

Perspective

Managing Adverse Effects and Complications in Completing Treatment for Hepatitis C Virus Infection

The addition of direct-acting antivirals (DAAs) to hepatitis C virus (HCV) treatment regimens has made treatment more effective and patient management more complex. Shepherding patients through a full course of HCV therapy requires motivation and involvement on the part of the patient and the physician. Indeed, physician inexperience and lack of confidence in guiding patients through the challenges of treatment appears to be a primary reason for early discontinuation of therapy. Among the many complications of HCV treatment that must be managed efficiently and effectively are depression and other psychiatric disorders; hematologic abnormalities including DAA- and ribavirin-associated anemia and peginterferon alfa-associated neutropenia and thrombocytopenia; rash and drug eruptions, including telaprevir-associated rash; and weight loss. Practical considerations in management of these common complications are offered. This article summarizes a presentation by Kenneth E. Sherman, MD, PhD, at the IAS–USA live continuing medical education course held in New York in June 2012.

In clinical trials, treatment with a direct-acting antiviral (DAA) in combination with peginterferon alfa and ribavirin for 48 weeks produced a sustained virologic response (SVR) in approximately 65% to 75% of patients with genotype 1 or 4 hepatitis C virus (HCV) infection. Peginterferon alfa and ribavirin treatment for 24 weeks produced an SVR in approximately 70% to 85% of patients with HCV genotype 2 or 3 infection. SVR rates in clinical practice are not as high, in large part because early discontinuation of HCV therapy is frequent for reasons unrelated to treatment futility (ie, stopping treatment for failure to achieve specific reductions in plasma HCV RNA level by specific time points). Major reasons for early discontinuation of anti-HCV therapy are discussed herein.

Physician Inexperience

Treating HCV infection with available regimens can be daunting to both patient and physician, and physician

inexperience can result in a lack of confidence in initiating and following through with treatment. A recent analysis in a study population receiving peginterferon alfa and ribavirin therapy showed that treatment was discontinued in 44% of patients, with physician reasons accounting for 75% of discontinuations and patient reasons accounting for 25%.¹

Whereas treatment futility accounted for 33% of physician discontinuations, no reason for discontinuation was given for 39% of cases. Comorbidities and lack of adherence were cited as reasons in 5% of cases each. Patients often cited adverse effects as a reason for stopping treatment, but some also reported that they got the sense from their physician that they should stop or were encouraged to stop. In the WIN-R (Weight-Based Dosing of Peginterferon alfa-2b and Ribavirin) trial, which was performed at 236 community and academic sites, 41.3% of subjects discontinued therapy.² Clinicians who are inexperienced and not confident in their ability to guide a patient through the treatment course may discontinue treatment early, depriving the patient of a chance for cure. As health care providers, we need to move past any such hesitancy in order to provide effective treatment and management.

Psychiatric Complications

Depression is the most common psychiatric complication encountered in HCV patients, with mild to moderate depression found in as much as 80% of patients. Bipolar disorder and schizophrenia are also not infrequently encountered.

There is little evidence to support a benefit of preemptive antidepressant therapy in all patients undergoing HCV treatment, though a recent randomized trial of HCV patients without psychiatric history suggested that major depression risk was decreased in a group of patients randomized to receive escitalopram prior to interferon-based therapy.³ For patients who are actively depressed, antidepressant treatment is likely to be required. Mild and moderate depression can be assessed by and readily treated by the HCV physician and in most cases, referral to psychiatry is not necessary. The primary issue for the HCV physician is to determine whether the depression is manageable in the context of HCV treatment. The physician should become comfortable with the use and effects of several antidepressants, including sertraline, paroxetine, and mirtazapine.

A thumbnail guideline for use of these agents is to use sertraline if the depression is characterized by sadness and crying episodes and paroxetine if it is characterized by anger. Mirtazapine is especially useful in patients who are suffering weight loss, because it is associated with significant appetite stimulation and weight gain. All of these drugs have potential interactions with telaprevir and boceprevir and should be started at the lowest possible therapeutic dose. Psychiatric assistance is needed for patients with more severe depression—eg, those with suicidal ideation—and HCV treatment should be delayed until such patients are stable. The most effective way to

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manage such patients is not to refer to psychiatry and wait for clearance, but to form a partnership with the psychiatrist throughout the duration of the patient's treatment.

Psychiatric expertise also usually is needed for patients with bipolar disorder or schizophrenia prior to starting HCV treatment. It is important that these patients have a commitment to psychiatric care. A contract with such patients sometimes ensures that they will stay with their psychiatric care. With patients who have bipolar disorder, it is best to try to initiate HCV treatment during a hypomanic phase. It is difficult to start and maintain therapy in a manic or actively delusional patient even with the help of a psychiatrist. There is evidence from several small studies that partnering with psychiatry can help in getting patients with bipolar disorder or schizophrenia through an HCV treatment course. In one study, 22 patients with psychiatric disorders and 17 control patients were treated with peginterferon alfa and ribavirin in an interdisciplinary setting that included psychiatry. The outcomes in the 2 groups were similar, with SVR being achieved in 50% and 58.6%, respectively.⁴

Hematologic Toxicities

Anemia

Anemia beyond that associated with ribavirin alone is a major adverse effect with both telaprevir and boceprevir. For example, anemia occurred in 37% and 41% of patients receiving telaprevir in the ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir)⁵ and ILLUMINATE (Illustrating the Effects of Combination Therapy with Telaprevir)⁶ trials, respectively, compared with 19% of patients receiving peginterferon alfa and ribavirin alone. No erythrocyte-stimulating agents were used in the telaprevir trials, with anemia being managed by ribavirin dose reduction. Similarly, 49% of patients in each of the 2 boceprevir arms in the SPRINT-2 (Serine

Protease Inhibitor Therapy 2) trial developed anemia, compared with 29% of patients receiving peginterferon alfa with ribavirin and placebo.⁷ Treatment was discontinued because of anemia in 2% of each boceprevir group and in 1% of placebo patients. Dose reductions were implemented in 20% to 21% of boceprevir patients and in 13% of placebo patients, and epoetin alfa was used to treat anemia in 43% of boceprevir patients and 24% of placebo patients.

Ribavirin dose reduction should be considered the first strategy for treating anemia in patients receiving DAA-containing regimens, because it does not appear to compromise response, and is less expensive and safer than initiating epoetin alfa treatment or other erythrocyte-stimulating growth factors. In a recent trial in 500 patients receiving boceprevir-containing regimens, patients with hemoglobin levels dropping below or about to drop below 10 g/dL were randomized to receive a 200 mg/d to 400 mg/d reduction in ribavirin dose or to get an addition of 40,000 U/wk of subcutaneous epoetin alfa.⁸ SVR rates were approximately 70% in both groups, suggesting no difference between the 2 approaches with regard to compromising response. In addition, a retrospective analysis of outcomes in the ADVANCE and ILLUMINATE telaprevir trials showed slightly, but not statistically significantly lower SVR rates in patients with ribavirin dose reduced to a range of 800 mg/d to 1000 mg/d, or 600 mg/d, than in patients with no ribavirin dose reductions (all SVR rates were between 74% and 79%).⁹ Similar outcomes were observed in an analysis of previously treated patients in the REVEAL (Risk Evaluation of Viral Load Elevation and Associated Liver Disease) study of telaprevir.

Neutropenia

Neutropenia is common during peginterferon alfa and ribavirin therapy and is attributed primarily to peginterferon alfa. Considerable anecdotal evidence, analyses of clinical trials, and one large single center experience indicate that

there is no increased risk of infection associated with neutropenia, even when the absolute neutrophil count (ANC) drops below 500/ μ L.^{10,11} Neutropenia should be managed with filgrastim (5-10 μ g/kg) only when the ANC drops below 500/ μ L and before any reduction in peginterferon alfa dose.

Thrombocytopenia

Thrombocytopenia is a frequent cause of treatment discontinuation in clinical practice. Platelet counts plummet during the first 6 weeks to 8 weeks in some patients, and physicians justifiably become alarmed. However, it does not appear that a declining platelet count should prompt substantial concern until it reaches about 30,000/ μ L. When platelet counts are in the range of 20,000/ μ L to 30,000/ μ L, the thrombocytopenia should be managed by peginterferon alfa dose reduction. In the absence of substantial anemia, the ribavirin dose should not be changed, because ribavirin increases platelet count when compared with use of peginterferon alfa alone.¹²

Eltrombopag is a platelet growth factor that is very expensive, sometimes difficult to get insurance approval for, and not widely used. However, its use can be considered in a patient who has a platelet count of 20,000/ μ L to 30,000/ μ L in whom no further peginterferon alfa dose reductions can be made and who is otherwise doing well. A study reported several years ago showed that starting eltrombopag treatment in patients with low platelet counts prior to beginning HCV therapy was successful in increasing platelet counts such that they remained at high levels throughout the course of therapy.¹³ This approach would be very expensive and is not a US Food and Drug Administration–approved use of eltrombopag, but the drug can be effective in adjunctive therapy for thrombocytopenia.

HCV treatment should be discontinued in most cases if the platelet count drops below 20,000/ μ L. In patients who have hemophilia, the threshold for stopping therapy is much higher (eg, about 50,000 cells/ μ L).

Dermatologic Issues

Peginterferon alfa, ribavirin, and telaprevir, but not boceprevir, are associated with rash. Peginterferon alfa can cause dermatitis, local reactions, and exacerbation of psoriasis. The local reactions are rare but can be quite severe. Treatment should be stopped in patients who develop a depression or ulcer at the injection site; if treatment continues, the lesion will continue to widen and deepen. Psoriasis may progress from tiny patches to that covering large portions of the body. In such cases, aggressive treatment with topical steroids should be started in consultation with a dermatologist. Light therapy sometimes helps. Treatment with injectable methylprednisolone or other injectable steroids has been successful at more advanced stages of psoriasis, but should not be used for initial treatment. Ribavirin is associated with drug eruption that often occurs between 6 weeks and 16 weeks and up to 20 weeks of therapy. It frequently overlaps with telaprevir-associated rash, which is the rash of greatest concern.

Telaprevir is associated with eczematous rash and drug rash with eosinophilia and systemic eruptions (DRESS). A summary of data from telaprevir placebo-controlled phase II and III trials indicates that rash occurred in approximately 56% of telaprevir patients compared with approximately 35% of control patients, with rash being mild in severity in 37% of telaprevir patients, moderate in 14%, and severe in 5%.¹⁴ Rash was typically pruritic and eczematous, covering less than 30% of the total body surface area. Rash started within the first 4 weeks of treatment in approximately 50% of patients, but was observed at any time during treatment. Progression of rash to greater severity occurred in less than 8% of patients.

Grading of skin eruptions is important. It was learned in the telaprevir trials that even experienced clinicians overestimate the percentage of body surface area affected by rash compared with dermatologist findings. A mild eruption is a localized eruption with

limited distribution in separate, isolated sites on the body.¹⁵ A moderate eruption is a diffuse rash that involves less than 50% of body surface area. Severe rash affects more than 50% of body surface area or is accompanied by substantial systemic symptoms, mucous membrane ulceration, target lesions, or epidermal detachment. Severe cutaneous adverse reaction (SCAR) comprises DRESS (usually involving fever and increased liver enzymes); Stevens-Johnson syndrome with toxic epidermal necrolysis; acute generalized exanthematous pustulosis; and erythema multiforme. Figure 1 illustrates DRESS. The patient's skin was peeling off in layers, and he had lesions in the mouth, dramatic swelling of the lips, and a very high eosinophil count. DRESS requires immediate hospitalization.

Mild rash developing in patients receiving telaprevir should be managed conservatively with topical steroids. For moderate rash without mucosal involvement, management includes stopping telaprevir, especially if the patient has had more than 8 weeks of treatment, but continuing peginterferon alfa and ribavirin. If the physician suspects that the rash is caused by ribavirin, the drug can be held for 1 week to 2 weeks and then restarted at a lower dose. For patients with severe rash or SCAR, all HCV treatment should be stopped.

Weight Loss

Weight loss associated with peginterferon alfa treatment is fairly common. Body weight loss of more than 10% is considered serious. Serious weight loss is more common among patients who have HCV and HIV coinfection. Primary management



Figure 1. Drug rash with eosinophilia and systemic eruptions (DRESS). This patient's skin is peeling off in layers, he had oral lesions in his mouth with blisters, and his lips were swollen. He had a high eosinophilic count.

consists of calorie supplementation using milk shakes or nutrition drinks. As noted above, the antidepressant mirtazapine is often effective in promoting weight gain.

Conclusion

With the availability of DAAs, the management of HCV treatment has become more, not less, complex. Specific management techniques are evolving as we learn more about both safety and efficacy of the currently available regimens.

The decision to initiate therapy now, versus waiting for next-generation therapies that may not contain peginterferon alfa, is also complex. In general, patients with stage 1 or 2 hepatic fibrosis are unlikely to progress to cirrhosis (stage 4) within 3 to 5 years and may choose to wait for newer therapies. However, these patients do represent a potential public health risk to others, and there is no guarantee that newer therapies will truly be more efficacious with fewer adverse effects than current therapy.

In contrast, patients with stage 3 fibrosis and compensated cirrhosis should probably be offered treatment now. Effective treatment may prevent

hepatic decompensation. A patient with decompensated disease (ascites, bleeding varices, encephalopathy) is not a candidate for the current generation of HCV antiviral therapies.

Management of treatment with the next generation of DAAs may be easier, but it is likely that challenges will continue for decades to come.

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Additional Suggested Reading

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