INTRODUCTION

In the 25 years since the discovery of the hepatitis C virus (HCV) in 1989, there have been dramatic advances in our understanding of the virus and treatment of its disease. As recently as the 1990s only a fraction of patients could be cured by interferon, the immunomodulatory agent that was the only available therapy at that time, and the backbone of treatment for the next two decades. More recently, however, the majority of patients treated with new, direct-acting antiviral agents can expect to be cured.

EPIDEMIOLOGY AND SCREENING

More than 3.2 million people in the United States are chronically infected with hepatitis C, 70% of whom are in the generation born between 1945 and 1964.1 This number may underestimate the infection rate, as those not sampled in the study population included the homeless, incarcerated, hospitalized, and those on active duty in the military. Further, more than half of those infected are not aware of their infection, which recently led the CDC (Center for Disease Control) and USPSTF (U.S. Preventive Services Task Force) to recommend that all those born between 1945-1965 should receive a one-time screening test for hepatitis C.2,3 Those in other age groups should also be screened if risk factors are present. Since the USPSTF categorized this recommendation as Grade B, the test should be paid for by insurance, as The Affordable Care Act requires health plans to cover preventive services.

RISK FACTORS

Those at high risk for infection include people who have a history of using drugs by injection or intranasally, have received a blood transfusion or an organ transplant before 1992 or clotting factors before 1987, have a history of incarceration, have been on long-term hemodialysis, have tattoos, or were born to an HCV-infected mother. Additional risk factors include HIV infection, sexual activity with an infected person, needle or mucosal injury while working in health care, working in public safety, or having evidence of liver disease.4

DIAGNOSIS

Hepatitis C is a heterogeneous RNA virus, with 6 known genotypes and numerous subtypes.5 Genotype testing, usually with the line probe assay, is important because it helps guide therapy. In this country, 75% of those infected have genotype 1, followed by 15% with genotype 3, and 10% with genotype 2.

HCV antibodies, which can be detected by enzyme immunoassay (EIA), appear 6-8 weeks following acute infection. Seropositive patients should have follow up testing to check for HCV RNA, which—in some assays—can detect virus in concentrations as low as <5 IU/ml. A rapid point-of-care antibody testing kit called the OraQuick HCV test has been approved by the FDA.6

The majority of patients who are antibody positive are viremic, unless they have resolved an acute infection, have been successfully treated, or fall below assay detectability. Once patients are found to be viremic, genotype testing should be done and referral for appropriate treatment should be made.

CLINICAL SYMPTOMS

Patients are often asymptomatic in the early stages of infection, which can last years or decades. When symptoms occur, they are usually mild and nonspecific and may include fatigue, myalgias, arthralgias, fever, abdominal pain, and nausea. Since jaundice is rare, typical hepatitis symptoms such as dark urine and grey-colored stools are infrequent.7 Late stages of the disease include advanced cirrhosis and hepatocellular carcinoma, and symptoms and signs then include variceal hemorrhage, ascites, jaundice, portal hypertension, encephalopathy, and hepatorenal syndrome. These manifestations of advanced disease necessitate careful timing of liver transplantation.
Extrahepatic manifestations of HCV are common, so consideration of this diagnosis is important for specialties outside of hepatology. Those diseases strongly associated with hepatitis C include mixed cryoglobulinemia, lymphoproliferative disorders, porphyria cutanea tarda, sicca syndrome, membranoproliferative glomerulonephritis, neuropathy, and cryoglobulinemic vasculitis. There are also associations with insulin resistance, Type 2 diabetes, corneal ulcers, lichen planus, ITP, and thyroid disease.

**NATURAL HISTORY**

Clearance of acute infection is possible, and occurs in 15-25% of those infected. As chronic infection takes hold, a long latent asymptomatic phase can occur which may lead to progressive fibrosis and cirrhosis in 16% over 20 years. Once cirrhosis is established, hepatocellular carcinoma occurs at a rate of 1-4% per year. When decompensation occurs, five year survival without a transplant is 50%. Currently, hepatitis C is the most common reason for liver transplantation in the United States. Although the prevalence of hepatitis C peaked in the 1990s, the disease burdens of end stage cirrhosis, transplant, and hepatocellular carcinoma are on the rise and are expected to peak in the 2020s if patients do not achieve a cure. This will be a huge health care cost burden projected to cost in the billions of dollars.

**COUNSELING RECOMMENDATIONS**

All patients with a diagnosis of hepatitis C should be counseled to avoid alcohol consumption, which could lead to increased viral replication and progressive liver disease. Patients should stop using illicit drugs and be referred for addiction counseling. They should be vaccinated against hepatitis A and B if they are not immune, and should receive yearly flu shots. All patients who test positive for HCV should have HIV testing. In order to prevent the spread of infection, those infected with hepatitis C should be counseled to avoid sharing toothbrushes and razors and to use condoms for sexual activity. Family members should be screened, especially sexual partners and those born to infected mothers. All patients should be referred for evaluation and consideration of treatment.

Currently, only 5-6% of patients infected with hepatitis C in the United States have been successfully treated. The reasons include non-response to therapy, lack of access to care, continued drug and alcohol use, cost, contraindications to therapeutic modalities, under diagnosis, intolerance to the medications, and unwillingness to undergo therapy. The term sustained virological response (SVR) is defined as being viral negative 12 or 24 weeks after successful treatment, and has been used in the past to describe treatment success, but hepatologists are now comfortable using the term cure. Ninety nine percent of patients who achieve an SVR have undetectable viral levels throughout long-term follow up.

**TREATMENT**

The evolution of treatment for hepatitis C has culminated in the recent approval in December 2013 of highly effective drugs with increased safety and tolerability, an all-oral regimen for Genotypes 2 and 3, and the highest treatment success to date for HIV co-infected patients. The discovery of the virus and understanding of the HCV life cycle has led to a pipeline of direct acting antiviral agents with the hope that HCV can be eradicated in the not too distant future. Although interferon is still used and is part of the treatment regimen for previously untreated and relapsed patients with genotype 1 and all interferon eligible patients with genotype 4, this situation should be eliminated within the next few years as more direct acting antivirals emerge on the market.

It was only in 2011 that the first direct acting antiviral protease inhibitors, boceprevir and telaprevir, were approved for use in combination with standard immunomodulating agents, interferon and ribavirin, for genotype 1 chronic hepatitis C. Until December 2013, this regimen of triple therapy was the standard of care for genotype 1 patients. Also, no direct acting antivirals were available for genotypes 2, 3, 4, 5 or 6, which still relied on dual therapy with interferon and ribavirin.

Although these drugs advanced the treatment of genotype 1 patients, resulting in cure rates between 69-78%, the adverse side effects were considerable, adding to the already significant side effect profile of interferon and ribavirin. Rashes occurred with telaprevir, with cases of drug rash with eosinophilia and systemic symptoms (DRESS), and reports of Stevens-Johnson syndrome. Many patients with less severe rash had to stop therapy prematurely to prevent progression. The use of both interferon and ribavirin resulted in significant anemia, often requiring reduction in the dose of ribavirin, use of erythrocyte stimulating agents, blood transfusions, or hospitalization. In addition, there was a considerable pill burden that required...
patients to take these medications on a strict regimen to avoid the development of resistance. Because of the drug’s dependence on the CYP3A pathway of metabolism, significant and sometimes severe drug-drug interactions occurred. All of these factors limited their use to highly motivated patients who accepted very close monitoring.

In December 2013 the FDA approved 2 new medications for hepatitis C, a first-in-class polymerase inhibitor, sofosbuvir, and a second-generation protease inhibitor, simeprevir. Not only has there been improvement in the side effect profile and a decrease in the pill burden, but the efficacy has also increased. For the first time, genotypes 2, 3, and 4 can also be treated with a direct acting antiviral, the agent sofosbuvir. Additionally, the duration of treatment with sofosbuvir is shorter, which should improve compliance and the willingness of patients to undergo therapy. Formal recommendations for treatment of HCV from the collaboration of the American Association of the study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA) were recently released.20

Sofosbuvir, 400mg once daily, is the preferred medication of many hepatologists (personal communication). It has received a broad indication from the FDA, including treatment for genotypes 1, 2, 3 and 4, use in treatment naïve as well as treatment experienced patients, monoinfected and HIV coinfected patients, and patients with hepatocellular carcinoma awaiting transplantation. This medication must be used with ribavirin in all indicated treatment regimens except those that combine 2 direct acting antivirals. For genotypes 1 and 4, interferon improves efficacy rates, but interferon-free treatment can be considered in genotype 1. Simeprevir, 150 mg once daily in combination with interferon and ribavirin, has been approved for HCV genotype 1 patients with compensated liver disease who are naïve to treatment and those who previously failed interferon and ribavirin. Although not an FDA approved regimen, the interferon free regimen of combining these direct acting antivirals, sofosbuvir and simeprevir with or without ribavirin has been endorsed by AASLD/IDSA for genotype 1 patients who previously failed interferon and ribavirin treatment and for patients with genotype 1 who are ineligible to receive interferon. This guideline is based on data from a small Phase 2a study which highlighted its effectiveness.20

**CURRENT NEWER REGIMENS FOR GENOTYPE 1**

The combination of pegylated interferon, weight-based ribavirin, and sofosbuvir for 12 weeks is the currently preferred treatment for monoinfected and HIV coinfected patients with genotype 1 chronic hepatitis C with or without cirrhosis who were never treated or previously relapsed after successful treatment. This regimen results in an 89% SVR.21 Of note, genotype 4, although rare in this country, is treated with the same regimen and results in a 96% SVR.21

It must be understood, however, that this regimen has not been studied in interferon experienced patients (relapsers and nonresponders) but was approved by the FDA for those patients based on mathematical modeling.22 The model used previously known poor predictors of response—including higher viral load, advanced fibrosis, and IL28B non-CC polymorphisms—and determined that those patients, who in the naïve trial had a 71% SVR,21 should be considered analogous to previously treated patients who failed therapy. Although this is an acceptable regimen, the recent guidelines recommend not using interferon but combining sofosbuvir and simeprevir with or without ribavirin for 12 weeks for the subset of treatment experienced patients who never responded.

For genotype 1 patients who are ineligible for interferon, the FDA has approved a regimen of sofosbuvir and ribavirin without interferon for 24 weeks, although this is not the preferred regimen because of lower SVR rates—as seen in the HIV coinfected trial PHOTON-121 and another small study.24 (Ineligibility can be due to concomitant autoimmune disease or neuropsychiatric disorders, which are contraindications to interferon.) As stated above, the combination of 12 weeks of sofosbuvir and simeprevir with or without ribavirin can also be used.

For patients with hepatocellular carcinoma awaiting transplant for up to 48 weeks, dual therapy of sofosbuvir and ribavirin without interferon has been found effective for reducing HCV recurrence post-transplant.25

Simeprevir, a second generation protease inhibitor, has advantages over first generation protease inhibitors because of its ease of dosing and lower chance of anemia. Because of lower SVR rates in subtype 1a patients who possess the Q80K polymorphism, alternative therapy should be considered for them. Treatment duration is 24 or 48 weeks, with the first 12 weeks including the protease inhibitor in combination with interferon and ribavirin, and either an
additional 12 or 36 weeks of interferon and ribavirin. Length of therapy depends on whether the patient is treatment naïve or treatment experienced, and on the initial viral response to the regimen. With this plan, SVR rates are 80% in patients who are naïve to treatment and those who previously relapsed. Nonresponders do not do as well, especially those who are genotype 1a, in whom response rates vary between 42-88%. Adverse reactions from these regimens are mostly due to the known side effects of interferon and ribavirin. The side effect profile for interferon is extensive and can include a flu-like illness, cytopenias, depression, irritability, thyroid dysfunction, nausea, diarrhea and exacerbation of underlying autoimmune disorders. Ribavirin is a known teratogen and has a pregnancy category X label. It can also cause anemia, rash and insomnia. However, the addition of the polymerase inhibitor, sofosbuvir, has only a small effect on adverse events with headache and fatigue occurring more frequently with the addition of this drug. Simeprevir, however, has less tolerability than sofosbuvir and side effects include rash, photosensitivity, and anemia and similar drug-drug interactions as first generation protease inhibitors.

Sofosbuvir, a specific inhibitor of the RNA-dependent RNA polymerase of the hepatitis C virus is not metabolized by the CYP3A pathway and therefore has fewer drug interactions than the protease inhibitors. The only potential drug interactions are with intestinal P-glycoprotein (P-gp) inducers, such as St. John’s Wort and rifampin, which have the potential to decrease sofosbuvir exposure. Only one antiretroviral, tipranavir/ritonavir, decreases sofosbuvir levels through the same mechanism and is not recommended for concurrent use.

CURRENT PREFERRED REGIMEN FOR GENOTYPE 2 AND 3

The recent approval of sofosbuvir has marked a milestone in hepatitis C treatment because it is the first time an interferon-free regimen has been approved. For genotypes 2 and 3, monoinfected and HIV coinfected patients, naïve or previously treated, sofosbuvir and ribavirin alone is associated with an 88-95% SVR after 12 weeks of treatment for genotype 2 and 84-92% SVR after 24 weeks of treatment for genotype 3. Cirrhotic and treatment experienced patients have lower SVR rates although the numbers in the trials are small. The addition of interferon in these patients could be considered, although data are limited.

THE FUTURE OF THERAPY

Within the next few years, therapy will continue to advance as more direct acting antiviral regimens continue to be developed and are approved for treatment. The research should result in higher SVR rates, shorter drug regimens, a better side effect profile, and the total exclusion of interferon in all patient types. However, there is much work to be done, as there are no firm recommendations for children, decompensated cirrhotics, dialysis patients, and post-transplant populations. As a matter of public health, these patients need to be identified and treated in order to prevent the increasing mortality and morbidity associated with chronic hepatitis C. Problems related to access to care and the cost of treatment will slow the progress towards elimination of this disease, and also need to be addressed.

REFERENCES


