Effectively Managing Side Effects of Treatment for Hepatitis C Virus

Hepatitis C virus (HCV) is one of the leading causes of chronic liver disease in the U.S. Treatment with peginterferon (PEG IFN alfa-2a or alfa-2b) and interferon alfa (IFN-alfa) in combination with ribavirin are effective in treating the virus, but a range of side effects, combined with the 24-to-48 week treatment duration, can interfere with adherence and satisfactory patient outcomes. Clinicians can benefit from an awareness of predictable side effects and their time course, and from management strategies that have been shown to minimize their impact. A discussion with the patient of potential side effects, clinician guidance on their manageability, and incorporation of credible HCV education resources can help support the clinician’s efforts to inform patients on the clinical course of the disease, the anticipated benefits and effects of treatment, and the importance of adopting healthy lifestyle habits and self-care to promote adherence and achieve sustained viral clearance.

INTRODUCTION

Hepatitis C virus (HCV) is the most common chronic blood-borne virus in the United States (1,2) and a leading cause of chronic liver disease (1) and liver failure requiring transplantation (3). It is estimated that more than 3.9 million persons in the U.S. are positive for HCV antibody, and 2.7 million are chronically infected (2). Of those tested positive for HCV, 65% of cases have been found in persons born between 1945 and 1964 (2).

The most recent surveys identify illegal use of injected drugs as the primary risk factor for HCV infection (2). Infection is also higher in persons who have engaged in high-risk sexual practices (including multiple partners and age of first sexual intercourse at <18 years) and having a history of blood transfusion prior to the introduction of widespread donor screening in 1992 (2).

The age profile of the majority of HCV-infected patients reflects the Baby Boom demographic, and
many HCV patients who once engaged in high-risk behaviors may have abandoned the practices years ago (2). Still, these behaviors put them at risk for a chronic disease—the effects of which are only now beginning to emerge (2).

HCV infection carries significant morbidity and is potentially life-threatening. Statistics show that an estimated 85% of infected persons will develop chronic infection. A fraction of those will go on to develop cirrhosis or hepatocellular carcinoma (3). Recent data suggest that HCV may also play a role in the development of non-Hodgkin lymphoma and lymphoproliferative precursor diseases (4). Between 1% and 5% of all infected persons can be expected to die from HCV complications. (5)

Interferon alfa (IFN-alfa) and peginterferon (PEG IFN alfa-2a or alfa-2b) alone or in combination with ribavirin and consensus interferon monotherapy are currently approved by the U.S. Food and Drug Administration to treat HCV. Treatment with PEG IFN/ribavirin combination therapy typically results in sustained viral clearance rates of up to 56% (6). PEG IFN provides the benefit of once-weekly dosing. PEG IFN alfa-2a comes in prefilled syringes and PEG IFN alfa-2b offers a self-contained dosing pen delivery system, which may enhance patient convenience and dosing accuracy.

While effective therapeutic strategies, IFN and PEG IFN treatment are known to induce a range of side effects that, when combined with the 24-to-48 week treatment duration, pose challenges to patient compliance and adherence that can negatively affect outcomes. The role of the clinician in treatment adherence cannot be overstated. Through their approach to the management of side effects and their attention to the impact of the clinician-patient dialogue, clinicians can play a critical role in motivating patients throughout the course of treatment to support compliance and achieve sustained virological response (SVR).

SIDE EFFECTS IN PERSPECTIVE

Although side effects with IFN and PEG IFN/ribavirin treatment are frequent and can be troublesome, research has shown that they can be effectively managed throughout the course of therapy. Serious adverse events, including neutropenia, are uncommon, and concern over their potential occurrence may be somewhat exaggerated in practice. The development of the most common side effects typically follows a predictable time course. Flu-like symptoms generally begin during the first few weeks of treatment(6), but dissipate over time. Fatigue can be another prominent side effect of therapy that may progress during the course of treatment (7). For people who experience treatment-related depression, symptoms typically manifest at week four of treatment, persisting and worsening over the course of therapy (8). In addition, a majority of patients experience a significant reduction in hemoglobin (Hb) levels within the first few weeks of treatment, resulting in anemia, which can exacerbate fatigue and produce other quality-of-life side effects (9) (Figure 1).

A discussion of potential side effects can be broached in a straightforward and reassuring manner to cultivate a rapport that sustains a patient’s commitment to compliance and encourages open communication regarding side effects as they emerge. Importantly, a recommendation to time injections to better suit a patient’s work schedule can minimize impact of treatment on day-to-day activities. For example, patients with typical Monday through Friday employment may
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benefit from Friday injections that enable them to rest over the weekend before returning to work.

incorporating reliable patient resources can serve to assist the clinician with patient management demands, and provide additional support and information to patients. Pharmaceutical companies that manufacture the interferons sponsor extensive support for patients and health care providers. The resources, Be In Charge®, www.beincharge.com, sponsored by Schering-Plough Corp., Aspiresm Program, http://www.infergen.com/5-Aspire/index.html, sponsored by Three Rivers Pharmaceuticals, and Pegassist®, www.pegassist.com, sponsored by Roche Pharmaceuticals, are comprehensive and easy to use. The Web sites offer information on the disease and its treatments, and provides access to extensive support materials such as a patient diary to record symptoms, handbooks/brochures for patients receiving treatment, and phone numbers for 24-hour, toll-free access to a call center staffed by registered nurses in more than 150 languages, with the Be in Charge® call center offering 24/7 live support. Videos that describe the patient experience with hepatitis C treatment can be found on some of the sites.

for those without Internet access, the nursing hotlines referenced above can be invaluable. The call center can not only provide information immediately over the phone, but can also assist with sending out written materials. Internet resources for healthcare providers include: www.clinicaloptions.com, www.aasld.org, and www.projectsinknowledge.com. These resources can serve as a valuable complement to clinician-patient dialogue to better prepare the patient for treatment, enlist family members’ support in patient compliance, and encourage patients to incorporate self-care strategies, including adequate sleep, hydration, and nutrition, into their daily routines.

managing hcv treatment side effects

fatigue

fatigue is the most commonly reported symptom of treatment for hcv (7), and one of the reasons often cited by patients for discontinuing therapy (7). Recognized as both a symptom of disease and a side effect of treatment, fatigue may result from insomnia, depression, anemia, poor nutrition or other factors, including detrimental sleep habits. As a primary symptom of depression, patients experiencing fatigue should be assessed using a standard depression screening tool. If depression is suspected, selection of pharmacotherapy can be tailored to avoid treatments that can induce insomnia.

good nutrition, hydration, and exercise may help to alleviate the fatigue associated with therapy. As combination therapy can lead to mild dehydration, maintaining adequate hydration is especially important. One 12-ounce glass of water every three-to-four hours may be very effective in treating fatigue and other flu-like symptoms that result from therapy (10).

Additionally, a thorough discussion of patient sleep patterns is important to determine habits that may contribute to fatigue. Patients should be counseled against daytime sleeping, as extended naps may interfere with quality nighttime sleep. Patients should also be screened for alterations in thyroid and glucose levels and be appropriately treated for hypo- or hyperthyroidism, or hyperglycemia.

If these approaches fail, clinicians may consider exploring with patients medications to help mitigate fatigue and enable rest. Studies evaluating medications with noradrenergic/dopaminergic activity show that treatments such as methylphenidate HCL or amphetamine salts can be useful for appropriate patients. However, caution is advised when using these treatments for such off-label indications(11) with particular concern regarding their addictive potential.

depression

Depression is common in patients undergoing standard treatment for HCV and correlates to negative treatment outcomes. While the relationship remains unclear, studies suggest that depressive symptoms may be related to bio-directional immune system pathways involved in immune and nervous system regulation (12). Importantly, development of depression has been linked to discontinuation of therapy or decrease in dosage either by the patient or the clinician, with a corresponding negative impact on outcomes (12).

An evaluation of 162 patients receiving PEG IFN alfa-2b plus ribavirin showed that symptoms of mod-

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erate to severe depression, indicated by a score of >60 as measured on the Zung Self-rating Depression Scale (SDS), increased significantly from 6.8% at baseline to 38.9% at some point during the 24-week treatment period (p = .001). Mild depression also increased significantly during treatment, from 24.7% at baseline to 55.7% at 24 weeks (p = .001), with 72% of patients reporting an SDS rating of >50 at some point during the treatment period. (8)

Risk factors for developing depression included baseline SDS scores of ~50 or greater and history of depression. In addition, the data show a correlation between the development of moderate to severe depression and ribavirin dosing, with patients receiving the fixed low-dose (800 mg/day) less likely to develop depressive symptoms as compared with patients receiving higher dosages (800–1400 mg/day) (p < .05) (8).

All HCV patients should be assessed at baseline for depressive symptoms prior to treatment, using a standard depression screening tool. Preliminary data with psychiatric patients with HCV suggest that antidepressant pre-treatment may reduce the risk of patients becoming depressed during treatment (8) and is a viable strategy, as is careful monitoring for depressive symptoms and initiation of treatment when they occur (13).

When selecting an appropriate antidepressant, the patient’s symptom profile should be considered, as well as the potential for side effects and drug-drug interactions. In general, newer antidepressants, notably the selective serotonin reuptake inhibitors (SSRIs) are considered to be safe and effective, with mild side effects (13). The prescribing of antidepressant treatment and the management of depression in the HCV patient should follow the typical standard of care employed with management of depression in the non-HCV patient. Antidepressant selection should be tailored to the patient and the lowest effective dose should be used. It is important to discuss with patients that a two-to-three week therapeutic trial may be necessary to determine efficacy, and that treatment selection can be switched until symptom relief is obtained. Antidepressant therapy can be slowly stopped three to six months following cessation of interferon and ribavirin therapy with close monitoring to detect relapse of depression.

Anemia

Treatment with IFN-alfa or PEG IFN and ribavirin are associated with significant decreases in Hb levels, most commonly seen within the first four to six weeks of treatment. Anemia is a side effect of both monotherapy and combination therapy with ribavirin, causing a dose-dependent “mixed anemia” in which hemolysis and relative bone marrow suppression occur (9).

Studies show a decrease of 3 g/dL or more in 54% of patients, and a decrease of more than 25% of baseline values in more than 35% of patients treated with standard combination therapy (9). Standard of care recommendations have called for reductions in ribavirin dosage from 1,000–1,200 mg/day to less than 600 mg/day in patients with Hb levels less than 10 g/dL and discontinuation of ribavirin when levels fall to less than 8.5 g/dL. However, ribavirin dosages of less than 800 mg/day have been shown to reduce SVR, and a prospective clinical trial with PEG IFN/ribavirin showed a higher response rate for patients receiving doses of between 1,000–1,200 mg/day based on body weight (9). As such, it appears that decreasing ribavirin dosing may hinder SVR and increase the risk of virological relapse (9).

Data show that effective management of anemia can be achieved with once-weekly administration of epoetin alfa. In one study, 40,000 units s.c.q.w., epoetin alfa significantly increased Hb levels, compared with standard of care (SOC; ITT analysis, mean Hb change +2.8 g/dL versus +0.4 g/dL, at week 16). Further, the effective management of anemia enabled 83% of patients to remain on ribavirin dosages of 800 mg/day or more compared with 54% of patients in the SOC group (p = .022).

Additionally, epoetin alfa administration has been found to confer quality-of-life benefits, notably a reduction in fatigue and cognitive impairment caused by reduced oxygen-carrying capacity that may also produce patient noncompliance with treatment (9). When using epoetin alfa, overcorrection of anemia should be avoided, with target hemoglobin levels of no greater than 12 to 12.5 g/dL to minimize risk of thrombotic events.

Insomnia

A side effect of IFN-alfa and PEG IFN treatment, insomnia is also associated with the use of SSRIs for
treatment of depression (14), posing clinical challenges in the co-management of these side effects. Taking SSRIs in the morning may help minimize insomnia.

Trazodone, an older, second-generation serotonin 5HT-2 receptor antagonist frequently prescribed for treatment of depression is often selected for its sedating qualities (15). A survey of 439 psychiatrists found that 78% chose to add trazodone to SSRI treatment to manage SSRI-induced insomnia (14). For patients with HCV, the initial selection of trazodone as the sole therapy for depression may mitigate symptoms of insomnia that appear early in treatment. The newer hypnotics, including zolpidem and zaleplon, can be effective in treating insomnia short-term, although co-administration with SSRIs may enhance central nervous system effects (16,17).

**PATIENT VIGNETTE**

John Smith will be starting treatment with PEG IFN and ribavirin for hepatitis C soon. He sees a community-based gastroenterology practice that includes three physicians, a nurse practitioner, two registered nurses (RN) and a medical assistant. He works full-time in a warehouse driving a forklift. He is fearful of needles and concerned about taking time off from work while on treatment. One of the RNs provides him with the toll-free phone number for the nurse education line associated with the interferon that she will be prescribing him. Mr. Smith talks with a nurse that is assigned to his case on three occasions. These phone calls occur after his work hours. He is sent written materials and then the materials are reviewed by phone. These materials include a step-by-step guide to injections, descriptions of the necessary safety monitoring lab work, and a booklet for his wife describing what to expect and how she can best support him. After these conversations, Mr. and Mrs. Smith come into the office together stating they are ready to begin treatment. The nurse practitioner sees them for his baseline physical prior to his first injection. Together, they quickly understand injection technique and leave with a schedule of return visits. Although the time between recommendation for treatment and start up of treatment now exceeds two months, the Smiths have worked through many spoken and unspoken anxieties regarding treatment and are better prepared to be fully compliant with therapy.

At week four of treatment, Mr. Smith is having a hard time keeping up with all of his work duties. He finds that he is okay in the mornings but by lunchtime is feeling drowsy and has difficulty paying attention. When the RN checking him reviews his complaints, it is noticed that he often has heartburn. Review of his eating habits reveals that he is not following typical recommendations for reflux precautions. Additionally, he is eating one large meal in the evenings and is not eating much otherwise throughout the day. His wife feels like his overall consumption is down since starting treatment. He is advised to work toward eating several smaller meals or snacks throughout the day. He also begins taking his ribavirin with food and following standard reflux precautions. This leads to better daytime energy levels and stabilized weight. While he still feels tired throughout much of the day, he is better able to tolerate the fatigue and is more alert at work, which is critical to his safe performance as a forklift driver.

**DISCUSSION**

The management of the HCV patient poses considerable challenges. The duration of standard treatment and the range of side effects can have a negative impact on treatment adherence, as well as on clinical decisions regarding continuation of treatment regimens known to produce SVR.

The severity of complications from inadequately treated HCV underscore the importance of achieving successful outcomes through optimum dosing of IFN or PEG IFN/ribavirin treatment and careful management of side effects. Open, measured dialogue between clinician and patient can help patients prepare for the potential of side effects, encourage them to communicate their occurrence, and be assured that these effects can be minimized. Engaging patients in their treatment through recommendations for heightened self-care—adequate nutrition, sleep hygiene, exercise and hydration—and the use of potentially helpful educational resources can keep patients motivated to reach their treatment goals. Although the interventions to be made often seem minimal in nature
or too simplistic to be of any great significance, the sum total of these recommendations can cumulatively help make the long treatment course a success.

HEPATITIS C RESOURCES

Patient Support Resources

Be in Charge®, sponsored by Schering-Plough Corp. www.beincharge.com

Pegassist®, sponsored by Roche Pharmaceuticals www.pegassist.com


Online Resources for Healthcare Providers

Clinical Care Options www.clinicaloptions.com

American Association for the Study of Liver Diseases (AASLD) www.aasld.org

Projects in Knowledge www.projectsinknowledge.com

References