New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy: A Case-Based Series

VOLUME 1 • PART 3

Dear Colleague:

Managing the side effects of treatment for hepatitis C virus (HCV) infection can be a significant clinical challenge. More challenging is managing treatment and its attendant side effects when the patient is coinfected with HIV. Each infection can impact the prognosis and management of the other, the net effect being that each speeds the progression and worsens the outcome of the other, making treatment of both infections more difficult. Furthermore, severe side effects leading to discontinuation of treatment are more likely to be encountered during treatment of HIV/HCV coinfected patients than monoinfected patients. However, it is more urgent than ever to treat HCV infection in coinfected patients than monoinfected patients. Anti-HCV treatment can result in a sustained virologic response (SVR), halt liver damage, and probably reduce the risk of hepatocellular carcinoma. Furthermore, eradication of HCV infection reduces the likelihood of an adverse reaction to antiretroviral therapy (ART) and increases the likelihood that ART can be continued.

The case presented in this newsletter, New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy: A Case-Based Series, illustrates several key points: various forms of anti-HCV therapy, strategies for planning and implementing therapy for HIV/HCV coinfection, strategies for managing side effects, and difficulties that can arise during treatment with both ART and anti-HCV therapy. Our case begins with a coinfected patient with a poorly controlled HIV infection who tests positive for HCV antibodies. Severe side effects develop after changes in the patient’s ART, compounded by his anti-HCV therapy. Anemia associated with the use of ribavirin is effectively treated with epoetin alfa, which enables this patient to remain on the prescribed treatment regimen without dose reduction or discontinuation. Read on to see how you can manage a complex case of HIV/HCV coinfection.

I am pleased to have assembled an outstanding faculty of experts in the treatment of hepatitis C infected patients with anemia, with critical new information and strategies for managing anemia that you can incorporate into your clinical practice. I hope that you will find this four-part newsletter series to be interesting, thought-provoking, and educational.

Sincerely,

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Patient Description

Oliver is a 46-year-old 72-kg Caucasian male, diagnosed with HIV in 1992. Past medical history included intravenous drug abuse in the 1980s, alcoholism, and significant depression with a suicide attempt in 1987. He has been free from both drugs and alcohol since 1990. Oliver’s initial antiretroviral therapy (ART) regimen was zidovudine and zalcitabine, which stabilized his CD4+ cell count above 200 cells/mm³. In 1996, his ART regimen was changed to zidovudine and lamivudine.

Oliver presented to our clinic in late 1998 with a poorly controlled HIV viral load of 104,000 copies/mL, although he was asymptomatic. He also had the following laboratory results: AST 41 U/L; ALT 55 U/L; normal CBC; and reactive antibodies to HCV. Oliver’s ART regimen was changed to stavudine, didanosine, and indinavir (a protease inhibitor), resulting in complete suppression of his HIV viral load 3 months later. Six months thereafter, he developed low-grade nausea and right upper quadrant discomfort. His HIV viral load remained undetectable and his abdominal ultrasound was unremarkable. His AST was 292 U/L and his ALT, 387 U/L. Oliver’s HCV viral load was 3,200,000 copies/mL, genotype 1a. A CT-guided liver biopsy was performed in 2000 and was consistent with advanced chronic hepatitis C—grade 3/stage 3.

Question 1

What issues are important to this case?

a. The impact of an active HIV infection on the prognosis and management of Oliver’s HCV infection
b. The impact of an active HCV infection on the prognosis and management of Oliver’s HIV infection
c. The etiology of Oliver’s elevated transaminases
d. The appropriateness of treating Oliver for his HCV infection
e. All of the above

(continued on page 2)
Learning Objectives
This case-based educational activity is designed to update gastroenterologists on emerging data on the use of growth factors to manage treatment-related anemia in HCV-infected patients.

After participating in this activity, physicians should be able to:
- Review the prevalence of treatment-induced adverse hematologic events in HCV-infected patients and their impact on treatment outcomes
- Discuss the pharmacology, risks, and benefits of epoetin alfa to treat chemotherapy-associated anemia and extrapolate treatment principles to managing anemia associated with anti-HCV therapy
- Examine new data on the use of epoetin alfa in patients on anti-HCV therapy
- Develop treatment strategies based on new and emerging data on the use of growth factors in treating anemia in HCV-infected patients

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Patient Description (continued from page 1)

Discussion
(e) It is estimated that 30% of the 800,000 Americans living with HIV are coinfected with HCV. Oliver was likely exposed to both viruses during his first year using intravenous drugs in the 1980s, giving us an estimate of the relatively short time it has taken for significant fibrosis to develop. Various data indicate that coinfection with HIV and HCV accelerates the progression of HCV disease and fibrosis compared with HCV-monoinfected patients, and carries a 3.6-fold increased risk of progression to cirrhosis. Unfortunately, complete control of HIV infection with ART seems to have no direct effect on HCV infection; however, some recent data suggest that protease inhibitor-based regimens may slow hepatic fibrosis in coinfected patients. Hepatocellular carcinoma (HCC) also appears to develop faster in the coinfected population. The clinical impact of coinfection has become particularly evident in the current era of ART. Morbidity and mortality due to end-stage liver disease continue to rise substantially in the coinfected population despite the ability to control HIV infection. End-stage liver disease from hepatitis C is assuming greater importance as a cause of death in HIV-infected persons in the United States.

Hepatitis C also appears to hamper HIV disease control. HCV is associated with diminished immune reconstitution with ART in HIV-infected patients. This is evidenced by blunted increases in CD4+ cells in coinfected patients treated with ART. Coinfected patients with low HIV viral levels and high HCV viral loads progress more quickly to AIDS and death compared with those with low HCV viral loads.

Studies indicate that HIV-infected patients are at increased risk of hepatotoxicity due to potent ART regimens and that discontinuations of ART due to hepatotoxicity are on the rise. Protease inhibitors have been the most common but not exclusive offenders. The etiologies of liver damage in this population are diverse, ranging from direct toxicity of the medication to indirect toxicity related to ART-induced reconstitution of immune function in individuals with underlying chronic viral hepatitis who can now mount an inflammatory response in the liver. The rate-limiting step in successful ART therapy in many coinfected patients may be control of HCV infection.

Case Continues
Oliver is at significant risk from both the “traditional” complications (ie, liver failure, HCC) of advanced HCV infection and potentially life-threatening limitations on his ART due to concurrent viral hepatitis. Initial management consisted of stopping all antiretroviral medications for 6 weeks. His symptoms resolved and his transaminases declined, stabilizing at near-normal levels. Oliver was then given a regimen for his HIV infection that did not include a protease inhibitor (ie, stavudine, didanosine, and efavirenz), which he tolerated without any appreciable clinical or laboratory evidence of hepatotoxicity. His HIV viral load was again undetectable.

Next month, he began standard doses of interferon alfa-2b, 3 MU TIW and ribavirin 800 mg/d, after starting on a prophylactic antidepressant. In the first 12 weeks of anti-HCV therapy, Oliver’s hemoglobin level declined from a baseline of 13.5 g/dl to <10 g/dl, with fatigue. The addition of epoetin alfa 40,000 U SQ QW to his regimen maintained Oliver’s hemoglobin levels above 10 g/dl, making it unnecessary to reduce his ribavirin dose. Oliver’s fatigue also improved. By week 24, his HIV viral load remained controlled, his CD4+ counts were stable, and his transaminases were persistently normal. However, he still had a significant HCV viral load of 300,000 copies/mL (down from the baseline of 3,200,000 copies/mL). His interferon/ribavirin therapy was stopped.

Question 2
This patient failed to achieve an SVR after treatment with interferon/ribavirin. At this point, the only approach to treating this patient is to provide supportive care.

❑ True ❑ False

Discussion
(False) Combination therapy with peginterferon and ribavirin has now become the standard of care for HCV-monoinfected patients, with SVR rates approaching 50% to 60%. According to the 2002 National Institutes of Health Consensus Development Conference Statement on HCV, treatment with peginterferon and ribavirin may benefit some patients who have not achieved an SVR. The decision to treat these patients should be made after considering a number of factors (see box below). Data on mono-infected patients not responding to standard interferon/ribavirin combination therapy

(continued from page 1)
TREATMENT REPORTER  New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy:  A Case-Based Series

and subsequently treated with peginterferon alfa-2b plus ribavirin are limited. Furthermore, there are few data on treating coinfected patients with peginterferon/ribavirin. Two studies of peginterferon alfa-2b/ribavirin in HIV/HCV coinfected patients reported end-of-treatment response rates of nearly 50%,26,27 and one showed an SVR rate of 33%.26 Peginterferon alfa-2a/ribavirin combination therapy produced similar results in another trial, with 44% of HIV/HCV coinfected patients responding at week 24.24 Histologic response was observed in over one third of virologic nonresponders to peginterferon alfa-2a or interferon alfa-2a in combination with ribavirin.23 Peginterferon/ribavirin combination therapy is expected to offer coinfected patients treatment outcomes approaching those seen in monoinfected patients.

Re-treating HCV Patients Who Failed to Achieve an SVR: Factors to Consider25

• Patient’s previous type of response
• Potency difference of the new therapy relative to the previous therapy
• Severity of the liver disease
• Prognostic indicators for a favorable response, ie, viral genotype
• Tolerance of and adherence to the previous treatment

Case Continues

In the summer of 2002, Oliver was started on therapy with 96 μg peginterferon alfa-2b (1.5 μg/kg) weekly plus 100 mg (~13.2 ± 2 mg/kg) ribavirin daily. He tolerated the first month of therapy well, in general, but developed anemia again with symptoms of fatigue. As before, treatment with epoetin alfa weekly prevented having to reduce the ribavirin dose, ameliorated his fatigue, and improved his quality of life (QOL).

Question 3

Patients with HIV/HCV coinfection are less likely to develop ribavirin-related anemia than patients with HCV monoinfection.

❑ True  ❑ False

Discussion

(False) The primary side effect of ribavirin is hemolytic anemia seen within 1 to 2 weeks after treatment.20 Anemia rates in coinfect patients treated with interferon alfa/ribavirin are more than three times higher than in HCV-monoinfected patients.20-23 In a cohort of HIV/HCV coinfect patients at the Liberty Medical Group in New York for HCV infection, 35% developed ribavirin-related anemia with hemoglobin levels <11 g/dL. Thus, patients with HIV/HCV coinfection are very likely to have QOL problems because of anemia.

Ribavirin dose reductions have been recommended if hemoglobin levels fall below 10 g/dL, and discontinuation is recommended if hemoglobin levels are <8.5 g/dL.29 Criteria for dose reductions in patients with history of cardiac disease are stricter. However, reducing ribavirin produces only a small increase in hemoglobin level, 1.1 g/dL on average.30 Besides the limited effect on hemoglobin levels, reducing ribavirin dose means reducing the patient’s chance of an SVR, especially important for Oliver, who already has a history of partial response to anti-HCV therapy.

Treatment with epoetin alfa is emerging as an effective strategy to manage ribavirin-induced anemia in HIV/HCV coinfect patients being treated for HCV infection. A panel of national and international thought leaders and clinicians in the area of HIV/HCV coinfection was surveyed about various strategies for managing patients with HIV/HCV coinfection.23 The panel responded that they were more likely to use epoetin alfa rather than to reduce the dose of ribavirin to manage anemia associated with anti-HCV treatment.

Case Continues

At his 8-week visit, Oliver complained of low-grade nausea, abdominal discomfort, mild increase in fatigue, and fleeting paresthesias of the upper and lower extremities. Laboratory evaluation revealed increased AST (67 U/L) and ALT (92 U/L). His hemoglobin was 11.7 g/dL, his HCV viral load was <600 copies/mL, and he had mild hepatomegaly on ultrasound. His ART regimen of stavudine, didanosine, and efavirenz had not been changed in more than 2 years with good control of his HIV infection. The symptoms were thought to be due to peginterferon alfa-2b and no medication changes were made at the time.

Two weeks later, Oliver was in the emergency room with abdominal pain, dyspnea, nausea, vomiting, and a 10-pound weight loss. Laboratory analyses showed: AST 120 U/L; ALT 157 U/L; WBC 7400/mm³; hemoglobin 11.9 g/dL; serum pH 7.31; serum bicarbonate 13 mmol/L; and serum lactate 7.6 mmol/L (normal <2 mmol/L). Chest x-ray, oxygen saturation on room air, and abdominal CT scan were unremarkable. After consultation with an infectious disease specialist, Oliver was hydrated with IV fluid and bicarbonate overnight; all antiretroviral and anti-HCV agents were discontinued. Oliver was discharged on vitamin B1 (thiamine) 100 mg/d; vitamin B2 (riboflavin), 50 mg/d; and L-carnitine 250 mg/d. After 4 weeks, he was completely asymptomatic with near-normal serum transaminases and a normal serum lactate.

Question 4

Lactic acidosis and the less severe symptomatic hyperlactatemia (SHL) are adverse reactions to treatment with nucleoside-analogue reverse transcriptase inhibitors for an HIV infection.

❑ True  ❑ False

Discussion

(True) Both lactic acidosis and its less severe form, SHL, are increasingly recognized complications of nucleoside-analogue reverse transcriptase inhibitor therapy for HIV infection (ie, zidovudine, stavudine, and didanosine)32 and are due to toxic effects of these drugs on the mitochondria.34 Recently, there has been increasing concern over the occurrence of SHL in patients treated with ART and anti-HCV therapy. Coinfected patients may be at increased risk for mitochondrial toxicity due to underlying liver disease. In addition, ribavirin appears to increase circulating levels of didanosine, enhancing its potential for mitochondrial toxicity. (Note that Oliver was treated with a higher dose of ribavirin during his second course of anti-HCV therapy.) Stavudine and didanosine have a relative risk of 2.2 and 8, respectively, associated with SHL in patients treated with peginterferon alfa-2a plus ribavirin or interferon alfa-2a alone.35

Case Continues

Oliver’s future treatment might include resuming peginterferon and ribavirin therapy while he is not on ART. His early clearance of HCV is certainly encouraging for the possibility of an SVR and better future tolerance of ART. The modest risk of suspending ART for 12 months could be reduced by frequent monitoring of his CD4+ count and outweighed by the overall survival benefit of HCV eradication. Alternatively, a different antiretroviral regimen with a lower risk of lactic acidosis could be established prior to restarting anti-HCV therapy.

Conclusion

Treating HCV in HIV-infected patients is very complicated. As these patients live longer than ever with their HIV infection, their risk of HCV-associated liver disease progression increases. As demonstrated in this case, protease inhibitors and nucleoside analogues used in HIV treatment can complicate anti-HCV treatment. It is important that we maximize the use of our
levels were maintained during two treatment cycles with interferon or peginterferon in combination with ribavirin. Moreover, Oliver was able to continue on the full ribavirin dose without dose reduction. This was especially important during his second anti-HCV treatment because he partially responded to his first anti-HCV treatment. Unfortunately, the lactic acidosis required discontinuation of all anti-HCV and anti-HIV medications.

The disease management strategy and prognosis for Oliver are uncertain, but it is clear that if he is treated for his HCV infection again and anemia develops, it can be treated effectively without requiring dose reduction of ribavirin.

References

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To receive documentation of your participation in this four-part CME activity for a total of 1 hour of CME credit, please complete the following steps:

1. Read each newsletter carefully.
2. Complete the CME Posttest included in each of the newsletters.
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Please indicate your answers below.

1. Active HIV and HCV infections do not have an impact on the prognosis and management of either infection.
   ❑ True    ❑ False

2. The protease inhibitors are the most common culprits in increased risk of antiretroviral-associated hepatotoxicity in HIV patients.
   ❑ True    ❑ False

3. The only option for treating HCV patients who partially respond to anti-HCV treatment is to provide supportive care.
   ❑ True    ❑ False

4. Nucleoside-analogue reverse transcriptase inhibitors are not likely to produce life-threatening lactic acidosis and symptomatic hyperlactatemia.
   ❑ True    ❑ False

5. Patients with HIV/HCV coinfection are more susceptible to ribavirin-related anemia and more likely to have problems with quality of life as a result.
   ❑ True    ❑ False

6. Managing anemia and associated quality-of-life problems in patients treated with anti-HCV medications by reducing the dose of ribavirin is more effective than using epoetin alfa.
   ❑ True    ❑ False
7. Patients who take 80% of their interferon dose and 80% of their ribavirin dose for at least 80% of the time are more likely to achieve a sustained virologic response.
   - True
   - False

8. Compared to all the antiviral medications that patients could be prescribed to treat their HIV/HCV coinfection, epoetin alfa is the least likely to have side effects if therapy is properly monitored.
   - True
   - False