Part 2 of 4: Frequently Asked Questions About Hepatitis C

Introduction

To give clinicians a practical front-line perspective on real-life clinical challenges, Projects In Knowledge launched a Care & Counsel listserv—an electronic discussion forum—last year. Clinicians who participated in the listserv asked questions, shared clinical cases, and engaged in dialogue with each other and with expert Care & Counsel faculty members. Due to its success, the listserv continues this year in an expanded form. This Tx Reporter contains information synthesized from discussions on the Care & Counsel listservs. These discussions often focus on managing challenges that clinicians face in daily practice for which there are few data to drive clinical decision making. In such circumstances, clinicians are forced to make care decisions based on their own best judgment and clinical experience. The listserv has provided a forum for clinicians to share those experiences and pool their knowledge, and that experience is reflected here. However, it is important to note that suggestions generated by the listserv participants are often made in the absence of clinical trial data and may not represent the standard of care. As such, suggestions offered here do not necessarily reflect the opinions or recommendations of the entire Care & Counsel faculty or Projects In Knowledge, but do represent the personal opinions of some of your colleagues in the field who are actively involved in the care of patients with hepatitis C.

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Treatment Considerations

Q: Is SVR tantamount to cure? Do patients relapse after SVR? Do I need to continue monitoring after a confirmed SVR?

A: Specific guidelines and clear recommendations are lacking for monitoring HCV RNA after a confirmed SVR at 6 months posttreatment. However, rare late relapses do occur, and one recent publication from the American Society of Microbiology documented the persistence of HCV in peripheral mononuclear cells and dendritic cells even 5 years after SVR in a very small study (N = 16).1 The NIH Consensus Statement on Management of Hepatitis C: 2002 states, “Until future studies determine whether [SVR] will be sustained over the long term following successful antiviral treatment, periodic measurements of HCV RNA may need to be performed,” but it does not define an appropriate follow-up interval.2 Participants in the Care & Counsel listserv said they generally continue monitoring, and the frequency and duration of monitoring varied from every 6 months for 1.5 to 2 years to annually for 5 years. A qualitative HCV RNA assay was recommended for this purpose, since it is more sensitive than quantitative HCV RNA assays for detection of very low levels of virus. Debate persists as to whether cirrhotic patients should continue screening for hepatocellular carcinoma (HCC) after an SVR. The NIH Consensus Statement indicates that monitoring for HCC every 6 months with alpha-fetoprotein and hepatic ultrasound in patients with cirrhosis is standard practice in the United States, despite a lack of evidence; however, the NIH Statement does not indicate whether this practice applies to patients who have had a treatment response.3 One recent study reported that 2.3% of sustained responders developed HCC, which was most common among those who were male, older, and had advanced-stage histologic disease.3 The authors recommended that high-risk individuals be followed up periodically for >10 years after completing therapy.3

Q: I always use longer treatment (48 weeks) for patients with genotype 1 infection, but are there any patients with genotype 2/3 infections that I should also treat longer than 24 weeks?

A: Treating genotype 1-infected patients for 48 weeks is standard practice, irrespective of other risk factors, since genotype is such a strong predictor of response and since peginterferon/ribavirin was given for 48 weeks in the registration trials. Many clinicians use shorter therapy (24 weeks) for patients with genotype 2/3 infection, based on excellent response rates to treatment in this population. A multivariate analysis of patients treated with 48 weeks of peginterferon alfa-2b/ribavirin identified the following predictors of response: genotype 2/3, fibrosis F0-F1, viral load <1.3 million IU/mL, and body mass index <27.4 A number of clinicians participating in the Care & Counsel listserv said they do treat for 48 weeks all patients with cirrhosis, irrespective of genotype, presumably because of the decreased likelihood of response in this population and the potentially serious consequences of nonresponse. However, clear guidelines to support this approach are currently lacking.

Managing Side Effects

Q: A 54-year-old patient developed a chronic cough after 1 month of therapy with peginterferon/ribavirin. I treated her cough with benzonatate (Tessalon Perles®), over-the-counter cough suppressants, antibiotics, and guaifenesin 600 mg without success. The patient is reluctant to continue therapy if her cough does not resolve.

A: Chronic cough after therapy for chronic hepatitis C is common, and is usually mild and self-limited. However, if the cough persists, it may resolve with an appropriate follow-up interval.2 Patients in the Care & Counsel listserv said they generally continue monitoring, and the frequency and duration of monitoring varied from every 6 months for 1.5 to 2 years to annually for 5 years. A qualitative HCV RNA assay was recommended for this purpose, since it is more sensitive than quantitative HCV RNA assays for detection of very low levels of virus. Debate persists as to whether cirrhotic patients should continue screening for hepatocellular carcinoma (HCC) after an SVR. The NIH Consensus Statement indicates that monitoring for HCC every 6 months with alpha-fetoprotein and hepatic ultrasound in patients with cirrhosis is standard practice in the United States, despite a lack of evidence; however, the NIH Statement does not indicate whether this practice applies to patients who have had a treatment response.3 One recent study reported that 2.3% of sustained responders developed HCC, which was most common among those who were male, older, and had advanced-stage histologic disease.3 The authors recommended that high-risk individuals be followed up periodically for >10 years after completing therapy.3

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A: Ribavirin can cause a persistent nonproductive cough, but it often resolves by week 12. It is prudent to rule out tuberculosis, pulmonary edema, and interstitial pneumonia. The first step is to increase hydration, and then treat the dry cough with the types of remedies you mentioned. If those are unsuccessful you can try an albuterol inhaler, fluticasone propionate/salmeterol, montelukast sodium, fexofenadine, cetirizine, loratadine or desloratadine, or a cough suppressant with hydrocodone or codeine. Other helpful strategies can include using a humidifier, lozenges, or Cepacol® spray. Smokers can have an exacerbation of chronic bronchitis that usually responds well to a course of antibiotics, particularly doxycycline. Keep in mind that other medications, such as angiotensin-converting enzyme inhibitors, may also contribute to cough. If available treatments do not work and the patient is bothered by the cough, ribavirin dose reduction may be necessary. Refractory cough or shortness of breath should also prompt a chest x-ray, as well as resting and walking pulse oximetry.

Q: A 57-year-old African American patient with genotype 1 infection developed significant anemia (hemoglobin 7.3 g/dL) 16 weeks into treatment with peginterferon alfa-2b 1.5 µg/kg and ribavirin 1000 mg/d. Ribavirin was discontinued, and the patient was treated with epoetin 40,000 U QW. Five weeks later, his hemoglobin level was 12 g/dL. HCV RNA at week 12 showed that he had had a >2-log decrease. Can ribavirin be restarted, and if so, at what dose?

A: Ribavirin should be restarted particularly if the patient has advanced fibrosis (stage III or IV). It should be reinitiated at the full dose, with weekly monitoring of hemoglobin level and continued epoetin therapy. An alternative approach would have been to restart ribavirin sooner (ie, at a hemoglobin level of ≥10 g/dL, or at 11–12 g/dL if there is a history of cardiovascular disease) using a lower dose (eg, 600–800 mg/d) and then gradually increase the dose if the hemoglobin level remains stable. A transfusion may also have been appropriate at a hemoglobin level as low as this patient exhibited (7.3 g/dL). Since anemia is of mixed origin (ie, caused by a hemolytic mechanism of ribavirin and by bone marrow suppression from interferon), some hematologists would temporarily reduce the peginterferon dose by .25 or .5 µg/kg as well, until the problem is corrected with the epoetin.

To get the greatest erythropoietic benefit from the epoetin, be sure the patient has normal iron stores (supplement if necessary) and have him start on a daily multivitamin. Several clinicians mentioned using epoetin doses up to 60,000 U QW if necessary, to avoid dose reductions or discontinuation of ribavirin. Epoetin dose should not exceed 60,000 U QW, and clinicians should keep in mind that it may take some time before full effects are seen. Weekly epoetin should be given 2 days prior to the peginterferon injection. It is usually not possible to return the hemoglobin level to baseline during continued treatment, so the goal is to reach a stable level that minimizes symptoms while maintaining as close to a full dose of ribavirin as possible. If hemoglobin level does reach >14 g/dL, then gradually reduce the epoetin by 10,000 U and titrate further as needed.

Q: A patient with a normal baseline triglyceride level had an increase at 3 months of therapy to 400 mg/dL. She also became hypothyroid, and despite treatment her thyroid stimulating hormone level is still 8.6 µU/mL. She is in her thirties and overweight. How should I manage this?

A: Hypertriglyceridemia is a common side effect in patients taking peginterferon/ribavirin, especially in those with a past history of it. It usually returns to normal posttreatment unless the patient is otherwise predisposed to hypertriglyceridemia. Most clinicians recommended careful monitoring without pharmacologic therapy unless the triglyceride level reached ≥1000 mg/dL, suggesting a risk of pancreatitis. At that point, gemfibrozil 600 mg BID should be considered.

Hypertriglyceridemia can also be a symptom of hypothyroidism, and adjusting the thyroid replacement therapy may help in this case. An endocrinologist can help with controlling the thyroid problem, which may be irreversible after antiviral therapy.

Q: What would you recommend for a patient who develops cheilosis with cracks at the corners of the mouth during peginterferon/ribavirin therapy?

A: According to anecdotal responses from the Care & Counsel listserve participants, various options may be helpful. Ms. Corbett, one of the co-chairs for this series, recommended Kenalog® (triamcinolone acetonide) in Orabase. Another participant suggested that the combination of bacitracin and Loprox® (ciclopinox) was very effective. Patients should put a “dot” of each on their fingertips, and then apply enough to the corners of the mouth every couple of hours to keep coated. Excessive moisture and secondary bacterial and/or fungal colonization can keep the lips from healing. Candida infection can also cause cheilosis, which can be treated topically with ketoconazole cream.
2%. twice a day. Patients should be advised to avoid licking their lips and mouth corners.

Q: I have a 45-year-old patient who showed early virologic response at 12 weeks, and who is now 24 weeks into peginterferon/ribavirin therapy. She is having new onset of anger outbursts and is so distraught at her inability to control her anger that she wants to discontinue therapy. She has been taking amitriptyline (Elavil®) 25 mg QHS for several months for insomnia and very mild depression and is sleeping well. How can I manage the anger problem?

A: If this patient is tolerating the amitriptyline well, you could increase to a full antidepressant dose (typically 50–150 mg QHS, stepwise). A few cautions, however. First, consider the risk of suicide in this patient, since high doses can be lethal (maximum recommended dose is 300 mg/d), and check an electrocardiogram before increasing the dose. Other tricyclic antidepressants may work better if the amitriptyline is too sedating, or consider a neutral or sedating selective serotonin reuptake inhibitor (SSRI). The SSRI paroxetine (Paxil®) was also specifically recommended for rage by one listserve participant. Mirtazapine (Remeron®) was recommended for patients with a combination of depression, anxiety, nausea, anorexia, and insomnia. Other possible options for treating anger problems or rage include gabapentin (Neurontin®), 300 mg BID–TID to start), olanzapine (Zyprexa®, which may be effective even at doses as low as 5 mg/d), quetiapine fumarate (Seroquel®), which has the added benefit of promoting sleep), oxcarbazepine (Trileptal®), or divalproex sodium (Depakote®).

Q: One of my patients reports dizziness with change of position during treatment with peginterferon/ribavirin. The patient is adequately hydrated, and his hemoglobin level is 13.0 g/dL. Is meclizine hydrochloride appropriate?

A: The symptom may be independent of the patient’s treatment. A Dix-Hallpike maneuver, a special test to determine when a small calcium particle gets lodged in a semicircular canal, can be used to check for benign positional vertigo. If this test is positive for nystagmus, then meclizine may help, as would exercises, to gradually reduce this effect. In addition, you should check his electrolytes and his blood pressure (both sitting and standing). Extra hydration might also be beneficial. Nonspecific dizziness can frequently be associated with psychiatric disorders (depression, anxiety, panic), so you should also perform a psychiatric evaluation.

Q: Is taste perversion associated with peginterferon/ribavirin therapy?

A: Patients with advanced liver disease may become zinc deficient. Zinc deficiency is associated with dysgeusia (taste alteration). Consider measuring blood levels and replace zinc as necessary with zinc sulfate 220 mg PO BID. Rare side effects of these supplements include nausea and diarrhea. Zinc replacement also improves muscle cramps that occur at rest, usually while sleeping.

Conclusion

Through vast clinical experience, clinicians have developed strategies for managing unusual treatment situations as well as side effects of peginterferon/ribavirin. Many such strategies have not been fully investigated in clinical trials, but have become part of common practice as experience confirms their utility. By sharing what works in their patient populations through forums such as the Care & Counsel III listserve, clinicians help each other identify effective management strategies, adjunctive treatments, and nonpharmacologic management approaches that can help patients through therapy.

References

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Please select the most appropriate response to each question.

1. Duration of peginterferon/ribavirin is most commonly based on:
   a. Fibrosis
   b. Body mass index
   c. Viral load
   d. Genotype

2. When ribavirin is discontinued for anemia, and hemoglobin subsequently returns to 12 g/dL with use of epoetin, which of the following is the most appropriate approach?
   a. Ribavirin should be reinitiated at the full dose, with weekly monitoring of hemoglobin
   b. Ribavirin should be reinitiated at 600 mg/d, with weekly monitoring
   c. A transfusion should be given before initiating ribavirin
   d. It is inappropriate to reinitiate ribavirin

3. Treatment with gemfibrozil should be considered for hepatitis C patients with a triglyceride level:
   a. ≥400 mg/dL
   b. ≥600 mg/dL
   c. ≥800 mg/dL
   d. ≥1000 mg/dL
4. If a patient has a documented SVR 6 months posttreatment, what does the NIH Consensus Statement on Management of Hepatitis C recommend?
   a. Continued monitoring of HCV RNA at a 6-month interval
   b. Continued monitoring of HCV RNA annually
   c. Periodic monitoring of HCV RNA (without specification as to the interval)
   b. Discontinuation of HCV RNA monitoring since the virus has been eradicated

5. Zinc supplements were recommended for patients with:
   a. Headache
   b. Anorexia
   c. Taste perversion
   d. Flulike symptoms

6. Which of the following was recommended as a strategy for treating ribavirin-related cough?
   a. Over-the-counter cough suppressants
   b. Antihistamines
   c. Albuterol inhaler
   d. Cough suppressant with hydrocodone or codeine
   e. Any of the above

7. Meclizine may be useful in treating:
   a. Benign positional vertigo
   b. Epistaxis
   c. Irritability
   d. Cough

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Thank you for your participation.
Care & Counsel III: Helping Patients Stay the Course on Treatment for Hepatitis C  
Part 2 of 4: Frequently Asked Questions About Hepatitis C

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2. Please rate the extent to which you achieved the learning objectives:  

   Excellent  Very Good  Good  Satisfactory  Poor

   ● Promote adherence to peginterferon/ribavirin, particularly during the critical early period of therapy.  

   ● Develop effective side effect management of peginterferon/ribavirin therapy using strategies that minimize the need for dose reduction or treatment discontinuation.  

   ● Describe the latest data on use of hematopoietic growth factors in hepatitis C patients with hematologic side effects of peginterferon/ribavirin.  

   ● Describe the latest data on use of other adjuvant therapies, including psychotropic agents, in managing peginterferon/ribavirin side effects.  

3. Please rate the extent to which this activity achieved the stated goal.  

   The goal of this activity is to provide practical information about the management of hepatitis C, including specific treatment challenges and side effect management.  

   Excellent  Very Good  Good  Satisfactory  Poor

   Strongly Agree  Agree  Disagree  Strongly Disagree

4. Activity was free from commercial bias:  

   If you “Disagree” or “Strongly Disagree,” why?.....................................................................................................................................................

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   Just Right  Too Advanced  Too Basic

5. Please rate the level of the material presented:  

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Thank you for your participation.