with PegIFN alpha-2a dosed at 180 µg weekly and RBV at 1,200 mg daily, in divided doses. His pretreatment viral load was 6,230,000 IU/mL, and at 4 weeks of therapy it had only dropped to 1,100,000 IU/mL (approximately a 0.5-$\log_{10}$ decrement). Despite maintaining his hemoglobin level at 12.7 gm, stable thyroid function tests, and low scores on Becks Depression Inventories, the patient complained of progressive fatigue. At 12 weeks of therapy, the patient's HCV RNA had declined to 59,500 IU/mL, an approximate 2-$\log_{10}$ drop from baseline. Although the patient was offered continued therapy, he declined. At this point, he was referred to our clinic.

After discussion of his limited options, the patient agreed to be treated with interferon alfacon-1, dosed daily

Table 1. Patient's Baseline Laboratory Values

AST, U/L	54
ALT, U/L	86
Albumin, mg/dL	3.8
Total bilirubin, mg/dL	1.23
HIV	Non-reactive
Alpha fetoprotein, ng/mL	3.4
HCV genotype	1b
HCV RNA, IU/mL	7,620,000
WBC cells/µL	3,800
ANC cells/µL	1,850
Hemoglobin, grams	13.6
Platelets x 1,000/mm^3	159
PT, seconds	11.5
PTT, seconds	31

AST=aspartate aminotransferase; ALT=alanine aminotransferase; WBC=white blood cells; ANC=absolute neutrophil count; PT=prothrombin time; PTT=prothromboplastin time.

with RBV. Informed consent was obtained, and 6 weeks after receiving his last dose of PegIFN, he was started on interferon alfacon-1 at 15 µg daily and 1,200 mg RBV daily in divided doses. Although the patient still complained of fatigue, he described it as bearable and less than that provoked by his prior treatment. Overall, his tolerability was acceptable with a single, minor injection site reaction, which improved spontaneously, and moderate oral thrush, which responded to clotrimazole trouches. Intermittent insomnia was treated with zolpidem as needed. His hemoglobin and neutrophil nadirs were 12.2 gm and 850/µL, respectively, requiring no dose reductions or growth factors.

Because of a laboratory error, a 4-week HCV RNA measure was unavailable. However, 12 weeks into therapy with interferon alfacon-1 and RBV, the patient's serum RNA was undetectable (<10 IU/mL). Aviremia was confirmed at treatment weeks 24, 36, and 48. Finally, at week 72, 24 weeks after therapy cessation, serum HCV RNA was again undetectable; thus, SVR had been achieved. Serum viral levels on both therapies are delineated in Table 2.

Discussion

HCV prevalence is higher in African Americans than among any other US ethnic group.[10-12] Despite improvements in antiviral therapy, SVR rates among African American patients are relatively poor,[4-6] even when con-

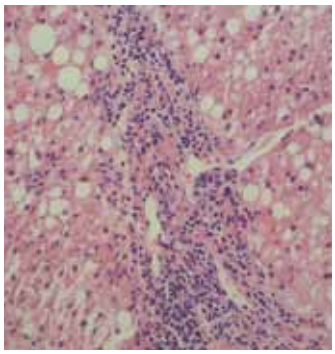

Figure 1. Medium power hematoxylin and eosin stain of liver biopsy demonstrating a portal area with irregular contour and expansion and infiltration of mononuclear cells with piecemeal necrosis (A2 Grade METAVIR). The subjacent parenchyma displays a patchy lobulitis with moderate macrovesicular steatosis.

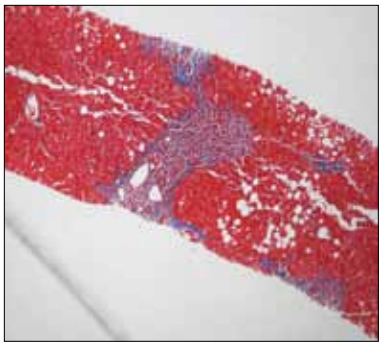

Figure 2. Low power trichrome stain of liver biopsy showing expanded portal areas with fibrosis (indicated by blue staining) and bridging septation (F3 stage METAVIR).

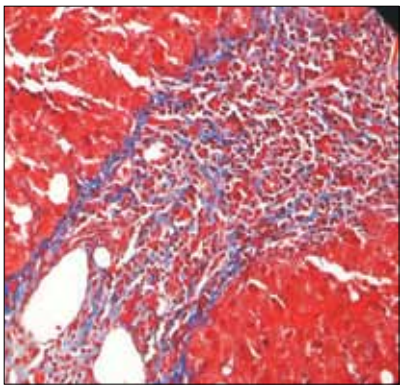

Figure 3. High power trichrome stain of liver biopsy demonstrating blue-staining fibrosis and broad irregular borders of an affected portal tract.

Table 2. Serum Viral Levels at Selected Time Points in Therapy

Type of therapy	Week of therapy	Viral load (IU/mL)	Log_{10} decline*
PEG/R	Baseline	6,230,000	n/a
PEG/R	4	1,100,000	0.5
PEG/R	12	59,500	2
CIFN/R	Baseline	7,620,000	n/a
CIFN/R	8	520	4
CIFN/R	12	<10	>5
CIFN/R	24, 48, 72	<10	>5

*Relative to baseline viral load.

PEG=peginterferon; R=ribavirin; CIFN=interferon alfacon-1; n/a=not applicable.

trolling for genotype-1 infection, which is more prevalent in African Americans relative to that in non-Hispanic whites.[10,13,14] Mechanisms invoked to explain suboptimal treatment response in this group include dysregulated virus-specific CD4 T-cell responses,[15] and compared to whites, discrepant viral kinetics,[16] dissimilar cytokine production,[17] and even differences in hepatic iron stores.[18] Despite relatively low virologic response rates to contemporary treatment, therapeutic nihilism is unwarranted with respect to HCV-infected African Americans; it was appropriate to treat this patient.

After 4 weeks of PegIFN-based treatment, the patient did not achieve an RVR. RVR, defined as undetectable HCV RNA after 4 weeks of therapy, is a useful predictive marker for ultimate viral clearance[19]; its positive predictive value for achieving SVR is excellent. However, its negative predictive value is poor; thus, clinicians should not make therapy cessation decisions based on failure to achieve this treatment milestone. Nonetheless, a new retrospective analysis of patients treated with PegIFN and RBV suggests that if patients fail to achieve at least a 1-log_{10} decline in HCV RNA at week 4, deemed early null response, consideration could be made to discontinue or modify therapy. In this study, early null responders had only an 8% chance of achieving SVR.[20] Although these preliminary data should be verified prospectively, it might have been prudent for our patient's PegIFN-based treatment to have been discontinued at week 4, sparing him 8 additional weeks of therapy-related side effects with unlikely virologic benefit.

At 12 weeks of treatment, despite excellent adherence, the patient's HCV RNA had dropped approximately 2 log_{10} from baseline. The patient and provider had several options at this point including treatment cessation, the use of an alternative agent, interferon alfacon-1 with RBV, or, if the patient were aviremic at week 24, the completion of a 48- or 72-week course of PegIFN/RBV.

Failure to achieve an EVR, defined by at least a 2-log_{10} decrement in HCV RNA from baseline at 12 weeks of therapy, has excellent negative predictive value for treatment success; an analysis of the PegIFN/RBV registration trials[21,22] revealed that patients unable to achieve an EVR have a 3% or less chance of achieving SVR.[23] Nevertheless, the treatment responses are widely disparate between patients who have at least a 2-log decrease in baseline HCV RNA yet still have detectable viremia at 12 weeks (pEVR) compared to those who achieve aviremia at 12 weeks (cEVR). In the phase III trial for PegIFN alpha-2b with RBV, patients with pEVR achieved SVR only about one-fourth as frequently than those with cEVR.[23]

Our patient had achieved a pEVR. Assuming therapy had been continued and his virus were undetectable at week 24, he would have been deemed a slow responder to therapy, and his chance of ultimately achieving SVR would range from 0% to 28% with a standard therapy duration of 48 weeks.[24-26] In one of these trials, 48% of the slow responders enrolled were of African American descent.[25] It should be emphasized that if our patient had detectable viremia at 24 weeks of therapy, there is virtually no chance an SVR could be achieved with standard treatment.

Nevertheless, if the patient had undetectable serum HCV RNA at 24 weeks, another option would have been extension of treatment to 72 weeks. A recent meta-analysis of randomized trials of response-guided therapy for slow responders to PegIFN/RBV showed a 12% increase in SVR with 72 weeks versus 48 weeks of treatment (n=355; pooled estimate; 95% CI: 5–19%).[27] Because of the patient's severe fatigue, however, he was not willing to consider an additional 36 weeks of PegIFN-based therapy, let alone another 60 weeks, had treatment been extended. On the other hand, the patient was unwilling to stop therapy entirely, once he learned his chance of histologic progression without treatment was approximately 73–100% in 5–10 years (estimated chance of untreated stage 3 fibrosis progressing to cirrhosis).[28] After a thorough discussion, our patient agreed to be treated with daily interferon alfacon-1 plus weight-based RBV. In the DIRECT trial, an open label study of over 500 nonresponders to previous PegIFN and RBV, patients randomized to a combination of 15 µg daily of interferon alfacon-1 and ribavirin had an SVR rate of 10.7% (intention-to-treat analysis).[29] Nevertheless, the estimated SVR for our patient using this protocol was much higher, because patients in the 15 µg arm of

the DIRECT trial, who were not cirrhotic (up to F3 fibrosis) with declines in HCV viremia of at least 2 $\log_{10}$ relative to baseline value on prior PegIFN/RBV, enjoyed an SVR of 32% (intention-to-treat); the rate of SVR for this same subgroup in the on-treatment analysis (those patients who did not modify their medication doses) was 38%. Physicians should use caution in interpretation of this data because of the small numbers of patients in this subgroup analysis (n=19, ITT). Among patients with F3 fibrosis specifically, with a greater than 2-$\log_{10}$ reduction in HCV RNA after 12 weeks of PegIFN-based therapy, one-third achieved SVR with daily interferon alfacon-1 and RBV. The aforementioned caution likewise applies to interpretation of this subgroup analysis (n=9, ITT).

A recently published study of daily interferon alfacon-1 (15 µg) with RBV for PegIFN and RBV nonresponders, showed an overall 37% rate of SVR.[30] One-third of these previously nonresponding patients identified themselves as African American. Although patients not of African American descent were significantly more likely to achieve an SVR than African Americans (P<0.09) and more likely to be HCV RNA negative at all time points analyzed, the latter group achieved an SVR rate of 27%. Twelve weeks into therapy with interferon alfacon-1 and RBV, our patient's serum HCV RNA was undetectable, consistent with a complete EVR (cEVR). At 12 weeks, patients in the 15 µg arm of the DIRECT trial who reached cEVR were 64% likely to ultimately achieve SVR.[29] This statistic helped to reinforce the patient's adherence to therapy, which was ultimately successful in clearing his virus.

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Successful Re-Treatment After Relapse Following Standard Therapy

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Case History

A 56-year-old African American male was referred for evaluation of hepatitis C status. The patient had an extensive history of excessive alcohol use, as well as intravenous drugs use starting in his late teens. He stopped drug use in 1989 as a result of incarceration and remained in jail for 10 years. Upon release, he was found to have elevated alanine aminotransferase (ALT) levels and was subsequently diagnosed with genotype-1 HCV infection, with an HCV RNA level of 190,000 IU/mL. A liver biopsy was performed in September of 2000. It revealed chronic active hepatitis with moderate to severe fibrosis (stage 4/6) and Histology Activity Index (HAI) of 12/18 using the Ishak Modified HAI scale.[1] He was treated for 48 weeks with PegIFN alpha-2b (1.5 µg/kg/wk) and RBV, 1,000 mg daily. He experienced typical flu-like symptoms while on treatment, but was able to tolerate therapy well, without any dose reductions or interruption of treatment. He cleared the HCV RNA virus by week 12, and had a consistent end-of-treatment response after 48 weeks.

Evidence of relapse was found at 3-month follow-up. The patient underwent a repeat liver biopsy in July of 2004, which was significant for chronic hepatitis with mild-to-moderate activity, early bridging fibrosis (stage 3/6) and an HAI of 7/18. He was re-treated with PegIFN alfa-2a (180 µg weekly) and RBV (1,000 mg daily). Therapy was once again well-tolerated without any significant adverse effects, dose reductions, or interruptions of therapy. The patient once again achieved an early virologic response, with clearance of HCV by week 12. An end-of-treatment response was also achieved but he once again relapsed within 3 months of cessation of therapy. His physician recommended re-treatment with daily interferon alfacon-1 and RBV but payment was denied by his insurance provider. The patient was subsequently referred for evaluation and possible enrollment into the DIRECT trial.

The patient's past medical history was significant for seizures and hypertension. Medications included phenytoin, phenobarbital, valsartan, and folic acid. Physical examination did not reveal any stigmata of chronic liver disease. Baseline laboratory values were as follow: ALT of 52 IU/L, bilirubin of 0.3 mg/dL, albumin of 3.9 g/L, white blood count of 12.0 K, platelet count of 210 K, and hemoglobin of 12.7 g/dL. Baseline HCV RNA was 18.2 million IU/mL.

As a relapser, this patient was not eligible for the DIRECT trial. However, at the time, our center was taking part in a pilot study, based on a previous nonresponder trial from Germany (Table 1).[2] RBV was not used for the first 12 weeks in this study due to concerns about tolerability of daily interferon alfacon-1 dosing. However, because daily interferon alfacon-1 was well-tolerated in this study and the importance of RBV dosing during the first 20 weeks of treatment had recently been confirmed,[3] we elected to utilize RBV, albeit at a lower dose, from the start of treatment. My own personal experience had been favorable using daily interferon alfacon-1 at 15 µg daily. We utilized 15 µg during the last 36 weeks of treatment instead of 9 µg (Table 2).

The patient was started on this regimen at the end of December 2005. His adverse effects included weakness, fatigue, and dyspnea on exertion. His hemoglobin levels dropped to 9.7 g/dL by week 8; erythropoetin alfa was started and RBV dose was reduced to 400 mg daily. Subsequently, his white blood count dropped to 1.9 K with an absolute neutrophil count of 665 by Week 8. Filagrastin was started but the interferon dose was not reduced. HCV RNA was undetectable at Week 8. The patient continued on both erythropoetin alfa and filagrastin until the end of treatment (48 weeks). His ribavirin dose was slowly increased to 1,000 mg daily. He tolerated this treatment regimen except for an episode of lightheadedness and dizzy symptoms at Week 43. He was treated with intravenous fluids in the

Table 1. Dosing Regimens for the German Trial of Interferon Alfacon-1

	4 Weeks	8 Weeks	36 Weeks	24 Weeks Follow Up
Arm 1	CIFN 18 µg QD	CIFN 9 µg QD	CIFN 9 µg QD + RBV 1,000–1,200 mg QD	
Arm 2	CIFN 27 µg QD	CIFN 18 µg QD	CIFN 9 µg QD + RBV 1,000–1,200 mg QD	

CIFN=consensus interferon/interferon alfacon-1; RBV=ribavirin.

Table 2. Modified Dosing Protocol for Study Patient

4 Weeks	8 Weeks	36 Weeks	24 Weeks Follow Up
CIFN 27 µg QD + RBV 800 mg QD	CIFN 18 µg QD + RBV 400 mg QD	CIFN 15 µg QD + RBV 1,000–1,200 mg QD	

CIFN=consensus interferon/interferon alfacon-1; RBV=ribavirin.

emergency room for dehydration and sent home without any interruption in treatment. He was HCV RNA negative at the end of treatment and remained so through 1-year follow-up.

Discussion

The current standard of care for the treatment of HCV infection is PegIFN alfa-2a or 2b with RBV. However, the majority of genotype 1 hepatitis C patients will fail this regimen as either nonresponders or relapsers. How should these patients be managed? Should they be re-treated or wait for the availability of more effective therapies?

It is clear that all patients who have failed previous therapy need to be considered for re-treatment in order to slow disease progression. However, other interventions can be instituted to slow down the progression of hepatitis C. Hepatitis C patients must maintain a healthy lifestyle. This includes abstinence from tobacco and minimal use of alcohol. Complete abstinence from alcohol is recommended for patients with a previous history of excessive alcohol use. Regular exercise and diet should be combined to keep body mass index as close to normal as possible, as concurrent nonalcoholic steatosis can hasten the progression of fibrosis. Higher body weight and insulin resistance can also decrease response to interferon/RBV-based therapies for hepatitis C. Cholesterol, triglycerides, and blood sugars should be kept within normal limits.

It has been my practice to consider both the grade (inflammation) and stage (fibrosis) of progression to determine those patients who should be re-treated. I have advised most nonresponding patients with grade 0–1/stage 0–1 to hold off on re-treatment and maintain a healthy lifestyle until newer agents are available. This is a reasonable treatment strategy for these patients with mild disease. I strongly recommend re-treatment for nonresponders with grade 2-or-higher/stage 2-or-higher disease status as they are at a higher risk for progression to cirrhosis within the next few years. For these patients, I offer treatment with either daily interferon alfacon-1 (15 µg) and RBV (weight-based) for 48 weeks as per the DIRECT trial),[4] or weekly PegIFN alfa-2a (180 µg daily) with weight-based RBV, for 72 weeks as per the REPEAT trial.[5] I also recommend consideration of treatment for all relapsers with grade 2-or-higher/stage 2-or-higher status on liver biopsy. However, I am more inclined to consider re-treatment in relapsers with grade-1/stage-1 disease as well, as their HCV virus has demonstrated susceptibility to treatment. However, treatment for relapsers must be modified, either with longer duration of treatment or higher doses of interferon and/or RBV. Kaiser has compared daily interferon alfacon-1 9 µg daily plus weight-based ribavirin for 72 weeks to PegIFN alfa-2a plus weight-based RBV for 72 weeks.[6] The sustained virologic response was 69% with daily interferon alfacon-1/RBV versus 42% in the PegIFN alfa 2a /RBV arm; tolerability between dosing regimens was the same. The SVR may have been higher, if daily interferon alfacon-1 was given at a dose of 15 µg but this concept needs to be confirmed in a clinical trial.

There are two specific points concerning this case that warrant further discussion. First, the patient was initially denied coverage for what eventually proved to be the only treatment resulting in a cure. It is unfortunate that

insurance companies base their coverage policies almost exclusively on US Food and Drug Administration (FDA) approval or published data in medical journals. Medicine moves more quickly than that. Patients should not have to wait for FDA approval or publication of an effective treatment before access to treatment is allowed. This patient had a significant chance of progression to cirrhosis if he was not cured. Furthermore, although he was treated with induction dosing of CIFN during the first 12 weeks, it appears that induction dosing of interferon alfacon-1 does not improve SVR rates.[7] It is unlikely that patients will be treated with interferon alfacon-1 doses greater than 15 µg daily in the future. The protocol under which this patient was treated had exceptional results by Week 12; 50% of patients had undetectable HCV RNA, whereas 76% had a 2 $\log_{10}$ decrease in HCV RNA. However, only 40% of patients were negative for HCV by the end of 48 weeks of treatment. The relapse rate was higher, such that only 12% of patients obtained SVR.[8] This higher relapse rate, which was also seen in the larger DIRECT trial, provides the rationale for longer duration of therapy, as well as higher doses of RBV, in order to minimize relapse.

The DIRECT trial proved the effectiveness of daily interferon alfacon-1 in hepatitis C nonresponders. The next step will be to modify the treatment regimen used in the DIRECT trial: higher dose of ribavirin, longer duration of treatment, and use of growth factors. These modifications should provide a reasonable and effective treatment regimen for nonresponders as physicians await the arrival of newer, safer, and more effective treatments for HCV.

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Notes


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