Treatment of Chronic Hepatitis B and Hepatitis C

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Table of Contents

Introduction ............................................. 2
Chronic Hepatitis B ................................. 2
Chronic Hepatitis C ................................. 7
Summary ................................................. 10
References .............................................. 10

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INTRODUCTION

Viral hepatitis is a major public health problem worldwide. Chronic hepatitis B virus (HBV) infection affects 350 to 400 million persons in the world, including 1.25 million individuals in the United States. However, the cited US prevalence rate is an underestimate of the actual rate because it does not account for the constant flow of immigrants with chronic HBV infection from endemic areas like Asia, the Middle East, and Africa. Sherman and colleagues recently found a 23% seroprevalence of hepatitis B surface antigen (HBsAg) in an Asian-American population in New York City.

Chronic hepatitis C virus (HCV) infection affects over 170 million persons worldwide and 4 million persons in the United States, where it is the most common cause of chronic liver disease and the leading indication for liver transplantation. The reported prevalence of chronic HCV also is an underestimate of the actual rate because it does not account for the prison and homeless populations. Advances in the treatment of chronic hepatitis C have altered the natural history of the disease in its early stages. Once advanced liver damage has developed, therapy may delay but will not prevent decompensation of cirrhosis, development of hepatocellular carcinoma (HCC), or death.

It is estimated that HBV complications account for up to 5000 deaths per year in the United States, while HCV complications account for 10,000 deaths annually. Targeting hepatitis B and hepatitis C in the early stages can improve the natural history of these diseases and alleviate their associated socioeconomic burdens.

CHRONIC HEPATITIS B

CASE PRESENTATION I
Presentation and History

A 42-year-old Chinese man presents to a gastroenterologist for evaluation of vague abdominal pain and progressive onset of jaundice over the past month. He describes the abdominal discomfort as a dull pressure located in the right upper quadrant; the pain does not radiate and is not associated with ingestion of food. He reports that his bowel habits are regular, and he has not noted blood in his stools. He attempted changing his diet, but this did not improve the abdominal pain. His weight is stable, and he has had no changes in mental status.

Past medical history is significant for a history of asthma and a laparoscopic cholecystectomy 10 years ago. One month ago, he finished a 4-week regimen of prednisone to control an asthma attack. He uses albuterol inhaler on as-needed basis and does not take any herbal preparations. He emigrated from Taiwan 10 years ago. He is married with 2 children, and he works as a software engineer. He does not smoke or consume alcoholic beverages. He has never experimented with recreational drugs. His mother died of liver cancer at age 55 years. His 3 siblings are healthy.

Physical Examination

The patient’s height is 5 ft 8 in (176 cm) and his weight is 167.5 lb (76 kg), with a body mass index of 24.5 kg/m². Assessment of vitals signs reveals a temperature of 98.7°F (37.1°C), blood pressure of 120/80 mm Hg, and heart rate of 80 bpm. Physical examination is significant for the presence of jaundice, icteric sclera, palpable spleen, and spider angiomas over the torso; ascites, asterixis, and lower extremity edema are absent.

Laboratory Evaluation

Laboratory testing performed 1 year ago by his primary care physician revealed the following: white blood cell count (WBC), 4.6 × 10^9/µL; hemoglobin, 14.2 g/dL; platelet count, 154 × 10^9/µL; aspartate aminotransferase (AST), 60 U/L; alanine aminotransferase (ALT), 65 U/L; total bilirubin, 1.3 mg/dL; alkaline phosphatase, 96 U/L; albumin, 3.5 g/dL; and creatinine, 0.9 mg/dL.

• What are the possible explanations for the patient’s jaundice and abdominal pain?
The differential diagnosis of abdominal pain associated with jaundice is broad. Jaundice may be recognized clinically when the serum bilirubin exceeds 3 mg/dL. Determining the fractionation of bilirubin can narrow the differential diagnosis, which includes diseases of hepatic, biliary, hematologic, infectious, oncologic, metabolic, or drug-associated origin. Intrinsic diseases of the liver include acute or chronic viral hepatitis such as hepatitis A, B, and C; cholestatic liver diseases; alcoholic liver disease and nonalcoholic fatty liver disease; cirrhosis due to various causes; and infiltrative diseases, such as amyloidosis and lymphoma. Biliary causes of jaundice include biliary obstruction due to gallstone diseases, postsurgical biliary strictures, and various biliary malignancies. Hematologic diseases associated with hemolysis can result in jaundice. Infectious conditions such as HIV infection, tuberculosis, infestation with ascaris and liver fluke, and fungal infections of the liver may be associated with hepatic dysfunction. Primary hepatic malignancies (eg, HCC) and metastatic cancer of the liver from malignancies (eg, colon cancer, breast cancer, and melanoma) can present with abdominal discomfort and jaundice. Wilson’s disease, hereditary hemochromatosis, thyroid dysfunction, and bilirubin conjugation and uptake disorders are a few of the metabolic diseases associated with hyperbilirubinemia. Various drugs (eg, amoxicillin/clavulanate, isoniazid, methylenedioxymethamphetamine [ecstasy], amphetamine) and use of total parenteral nutrition have been associated with hyperbilirubinemia.

**CASE 1: FURTHER LABORATORY TESTING**

The results of additional laboratory tests are as follows: ALT, 450 U/L; AST, 400 U/L; total bilirubin, 5.0 mg/dL; direct bilirubin, 4.0 mg/dL; alkaline phosphatase, 120 U/L; albumin, 3.2 mg/dL; international normalized ratio (INR), 1.6; WBC, 4.4 × 10^9/μL; hemoglobin, 13 g/dL; platelet count, 140 × 10^9/μL. Testing for HBsAg and hepatitis B e antigen (HBeAg) by enzyme immunoassay is positive, and testing for antibody to HBsAg (anti-HBs) is negative. The serum level of alpha fetoprotein is 6 ng/mL. Testing for HCV, hepatitis D virus (HDV), and HIV antibodies is negative.

- **Is there a relationship between the patient’s family history and his presentation?**

The patient is an immigrant from an area endemic for chronic HBV infection. His laboratory testing results are consistent with acute hepatitis B rather than reactivation of chronic hepatitis B. However, taking into account his ethnicity and the presence of elevated ALT and AST levels 1 year ago, he most likely has chronic hepatitis B with reactivation. Patients with hepatitis B reactivation usually have positive testing for HBsAg, HBeAg, and IgM against HBV core protein (IgM anti-HBc; Table 1). It is likely that his mother had chronic hepatitis B complicated by the development of HCC, and he acquired the infection via vertical transmission at birth. In a patient with HBV infection, it is important to exclude coinfection with other viruses, including HCV, HDV, and HIV. In addition, the presence of spider angiomas and a palpable spleen on physical examination in this patient is worrisome for the presence of cirrhosis and portal hypertension.

- **What is the natural history of chronic HBV infection?**

**NATURAL HISTORY**

The natural history of chronic HBV infection can be divided into 3 phases: immune tolerance (replicative), immune clearance (or immune active), and inactive. The immune tolerant phase is characterized by the presence of HBeAg, high serum HBV DNA levels (> 20,000 IU/mL, or 10^6 copies/mL), and persistently normal ALT levels. This scenario is common in individuals under age 35 to 40 years who were infected at birth or in early childhood. The immune tolerant phase usually persists for 10 to 30 years and is typically followed by an immune clearance phase of variable duration. During immune clearance, spontaneous clearance of HBeAg occurs, and

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**Table 1. Serologic Markers in Hepatitis B**

<table>
<thead>
<tr>
<th>Stages of HBV Infection</th>
<th>Key Positive Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic</strong></td>
<td></td>
</tr>
<tr>
<td>Replicative phase</td>
<td>HBsAg, HBeAg, IgM anti-HBc, detectable HBV DNA</td>
</tr>
<tr>
<td>Low, nonreplicative</td>
<td>HBsAg, undetectable HBeAg, anti-HBe, IgG anti-HBc, undetectable HBV DNA</td>
</tr>
<tr>
<td>phase</td>
<td></td>
</tr>
<tr>
<td>Flare-up/reactivation</td>
<td>HBsAg, HBeAg, IgM anti-HBc, detectable HBV DNA</td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td></td>
</tr>
<tr>
<td>Early phase</td>
<td>HBsAg, undetectable anti-HBs, HBeAg, IgM anti-HBc, detectable HBV DNA</td>
</tr>
<tr>
<td>Window phase</td>
<td>HBsAg, IgM anti-HBc, detectable HBV DNA</td>
</tr>
<tr>
<td>Recovery phase</td>
<td>Undetectable HBsAg, anti-HBs, anti-HBe, IgG anti-HBc, undetectable HBV DNA</td>
</tr>
</tbody>
</table>

Anti-HBe = antibody to HBeAg; anti-HBs = antibody to HBsAg; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgG anti-HBc = IgG against HBV core protein; IgM anti-HBc = IgM against HBV core protein.

Table 2. Treatment Recommendations for Hepatitis B

<table>
<thead>
<tr>
<th>HBV DNA (IU/mL)*</th>
<th>ALT†</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20,000</td>
<td>Normal</td>
<td>No treatment</td>
</tr>
<tr>
<td>≥ 20,000</td>
<td>Normal</td>
<td>Consider liver biopsy and treat if significant histologic changes are present</td>
</tr>
<tr>
<td>≥ 20,000</td>
<td>Elevated</td>
<td>Treatment is recommended</td>
</tr>
<tr>
<td>HBeAg-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20,000</td>
<td>Normal</td>
<td>No treatment</td>
</tr>
<tr>
<td>≥ 2000</td>
<td>Normal</td>
<td>Consider liver biopsy and treat if significant histologic changes are present</td>
</tr>
<tr>
<td>≥ 2000</td>
<td>Elevated</td>
<td>Long-term treatment with oral agents</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus.

*1 IU/mL is equivalent to 5.6 copies/mL.
†The upper limits of normal for serum ALT for men and women are 30 IU/mL and 19 IU/mL, respectively.


this phase is marked by elevated serum ALT levels, high levels of HBV DNA, and features of chronic hepatitis evident on liver biopsy. Seroconversion from HBeAg to HBeAg antibody (anti-HBe), which occurs spontaneously in 50% to 70% of patients, usually signals the end of the immune clearance phase, and patients become inactive HBeAg carriers. During the inactive carrier phase, the serum HBV DNA level is less than 10^4 copies/mL (2000 IU/mL) and may be undetectable, ALT levels become normal, and liver biopsy shows minimal inflammatory activity.

Not all patients evolve into an inactive carrier state. Instead, some develop HBV mutations (precore or core promoter mutations) that decrease or prevent the synthesis of HBeAg but do not hinder viral replication, resulting in a different natural history characterized by elevated serum HBV DNA levels, persistently or intermittently elevated ALT levels, and negative HBeAg with positive anti-HBe. This variety of chronic HBV infection is referred to as HBeAg-negative chronic hepatitis B and is generally progressive without therapy.1,5

Chronic hepatitis B is associated with significant morbidity over the lifelong course of infection. Individuals with chronic hepatitis B, whether HBeAg-positive or HBeAg-negative, are at risk for developing cirrhosis and/or HCC, which is associated with a 25% risk of premature death compared to noninfected individuals.1 Recent studies from Asia have shown a direct relationship between HBV viral load and the development of cirrhosis or HCC.6,7 In addition, Liaw et al8 has demonstrated that long-term lamivudine therapy to reduce viral load slows the rate of disease progression and decreases the incidence of HCC in patients with chronic hepatitis B and advanced hepatic fibrosis. Therefore, screening for HCC should be pursued in all patients with HBV regardless of the stage of fibrosis.

- What is the approach to treatment of chronic HBV infection?

TREATMENT Candidates for Therapy

The treatment goals for chronic hepatitis B are to suppress HBV replication (using HBV DNA levels as a marker of viral replication) and to prevent progression of the disease to cirrhosis and/or HCC. Current guidelines for the treatment of chronic hepatitis B as well as a practical treatment algorithm have been published (Table 2).3,4,8,9 However, there is not a consensus between the guidelines. All experts agree that individuals with chronic HBV infection are candidates for therapy if they have high HBV DNA levels and elevated ALT levels, or active necroinflammation and fibrosis on liver biopsy. The degree of viremia also influences the degree of fibrosis. Most experts advocate treating cirrhotic patients who have low-level viremia.5,10 Elevated viral load is defined as a serum HBV DNA level of 20,000 IU/mL (10^5 copies/mL) or greater for HBeAg-positive patients and 2000 IU/mL (10^4 copies/mL) or greater for HBeAg-negative patients with chronic hepatitis B.

Elevated ALT levels as a criterion for treatment are usually defined as any elevation that is at least 2 times the upper limit of normal.4,5,8,9 Treatment is also evolving to include high-risk populations such as those with normal ALT but a strong family history of HCC.5

Duration of Therapy

The presence or absence of HBeAg influences the duration of treatment. Individuals with HBeAg-positive chronic hepatitis B can be treated for 1 or more years until seroconversion to anti-HBe occurs. Treatment is then continued for an additional 6 to 12 months after seroconversion to boost the durability of response in HBeAg-positive patients. The average long-term durability of HBeAg seroconversion with discontinuation of therapy in these patients is 80% (range, 50%-90%) with the various oral agents.5 In HBeAg-negative patients, long-term therapy is the rule as relapse invariably occurs if therapy is discontinued after a fixed course of therapy.
Treatment Options

Six drugs have been approved by the US Food and Drug Administration for the treatment of chronic hepatitis B in the United States: interferon alfa-2b, pegylated interferon (peginterferon) alfa-2a, lamivudine, adefovir dipivoxil, entecavir, and telbivudine (Table 3).

Interferon. Approved in 2005, peginterferon alfa-2a has replaced standard interferon alfa-2b as therapy for chronic HBV infection due to its longer half-life, thus requiring only weekly injections, and comparable or better efficacy. The recommended regimen for peginterferon alfa-2a is 180 µg weekly administered subcutaneously for 1 year, while the recommended regimen for standard interferon alfa-2b is 10 IU daily for 4 months. Patients with low viral load and elevated ALT are the best candidates for interferon-based therapy. In HBeAg-positive individuals, therapy with standard interferon alfa-2b is associated with a 37% loss of detectable serum HBV DNA rate, an 18% HBeAg seroconversion rate, and an 80% to 90% durability of treatment response (defined as loss of HBsAg and HBeAg as well as undetectable HBV DNA 12 months after cessation of therapy). The rates are different for HBeAg-negative individuals: 60% to 70% have loss of serum HBV DNA, 48% have histologic improvement, and 20% to 30% have durability of response. Treatment with peginterferon alfa-2a is associated with 25% loss of HBV DNA and 27% HBeAg seroconversion at week 48 and 32% seroconversion at week 72.

The 2 primary advantages of peginterferon are a fixed duration of therapy and no risk of antiviral resistance, but few patients opt for this therapy because of the need for injections and the presence of side effects (Table 4). Interferon-based therapy is associated with higher risk or is contraindicated in patients with signs of underlying cirrhosis. If treatment with interferon is pursued, it is usually done under the guidance of a transplant center.

HBV genotype has been noted to predict the response to therapy with peginterferon: HBV genotype A has responded more favorably than genotype D, and genotype B has responded more favorably than genotype C in some but not all studies. Detection of HBV genotype is not helpful in predicting the response to treatment with any of the oral antiviral agents.

Lamivudine. Lamivudine (100 mg daily) was approved in 1998 as the first available oral agent for the treatment of chronic hepatitis B. It is virtually free of side effects and has efficacy similar to interferon-based therapy; however, it has a somewhat lower durability of response in HBeAg-positive patients (50%–80%) and an even lower durability in HBeAg-negative patients (20%–25%). Treatment is initiated for 1 year but is usually continued until HBeAg seroconversion occurs. After seroconversion, therapy is continued for an additional 6 months to enhance the durability of response in HBeAg-positive patients. Prolonged use of lamivudine therapy is associated with the emergence of the lamivudine-resistant YMDD mutation.
(tyrosine-methionine-aspartate-aspartate) at a rate of approximately 20% per year, increasing to approximately 70% by year 4 of therapy. In spite of this limitation, prolonged treatment has been shown to be beneficial in individuals with advanced fibrosis or cirrhosis by reducing the rate of disease progression and lowering the incidence of HCC. Patients with the YMDD mutation have been treated successfully with adefovir dipivoxil and entecavir.5

**Adefovir.** Adefovir dipivoxil is a nucleotide analogue that was approved in 2002 at a dose of 10 mg daily. It can cause significant nephrotoxicity at higher doses, but long-term monitoring has not shown significant nephrotoxicity at the 10 mg daily dose.14 After 1 year of therapy with adefovir 10 mg, 53% of HBeAg-positive patients and 63% of HBeAg-negative patients had histologic improvement compared with placebo patients.15,16 As with lamivudine, therapy is continued in HBeAg-positive patients until confirmation of HBeAg seroconversion, and HBeAg-negative patients are continued on long-term therapy. Once HBeAg seroconversion occurs with adefovir therapy, it is durable in 91% of patients.17 Recent studies have demonstrated the continuous beneficial effect (ie, improvement in fibrosis) of prolonged adefovir therapy up to 4 to 5 years in patients with HBeAg-negative hepatitis B.18,19 As with lamivudine, resistance can become an issue with prolonged therapy, albeit at a lower rate. No resistance was reported after 1 year of therapy.18 However, resistance started to emerge at year 2 (3%) and increased at year 4 (18%) and year 5 (29%). Resistance occurs most commonly in patients with persistently elevated HBV DNA levels after 48 weeks of adefovir therapy.20

**Entecavir.** Entecavir is a nucleoside analogue with the most potent viral suppression among the available hepatitis B therapies, with a dose of 0.5 mg daily leading to a 6.98 log10 copies/mL decrease in serum HBV DNA levels in HBeAg-positive patients.21 However, it has similar rates of HBeAg seroconversion as lamivudine after 1 year of therapy.22 Patients with lamivudine resistance require a higher dose of entecavir (1 mg daily) and after 1 year of therapy have a 10% incidence of development of genotypic resistance and virologic rebound, defined as an increase of more than 1 log10 copies/mL from nadir serum HBV DNA levels.23

Patients who have developed lamivudine resistance are usually switched to adefovir or entecavir. Adefovir can also be added to lamivudine therapy in this setting, especially if the patient has underlying cirrhosis and cannot tolerate a flare of hepatitis B.24 Patients who develop adefovir mutations can be successfully treated with lamivudine.25

**Telbivudine.** Telbivudine is a nucleoside analogue approved in 2006. Results from a large, 2-year, phase 3 trial of telbivudine versus lamivudine for the treatment of chronic hepatitis B were recently reported.26–28 After 1 year of therapy, telbivudine significantly reduced HBV DNA level in all patients to a greater extent than lamivudine. In addition, 60% of HBeAg-positive patients treated with telbivudine had a detectable loss of HBV DNA as compared with 40% of lamivudine-treated patients. A similar pattern was noted in the HBeAg-negative patients, with 88% of telbivudine patients and 71% of lamivudine patients clearing HBV DNA. At 1 year, the rate of resistance to telbivudine was 3% in the HBeAg-positive group and 2% in the HBeAg-negative group compared with rates of 8% and 7%, respectively, in lamivudine-treated patients. After 76 weeks of telbivudine treatment, there was a 6.6 mean log10 decrease in HBV DNA, with 69% of patients maintaining viral clearance and 40% maintaining loss of HBeAg. However, resistance at 2 years was 21% in HBeAg-positive patients and 8.6% in HBeAg-negative patients.29

**Drug-Resistant HBV**

Multidrug resistant HBV has been isolated in patients receiving sequential treatment with nucleoside analogue monotherapies.30 Many experts recommend adding adefovir to lamivudine-resistant HBV rather than switching to adefovir monotherapy.3 As more drugs are approved for treatment of hepatitis B, future therapy will include the use of multiple agents simultaneously to minimize the emergence of resistance seen with monotherapy and to maximize viral suppression. Multiple drugs for the treatment of chronic hepatitis B are currently in development, including clevudine, tenofovir, emtricitabine, pradefovir, and valtorcitabine. Pradefovir and clevudine are in phase 2 of development, while tenofovir and emtricitabine are undergoing phase 3 studies.

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**Table 4. Selected Side Effects of Interferon and Ribavirin**

<table>
<thead>
<tr>
<th>Interferon</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia, thrombocytopenia</td>
<td>Hemolytic anemia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Flu-like symptoms, anorexia, diarrhea</td>
<td>Teratogenicity</td>
</tr>
<tr>
<td>Depression, suicidal ideation</td>
<td>Fatigue, headache</td>
</tr>
<tr>
<td>Emotional lability, arthralgia</td>
<td>Anxiety, insomnia</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>Rash, pancreatitis</td>
</tr>
<tr>
<td>Autoimmune disorders, seizure</td>
<td>Myalgia, arthralgia</td>
</tr>
</tbody>
</table>

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**References:**

1. Presentation of various types of hepatitis B and their classification.
2. Description of the pathogenesis of hepatitis B and the role of the immune system.
3. Discussion of the clinical presentation and diagnosis of hepatitis B.
4. Overview of the treatment options for hepatitis B, including antiviral therapy.
5. Comparison of the efficacy and safety of various antiviral agents.
6. Discussion of the role of vaccination in the prevention and control of hepatitis B.
7. Examination of the long-term outcomes and complications of hepatitis B.
9. Examination of the role of hepatitis B in global health.
10. Discussion of the research and future directions in the field of hepatitis B.

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HBV Reactivation with Chemotherapy

Reactivation of HBV infection has been reported to occur at an average rate of 54% in HBsAg-positive patients receiving chemotherapy, especially chemotherapy regimens containing prednisone. Prophylaxis with a nucleoside analogue such as lamivudine has significantly decreased HBV reactivation to an average rate of 9.2. The timing and duration of therapy is not well defined. Most studies have used lamivudine 1 to 28 days prior to initiation of chemotherapy and continued therapy for 28 days to 1 year after cessation of chemotherapy.

CASE 1: INITIATION OF THERAPY AND FOLLOW-UP

Treatment with adefovir 10 mg daily is initiated after laboratory tests show elevated serum levels of HBV DNA and ALT. Screening for HCC with abdominal computed tomography (CT) is performed given the patient’s family history of liver cancer and the high likelihood of underlying cirrhosis due to the presence of spider angiomas and a palpable spleen on physical examination. CT reveals a shrunken liver and splenomegaly but no evidence of a liver mass. Laboratory testing 1 month after initiation of therapy reveals decreased serum ALT and AST levels as well as a significant decrease in serum HBV DNA levels. Long-term treatment is planned with regular monitoring for a continued antiviral effect and any evidence of antiviral resistance. The patient also will be screened for HCC every 6 months.

CHRONIC HEPATITIS C

CASE PRESENTATION 2

Presentation and History

A 56-year-old Caucasian engineer presents to a gastroenterologist for management of chronic hepatitis C. He was told he has chronic hepatitis C while applying for a life insurance policy. He denies abdominal pain, history of jaundice, pruritus, hematemesis, weight loss, and rashes. He snorted cocaine while in college and had a tattoo placed while he served in Vietnam.

Past medical history is significant for hypertension and depression, both of which are well controlled with medical therapy. He has no history of suicidal ideation. He takes hydrochlorothiazide and citalopram daily. He is married and has no children. He consumes wine socially once weekly. His father had diabetes mellitus. His siblings are in good health.

Physical Examination

The patient’s height is 5 ft 7 in (170 cm) and his weight is 159 lb (72 kg), with a body mass index of 24.9 kg/m². Assessment of vitals signs reveals a temperature of 98.7°F, blood pressure of 110/70 mm Hg, and heart rate of 70 bpm. Physical examination reveals no jaundice, hepatomegaly, splenomegaly, spider angiomas, or lower extremity edema.

• What are risk factors for HCV infection?

RISK FACTORS

Chronic hepatitis C is a major cause of morbidity and mortality worldwide. Infection with HCV is mainly spread by contact with blood. The major risk groups for acquisition of HCV infection are injection drug users, persons who received a blood transfusion prior to 1992, health care workers with needle-stick injuries, persons with high-risk sexual behavior, individuals receiving tattoos with use of unsterilized needles, and intranasal cocaine users (as is in this case).

CASE 2: LABORATORY TESTING

Further testing for hepatitis C confirms the presence of anti-HCV, shows an HCV RNA level of 300,000 IU/mL, and shows that the patient is infected with HCV genotype 2a. Results of liver function tests are reported as follows: AST, 70 U/L; ALT, 85 U/L; total bilirubin, 1.2 mg/dL; and alkaline phosphatase, 76 U/mL. Complete blood count reveals a WBC of 6.4 × 10³/mL, hemoglobin of 14.2 g/dL, and platelet count of 250 × 10³/mL. INR is 1.0.

• What is the approach to treatment of chronic HCV infection?

TREATMENT

Factors that Influence Treatment Decisions

The treatment goal for chronic hepatitis C is to eradicate the virus and prevent disease progression to cirrhosis and HCC. Decisions regarding treatment are influenced by genotype, stage of the disease, and presence of comorbidities. There are 6 genotypes of hepatitis C virus. Genotypes 1, 2, and 3 are found worldwide, whereas genotype 4 is found mainly in Africa and the Middle East, genotype 5 in South Africa, and genotype 6 in Vietnam and Hong Kong. Genotype affects the treatment duration and impacts the likelihood of achieving a sustained virologic response (SVR), defined as undetectable virus 24 weeks after completion of therapy. Genotypes 2 and 3 are associated with a high SVR (defined as absence of HCV RNA in serum 6 months after completion of therapy) rate, while genotype 1 is associated with a low SVR rate. Other predictors of a poorer SVR are high
viral load, advanced fibrosis, obesity, African-American race, and older age.\textsuperscript{36}

Disease status is best assessed by liver biopsy, which provides the grade of inflammation and stage of fibrosis as well as excludes any coexistent disease such as fatty liver. However, experts still debate the timing and indications for liver biopsy due to its invasive nature.\textsuperscript{36} Most clinicians obtain a liver biopsy when making recommendations regarding treatment for patients with genotype 1, but less often for patients with genotypes 2 and 3. Instead of liver biopsy, some clinicians use platelet count, INR, liver ultrasound, or other noninvasive tests as indirect markers to access for advanced liver disease.

The current treatment of chronic HCV infection is peginterferon and ribavirin, which are associated with significant adverse effects that limit broad application to all individuals with HCV infection. The physician must weigh the risk-benefit ratio of therapy by assessing whether the patient is likely to tolerate the expected side effects and whether therapy will aggravate any existing comorbidities. Some common adverse events include flu-like symptoms, worsening depression, irritability, sleep disturbance, anemia, leukopenia, thrombocytopenia, and precipitation or exacerbation of endocrine, pulmonary, and ophthalmologic conditions (Table 4).

**CASE 2: INITIATION OF THERAPY**

The case patient has a genotype that is associated with a high SVR rate, a normal platelet count, and normal INR. His depression is under good control. Liver biopsy is not pursued. Treatment is initiated with peginterferon alfa-2a 180 µg weekly and ribavirin 400 mg twice daily.

**Optimal Duration of Therapy**

Peginterferon alfa-2a or alfa-2b with ribavirin for 24 weeks (genotypes 2 and 3) or 48 weeks (genotype 1) is standard therapy for chronic hepatitis C. The overall SVR rate ranges from 54% to 65%.\textsuperscript{33-35} The SVR rate in patients with genotype 1 ranges from 42% to 52% with therapy, which decreases to 30% to 47% in the setting of high viral load (> 800,000 IU/mL [1 IU/mL is equivalent to approximately 2.2 copies/mL]).\textsuperscript{33-35} Patients with genotypes 2 or 3 have a SVR rate between 76% and 84%.\textsuperscript{33-35,36} As genotype 3 has a lower SVR rate compared to genotype 2 (79% versus 93%),\textsuperscript{36} some experts recommend prolonged treatment duration, especially in the presence of significant fibrosis, viral load, and metabolic syndrome.\textsuperscript{39}

The likelihood of achieving a SVR depends on patient compliance and ability to tolerate the usual adverse effects. Patients who receive less than 80% of 1 or both medications for less than 80% of the duration of therapy have a suboptimal response to treatment.\textsuperscript{38} Aggressive use of growth factors for cytopenia and treatment of psychiatric illnesses with antidepressants during therapy improve quality of life and compliance with therapy and may prevent dose reduction of the medications.\textsuperscript{40}

Several studies have suggested that a shorter duration of therapy for patients who achieve a rapid virologic response (RVR, defined as undetectable serum HCV RNA at week 4) might be associated with acceptable SVR rates.\textsuperscript{41-43} However, these studies have been criticized for having inappropriate control arms, not representing the general population (ie, including younger patients with lower body mass index and minimal liver fibrosis), and using substandard ribavirin doses. Further studies are needed to address the optimal duration of therapy, especially for patients with low viral load at initiation of therapy. RVR is most useful in predicting SVR with standard duration therapy.\textsuperscript{44} By contrast, longer duration of standard therapy might be pursued in patients not achieving RVR.\textsuperscript{45} Treatment is usually discontinued in patients who do not show a 2 log\textsubscript{10} decrease in viral load at 3 months after initiation of therapy.

**Monitoring**

Monitoring patients while on therapy is essential to avoid emergence of potential treatment complications. Monitoring includes serial complete blood cell counts to assess for the presence of anemia, leukopenia, and thrombocytopenia, and regular physician visits to assess for compliance and depression. Hemoglobin, WBC count, platelets, and chemistries including liver function tests are usually measured at weeks 1, 2, 4, 6, and 8, and then every 4 to 6 weeks. Thyroid-stimulating hormone is measured at baseline and every 12 weeks. Pregnancy test is performed prior to initiation of therapy in sexually active females and monthly thereafter. Pregnancy screening should be continued for 6 months after end of therapy. Strict contraception methods are recommended in patients during and for 6 months after end of therapy due to ribavirin teratogenicity.

**IMPACT OF THERAPY ON DISEASE PROGRESSION**

Several studies have documented the benefits of achieving an SVR, including a persistently normal ALT level, histologic improvement, and undetectable HCV RNA over 4 to 10 years of follow-up.\textsuperscript{46,47} Treatment also impacts the progression rate of fibrosis. Baseline fibrosis stage, SVR, age below 40 years, body mass index less than 27 kg/m\textsuperscript{2}, absence or minimal baseline inflammatory activity, and an HCV RNA serum level less than...
1.59 million IU/mL were found to be associated with absence of significant fibrosis after a course of treatment. Shiratori et al showed in a nonrandomized trial that patients who received therapy versus those who did not had a significant reduction in the risk of developing HCC. Finally, treatment of chronic hepatitis C has been associated with prolonged survival. It is important to emphasize that screening for HCC is vital in all cirrhotic patients regardless of their viremia status. Therefore, screening for HCC should continue in all cirrhotic patients who have successfully achieved SVR.

**SELECTED SITUATIONS IN CHRONIC HEPATITIS C**

**Cirrhosis**

Patients with compensated cirrhosis are good candidates for therapy; however, those with decompensated cirrhosis tolerate therapy poorly. Escalating doses of peg-interferon and ribavirin may be an option for decompensated patients, and this approach has been associated with a SVR rate of 13% in patients with genotype 1 and 50% in patients with genotypes 2 and 3. However, treatment of patients with decompensated cirrhosis has been associated with significant liver decompensation and death. Therefore, treatment is reserved for patients who are eligible for liver transplantation, and such treatment is best conducted at a transplant center under the direction of expert hepatologists.

**Patients with Normal ALT Levels**

The registration trials for interferon and peginterferon with ribavirin did not include patients with normal ALT levels. However, there is emerging good evidence showing that these patients have response rates similar to those in patients with elevated ALT levels. Furthermore, approximately 25% of patients with normal ALT have significant fibrosis on liver biopsy. Therefore, clinicians are more frequently recommending therapy for patients with normal ALT levels, even in the presence of stage 2 fibrosis or lower on liver biopsy. In addition to guiding therapy, liver biopsy can result in initiation of HCC screening in a patient with normal ALT and no signs of portal hypertension. Finally, patients with genotypes 2 and 3 are offered therapy regardless of the ALT level given the high response rates.

**Relapsers and Nonresponders**

A thorough investigation should be conducted to determine potential reasons for failure of therapy. Patients may fail to respond to initial therapy if inappropriately low doses of interferon and/or ribavirin are used, if doses are reduced, or if patients are noncompliant. As discussed earlier, a number of host factors (eg, obesity, African-American race) and viral factors (eg, genotype 1 and high viral load) play an important role in failure to achieve a SVR. If favorable factors are present and liver biopsy shows stage 2 fibrosis or higher, retreatment can be considered. Patients who do not respond to standard interferon plus ribavirin have a 6% to 15% likelihood of achieving a SVR with peginterferon plus ribavirin. Relapsers are defined as patients who have detectable HCV RNA on discontinuation of therapy after having undetectable HCV RNA during therapy. Patients who relapse following treatment with interferon plus ribavirin respond more favorably to retreatment than nonresponders, with a course of peg-interferon plus ribavirin achieving SVR rates of 32% to 50%. There are limited data on the use of interferon alfacon-1 plus ribavirin in patients who do not respond to peginterferon plus ribavirin therapy, and major trials are underway.

**HCV and HIV Coinfection**

HCV and HIV are spread by similar risk factors. HIV infection is present in 5% to 10% of HCV patients, and 15% to 30% of HIV-infected patients have HCV infection. With advances in highly active antiretroviral therapy leading to good control of HIV infection and prolonged survival, chronic hepatitis C is becoming a major cause of morbidity and mortality in HIV patients. In 3 major trials conducted over the past several years, overall response rates to peginterferon plus ribavirin in HCV and HIV coinfected patients were 14% to 29% for those with genotype 1 and 46% to 73% for those with genotype 2 or 3. Treatment of HCV infection does not impact HIV viremia but may result in a transient decrease in CD4+ cell counts. Adverse effects and early discontinuation are more frequent in coinfected patients.

**Extrahepatic Manifestations of HCV Infection**

Chronic hepatitis C is associated with extrahepatic manifestations, with type II cryoglobulinemia being the most commonly seen. Other reports have linked hepatitis C to development of non-Hodgkin’s lymphoma, lichen planus, sicca syndrome, and porphyria cutanea tarda. Cryoglobulins can be found in up to half of persons with HCV infection, and large amounts of HCV antigens and antibodies can be found in the cryoprecipitates. However, only a small fraction of affected persons (10%–15%) have symptomatic cryoglobulinemia. The symptoms are often secondary to vasculitis and consist of weakness, arthralgias, and purpura. Membranoproliferative glomerulonephritis is usually seen in severe cases. HCV is the chief cause of essential mixed cryoglobulinemia (type II cryoglobulinemia). Up to 90% of affected
persons have HCV viremia, and serum HCV RNA should be used for diagnosis of HCV infection in such patients because of frequent false-negative tests for anti-HCV in these patients. Cryoglobulinemia tends to improve with interferon and ribavirin therapy and tends to relapse if SVR is not achieved. Furthermore, the degree of mixed cryoglobulinemia is directly linked to the level of viremia. Symptoms usually improve even in the setting of incomplete virologic response. Cryoglobulinemia-associated cutaneous vasculitis responds best to treatment with interferon and ribavirin.

### SUMMARY

Chronic hepatitis B and C continue to be major causes of morbidity and mortality. The introduction of potent oral antiviral drugs for the treatment of chronic hepatitis B and advances in interferon-based therapy with combination peginterferon plus ribavirin for the treatment of chronic hepatitis C have significantly improved the natural history of these infections. There are more drugs under study, including newer nucleoside and nucleotide analogues for treatment of chronic hepatitis B and polymerase and protease inhibitors for the treatment of chronic hepatitis C. Peginterferon plus ribavirin will most likely remain the backbone of therapy for chronic HCV infection, and combination therapy will likely evolve to become the standard treatment of chronic hepatitis B to avoid the development of resistance.

### REFERENCES


Treatment of Chronic Hepatitis B and Hepatitis C


