Recent Developments in the Treatment of Chronic Hepatitis C

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ABSTRACT

Chronic hepatitis C virus (HCV) is a serious problem in the United States, affecting more than 3 million individuals. Recently, the Food and Drug Administration approved 2 direct-acting, antiviral protease inhibitors for the treatment of chronic hepatitis C, genotype 1, which has greatly affected success rates. Therapy, however, remains complicated, with a difficult medication regimen and a wide array of often debilitating side effects possible. This article discusses the role of nurse practitioners in this new triple agent therapy and provides them with strategies for implementing effective education and management throughout treatment.

Keywords: chronic hepatitis C, cirrhosis, protease inhibitors, sustained virologic response, treatment

Chronic hepatitis C virus (HCV) is a bloodborne infection afflicting approximately 3.2 million United States residents.[1] Left untreated, the virus can lead to fibrosis, with approximately 60%-70% of individuals with HCV progressing to chronic liver disease. Of the chronic liver disease population, 5%-20% will develop cirrhosis, and 1%-5% of the cirrhotic population will die from complications of the chronic infection, including those associated with cirrhosis or hepatocellular carcinoma (HCC). Chronic HCV infections are the most common cause for liver transplant in America. Furthermore, it is estimated that, by 2030, there will be approximately 13,000 deaths per year associated with HCV.[2]

Newer pharmacologic agents are revolutionizing the treatment of chronic HCV with the recent Food and Drug Administration (FDA) approval of 2 direct-acting antiviral (DAA) medications. Nurse practitioners now play an even more crucial role in chronic HCV therapy because educating patients on the treatment course and managing complicated side effects have become more challenging.

BACKGROUND

Chronic HCV is the most common chronic infection in the US, heavily prevalent among individuals born from 1945 to 1965.[1] People at risk include current or former injection-drug users, recipients of blood transfusions or solid organ transplants before 1992, recipients of clotting factor concentrates before 1987, chronic hemodialysis patients, health care workers with exposure history, individuals with human immunodeficiency virus (HIV), and children born to HCV-positive mothers. Prevalence of chronic HCV varies among high-risk populations, with 60% of HCV infections attributed to intravenous blood use; 10% to transfusions before 1992; 15% to high-risk sexual behaviors; 5% to health care exposures, hemodialysis, and perinatal transmission; and 10% to an unknown source of infection.[3] Spreading the virus through sexual contact is an infrequent method of transmission and considered an inefficient means of transmission by the Centers for Disease Control and Prevention (CDC).[1]

There are 6 genotypes of the virus, with genotype 1 comprising approximately 75% of the HCV population in the US. Unfortunately, genotype 1 infection is the most difficult treat. Genotypes 2 and 3 are less common but more responsive to traditional therapy with pegylated interferon and ribavirin (PEG-IFN plus RBV).[4] Signs and symptoms of an acute infection can include fever, jaundice, fatigue, dark urine, abdominal pain, nausea, vomiting, and loss of appetite.[1] However, only approximately

20%-30% of newly infected individuals will experience these symptoms.

Between 75%-85% of individuals who acquire HCV will not clear the virus and will go on to develop chronic infections. Most persons with chronic hepatitis C will be asymptomatic, unless progressive inflammation and scarring have lead to cirrhosis and its many complications. In fact, 75% of patients are estimated to be unaware of the presence of a chronic HCV infection until they present with symptoms of advanced fibrosis and cirrhosis.[1] HCV can also affect multiple organ systems other than the liver, including the kidneys (glomerulonephritis) and skin (porphyria cutanea tarda, lichen planus, cryoglobulinema).[1,5]

The goal of therapy is to eradicate the virus, known as sustained virologic response (SVR). SVR is defined as negative HCV ribonucleic acid (RNA) 24 weeks after therapy ceases.[6] For patients with earlier staged disease, eliminating continued inflammation and scarring stops progression to cirrhosis.[7] For individuals who have already developed cirrhosis, elimination of the virus has been shown to decrease liver-related mortality.[2] These studies have demonstrated that cirrhotic patients who achieve an SVR with therapy have lower rates of hepatic decompensation and HCC than cirrhotic patients who fail to achieve SVR. Thus, both preventing progression of advanced fibrosis and scarring or eliminating the virus in the setting of cirrhosis holds enormous benefits for individuals infected with HCV.

TRADITIONAL THERAPY

For the past several years treatment of chronic HCV has consisted of regimens of once-weekly subcutaneous injections of pegylated interferon and twice-daily dosing of 2-4 ribavirin capsules.[8] Duration of therapy with these medications has been and continues to depend upon genotype, level of advanced fibrosis, and response of RNA result to therapy.

Efficacy

For genotypes 2 and 3, treatment with PEG-IFN plus RBV is quite successful. SVR rates for these 2 groups are approximately 80%-85%.[4,9] SVR rates for genotype 1 are significantly lower, with estimates less than 50%.[4] With a success rate this low, the treatment failure population has grown quite large, comprising approximately 75% of the genotype 1 HCV population.[10]

Limitations/Contraindications

Side effects associated with these 2 medications are also complicating factors of treatment, with approximately 10% to 14% of patients discontinuing therapy.[5] These side effects can greatly alter a patient's life and daily activities, particularly during the first several months of therapy. Common side effects associated with these 2 agents include but are not limited to flu-like symptoms, fatigue, headache, gastrointestinal symptoms, rash, and hematologic symptoms (anemia, neutropenia, and thrombocytopenia).[11] Anemia and neutropenia occur frequently, often leading to dose-reductions or use of erythropoietin-stimulating agents and granulocyte colony-stimulating factors, respectively.

Certain major medical issues can be exacerbated by therapy with PEG-IFN plus RBV. Thorough evaluation and consistent monitoring throughout therapy are essential, especially necessary for patients with a history of pulmonary or cardiac disease, endocrine conditions (uncontrolled diabetes, uncontrolled thyroid disease), dermatologic conditions (psoriasis), and past or current history of psychiatric illness.[12]

Treatment is contraindicated in women who are pregnant and partners of women who are pregnant.[12] Teratogenic and embryocidal complications are possible with ribavirin therapy. For this reason, patients and their partners must practice 2 methods of contraception during therapy and for 6 months after treatment is completed.[11] Female patients on therapy are required to have baseline and monthly pregnancy testing.

Therapy with PEG-IFN plus RBV is also contraindicated in patients who are active substance users, including those who drink alcohol.[8] Other contraindications include individuals with autoimmune hepatitis, renal insufficiency, severe coronary artery disease, severe cerebral vascular disease, or decompensated liver disease.[8]

Milestones

Milestones with traditional therapy are used as indicators for determining positive responses to treatment. Rapid virologic response (RVR) is defined as undetectable HCV RNA at week 4.[7] RVR is considered a positive predictor of attainting SVR for patients with genotype 2 or 3, and some studies suggest achieving RVR allows for shorter treatment duration.[12] Early virologic response (EVR) can be partial (a $\geq 2 \log_{10}$ decrease in HCV RNA from baseline) or complete (undetectable HCV

RNA at week 12 of treatment).[6,12] End-of-treatment (EOT) response is an undetectable HCV RNA.[12]

Two terms that help define patient response to therapy include *relapse* and *viral breakthrough*. When a patient relapses on therapy, this is defined as an undetectable RNA at the end of treatment that becomes detectable at the 24-week follow-up or earlier.[6] Viral breakthrough is an undetectable HCV RNA on treatment that subsequently becomes detectable as therapy continues.[6]

Preventing progression of advanced fibrosis and scarring or eliminating the virus in the setting of cirrhosis holds enormous benefits for individuals infected with HCV.

DIRECT ACTING ANTIVIRAL AGENTS

In May 2011, the treatment of genotype 1 chronic HCV dramatically changed. Two pharmaceutical companies received approval of their DAA, common agents in the treatment of HIV but previously not used in treatment of HCV. Protease inhibitor Victrelis (boceprevir) received approval May 13.[13] Incivek (telaprevir) received approval May 23.[14] The new treatment combines the former standard of care (SOC) agents, PEG-IFN plus RBV, with 1 of the protease inhibitors and has resulted in significant increase in SVR rates. This triple-agent regimen is response guided: the response of the viral RNA suggests continuation and duration of therapy. This often allows for patients to be treated for shorter lengths of time, pending a good response in their viral loads.

Both DAAs are NS3/4A protease inhibitors, whose action on the RNA virus results in a dramatic reduction of viral particles through the prevention of viral replication.[9] Start of therapy with the protease inhibitor, duration of therapy, and dosing differ between these 2 medications.

Victrelis is initiated at week 5 of therapy after a 4-week lead-in with PEG-IFN plus RBV.[7] For naïve-to-treatment, noncirrhotic patients who have a negative viral load at weeks 8 and 24, treatment with triple therapy is continued until week 28, at which time all 3 medications are discontinued. For individuals who have been partial responders or who have relapsed with prior therapy and have a negative viral load at weeks 8 and 24, therapy is continued to week 36, when all 3 medications are discontinued.

In all groups, for patients who do not have a negative viral load at week 8 but do have a negative viral load at week 24, therapy with the 3 drugs is continued to week 36, after which therapy with PEG-IFN plus RBV is continued to 48 weeks. Additionally, the recommendation for patients with cirrhosis is for therapy to continue for a more extended period, continuing for 48 weeks. Victrelis is dosed as 4 pills taken every 8 hours (3 times daily), with a meal or light snack to enhance absorption.

Incivek is taken for the first 12 weeks of therapy in combination with PEG-IFN plus RBV.[7] After week 12, Incivek is discontinued, and treatment with PEG-IFN plus RBV is continued for an additional 12 to 36 weeks. Treatment-naïve patients and those who experienced a previous relapse, who have a negative viral load at weeks 4 and 12 of treatment, continue PEG-IFN plus RBV for an additional 12 weeks. Patients who had a partial or null-response to previous therapy continue with PEG-IFN plus RBV for an additional 36 weeks.

Cirrhotic patients may benefit from 12 weeks of triple therapy with Incivek and an additional 36 weeks of therapy with PEG-IFN plus RBV. Incivek is dosed as 2 pills taken every 8 hours (3 times daily).[15] To increase absorption, the drug is recommended to be taken with 20 grams of fatty food.

Efficacy

In HCV genotype 1 patients, promising results have been reported when the protease inhibitor Victrelis or Incivek is added to the SOC, increasing SVR rates from less than 50% (PEG-IFN plus RBV) to 70%.[4]

Individual rates for both protease inhibitors are quite similar. In clinic trials, treatment-naïve patients treated with Victrelis, SVR rates were as high as 75%, while rates for previous relapsers and partial responders were approximately 70%-75% and 40-52%, respectively.[16,17] In the ADVANCE and ILLUMINATE clinical trials with treatment-naïve patients treated with Incivek, SVR rates were 75% and 72%, respectively.[15] In the REALIZE clinic trial, 86% of patients who relapsed on prior therapy had

an SVR, 57% of prior partial responders achieved an SVR, and 31% of null responders had an SVR.[9]

Limitations/Contraindications

Victrelis and Incivek are currently approved only for triple therapy in patients with genotype 1. Traditional therapy with PEG-IFN plus RBV is still the preferred method of treatment for genotypes 2 and 3. The DAAs are also not approved for treatment in the organ transplant population, hepatitis B virus (HBV) co-infected population, or HIV co-infected patients, as safety and efficacy have not been studied. Neither protease inhibitor can be taken as monotherapy because resistance quickly develops.[18]

Side effects can occur with the DAAs. Those seen with Victrelis may include hematologic abnormalities (anemia, neutropenia, thrombocytopenia), fatigue, nausea, headache, and dysguesia.[13] Side effects associate with Incivek include a mild to moderate rash, anorectal syndrome (anal or rectal pain, itching, irritation), fatigue, nausea, diarrhea, and hematologic abnormalities (anemia, neutropenia, thrombocytopenia, hyperbilirubinemia).[14]

Milestones

Treatment milestones with the triple agent therapy have expanded, including those associated with traditional therapies, as well as milestones that identify earlier positive responses to therapy. Patients who are found to have a negative HCV RNA at week 4 and maintained this for the duration of treatment are said to have achieved an extended rapid virologic response (eRVR).[15] In trials with Incivek, pegylated interferon, and ribavirin, 57%-65% of treatment-naïve patients achieved an eRVR.

WHY TREAT NOW?

The development of advanced fibrosis typically occurs over an estimated 20-30 years.[12] Thus, the age group that acquired HCV 20-30 years ago is now presenting with complications of advanced fibrosis and cirrhosis, such as hepatic encephalopathy, varices, ascites, and, ultimately, liver failure or HCC.[1] Despite the decrease in the incidence of new infections, more patients are presenting with complications associated with advanced fibrosis.[8] Furthermore, an estimated 75% of the genotype 1 population falls into the treatment failure category. Studies demonstrate this group is more likely to have more significant fibrosis than treatment-naïve patients, which suggests there are a growing number of patients in need of immediate treatment.[2]

PATIENT CANDICACY

Many HCV patients will benefit from therapy and achieving SVR with the new triple therapy regimen, but 3 groups in particular are important to treat: individuals who already have progressing fibrosis, nearing stage 4 disease (on biopsy); patients who already have cirrhosis and are dealing with its associated complications; and patients who have failed previous treatment courses.

Patient readiness is essential for consideration. Individuals preparing to start on therapy should be fully aware of the complications that can be associated with treatment, as well as duration and likelihood of success. Medical necessity and readiness should be evaluated, which may or may not include a biopsy for liver disease staging.[8] Pre-existing comorbidities should also be considered. Individuals with an untreated psychiatric condition, uncontrolled diabetes, or heart or lung disease are examples of people in whom therapy should be postponed. Patients need to be ready emotionally, physically, and medically for the chronic HCV treatment.

CLINICAL VIGNETTE OF DEPRESSION

The patient is a 26-year-old man who recently broke up with his girlfriend and is dealing with depression and anxiety. He was diagnosed with chronic HCV, genotype 1b, 6 years ago, likely contracting the virus from a blood transfusion received as an infant. He is interested in eradicating the virus to prevent future complications. The patient has no other health concerns and denies taking any medications, prescriptive or over the counter.

Recommendations

Depression should be controlled before starting therapy. The pegylated interferon can lead to the development of depression in patients with and without prior histories and can exacerbate current symptoms.[8] For patients with a history of depression, psychiatric clearance is recommended, including providing documentation from psychiatry that the patient will be followed throughout the treatment course for complications of depression and pharmacologic management with antidepressants, if necessary. Stabilizing moods with antidepressants before or during therapy may improve patient outcomes.[6] Also, because of possible interactions

between the DAAs and other medications metabolized by the CYP3A pathway, a decrease or increase in serum levels of either medication should be considered with the initiation of appropriate monitoring.[19,20]

CLINICAL VIGNETTE OF LONGSTANDING HCV INFECTION

The patient is a 60-year-old man who experimented with intravenous (IV) drugs in 1967. He was diagnosed with chronic HCV, genotype 1a, 3 months ago during an annual exam. Abdominal imaging was normal, and a liver biopsy performed to assess the status of liver disease showed stage 0 disease. The patient currently is asymptomatic, working 6 days a week in a busy, self-owned restaurant business. He is not particularly interested in treatment at this time but will do what is medically recommended.

Patients need to be ready emotionally, physically, and medically for the chronic HCV treatment.

Recommendations

According to American Association for the Study of Liver Diseases practice guidelines, treatment of patients with minimal disease activity or scarring on biopsy should be individualized.[12] With minimal disease and patient disinterest in therapy, postponing treatment in this particular patient is acceptable because eradicating the virus is less urgent.[8] Current therapies are challenging, can be lengthy, and are physically draining. Treatments in the trial phases and those that will come in the future will likely have shorter duration, less side effects, and greater efficacy in eradicating the virus. While treatment success is estimated to be higher in patients without advanced bridging or cirrhosis, for this particular individual, waiting for future treatments in the setting of no scarring is a good option.[12]

CLINICAL VIGNETTE OF GENOTYPE 2 OR 3

The patient is a 36-year-old woman diagnosed 5 years earlier with chronic HCV, genotype 2. She likely contracted the virus through high-risk behaviors during her teenage years. The highly publicized release of the new medications for chronic hepatitis C had caught her attention, and she presents to clinic for evaluation and to determine if starting these new therapies is appropriate. The patient is naïve to therapy and at a position in her life where she can focus her attention and time on the treatment regimen.

Recommendations

Triple therapy treatment of chronic HCV with the DAAs has been approved only for use in genotype 1. The success of treatment with traditional PEG-IFN therapy in genotypes 2 and 3 is quite good, and this patient has 80%-85% chance of achieving an SVR.[4,9] She should be treated with the recommended dosages of PEG-IFN plus RBV and will likely need therapy only for 24 weeks.

CLINICAL VIGNETTE OF HIV

A 45-year-old man presents to clinic, referred for treatment by his primary care physician. He has genotype 1a and is a previous nonresponder to PEG-IFN plus RBV therapy, completing treatment 4 years ago. During the clinic visit, the patient states he is taking tenofovir/emtricitabine (Truvada), atazanavir (Reyataz), and retonavir (Norvir) for treatment of HIV, with his last CD4 count at 600. He has been reading information on the Internet showing the improvement in SVR, and he is interested in starting on therapy.

Recommendations

Currently, HCV triple therapy with DAAs in the co-infected HIV population is contraindicated.[18] Studies on safety and efficacy have not been thoroughly evaluated. However, treatment trials are underway, and a referral to an infectious disease specialist involved with co-infected patient clinical trials is recommended for this patient.

THE ROLE OF THE NP

NPs can play a pivotal role in chronic HCV therapy with the new triple therapy involving protease inhibitors. Patient education regarding side effect management is essential to adherence to the treatment plan and thus achieving a SVR. Educating about side effects the patient may encounter throughout the treatment course is also imperative. While not all patients will experience every side effect, it is important to prepare them for what can occur as this may lead to a decrease in anxiety when symptoms emerge, as well as promotes better adherence to the treatment regimen.[21]

Providing a support system for the patient is also important. Bringing family members or friends to the education sessions helps the relatives better understand what the patient might experience, which can contribute to the family having a more supportive attitude. Also, for the NP, establishing rapport with the patient and the family helps to promote a trusting environment. Furthermore, being available throughout treatment and responding promptly to problems verbalized by the patients may enhance the potential for completing the treatment course.

The quantity of daily medications with the new triple therapy presents a complicated dosing regimen involving a heavy pill burden. With 3 times a day dosing of the protease inhibitors, spaced at 8-hour intervals, in addition to twice-daily dosing of 2-4 capsules of ribavirin, adherence is essential to ensuring the greatest success in treatment. Instruction on this aspect of treatment before its start is fundamental and is a crucial element of the NP role. It is important for health care providers to consider that there is a potential for the development of drug resistance with the protease inhibitors, which further emphasizes the importance of patient adherence to the medication regimen.[9]

FUTURE OF HCV THERAPY

Therapy for HCV will likely be completely revolutionized in the next 10-20 years. Trials for second-generation protease inhibitors are in process, as well as trials with newer agents, such as polymerase inhibitors and NS5 agents.[15] These medications will likely involve fewer pills and less frequent dosing schedules, as well as higher SVR rates and shorter treatment duration. Since pegylated interferon represents a limiting factor for some individuals pursuing treatment, eliminating this agent from the treatment regimen is a goal of future therapy.

CONCLUSIONS

With clear benefits defined by eradicating HCV infection from the body, including decreased rates of hepatic decompensation and HCC, the new DAA agents represent a significant opportunity for the infected populations, for both treatment-naïve patients and those for whom previous treatment efforts failed. Acting now is essential. Identifying patients with chronic hepatitis C that need to be treated is critical, and prompt referrals to specialists in hepatology or gastroenterology is advised.[8] Practitioners of patients preparing to start therapy must be prepared to anticipate side effects, actively manage the symptoms, and support the patient throughout the treatment process. JNP

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