Current Management of Chronic Hepatitis B and C in Chronic Kidney Disease

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The landscape of therapeutic options for hepatitis B and C has changed drastically over the course of 2 decades. There are now novel, effective, well-tolerated, oral antiviral agents being used to successfully control chronic hepatitis B (HBV) infections and cure chronic hepatitis C (HCV) infections. However, patients with CKD were rarely included in the Phase II and III randomized trials for these medications. This paucity of data and the high prevalence of comorbidities associated with CKD pose distinct challenges to physicians treating chronic hepatitis B virus and hepatitis C virus infections in the setting of kidney insufficiency/failure. Thus, this review will attempt to summarize the current data regarding novel antiviral therapies for HBV and HCV in the CKD population.

Key Words: Therapy, HCV, HBV, Kidney disease

HEPATITIS B

Introduction

Hepatitis B virus (HBV) is transmitted by percutaneous or mucous membrane exposure to infectious body fluids. Perinatal transmission is the major route of infection among children, and sexual transmission is the major route for adults. HBV transmission that occurs at less than 5 years of age usually results in chronic infection, and the majority of the disease burden is secondary to long-term complications. Conversely, transmission that occurs in adulthood evolves into a chronic infection only in 1% to 5% of newly infected individuals, and the majority of the disease burden is related to acute hepatitis.[1]

Hepatitis B is not endemic in the United States, but its epidemiology has clinical relevance worldwide. An encouraging trend, as of recent, is that incidence of acute hepatitis B in the United States has declined dramatically (10.7/100,000 → 0.9/1000,000) from 1987 to 2012, which likely represents the effectiveness of vaccination programs and universal precautions in needle use.[1,2] Similarly, the prevalence in United States was estimated to be low at 0.30% in 2005 to 2006. However, this almost certainly under-represents foreign-born immigrants (of which some groups are estimated to have a prevalence as high as 15%), who are the likely explanation for why expenditure of resources on HBV is still increasing.[1] Furthermore, from 1993 to 2004, HBV was responsible for only 4.34% of the liver transplants performed (78% were for chronic HBV and 22% were for acute, fulminant HBV), although the rates were higher in states with larger immigrant populations.[3] In 2011, the mortality rate for hepatitis B was low at 0.5 deaths per 100,000 population ($n = 1804$).[2]

HBV infection does confer a high risk of hepatocellular carcinoma (HCC), even in the absence of cirrhosis: approximately 20% of HCC cases can be attributed to HBV infections in the developed Western world (in contrast to 60% in Africa and East Asia).[4] Additionally, a close relationship exists between chronic hepatitis B and CKD. The European Virgil database, which includes 24 European centers, revealed that of 381 chronic hepatitis B patients, 15% had an estimated glomerular filtration rate (eGFR) of 50 to 80 mL/min and 4% had an eGFR<50 mL/min before the start of therapy.[5] Furthermore, 35% to 45% of a cohort of 290 Asian patients in the United States with chronic HBV had CKD Stage 2 at baseline.[6,7] Finally, the prevalence of hepatitis B surface antigen (HBsAg) positivity among patients on hemodialysis (HD) is 0% to 7% in developed countries and 2% to 20% in developing countries.[8,9]

Decision to Treat

HBV infection is associated with characteristic changes in serum antigens and antibodies: surface antigen, which is suggestive of active acute or chronic infection; surface antibody, which confers lifetime immunity to hepatitis B; core antigen, which is not detectable in the serum; core antibody, which suggests a history of exposure to the virus; the e antigen (HBeAg), which is a marker of viral replication and infectivity; and e antibody, which can suggest remission of liver disease. A chronic, inactive carrier state is defined by HBeAg negativity with normal alanine aminotransferase/aspartate aminotransferase (AST/ALT) and minimal (<2000 IU/mL) or undetectable HBV DNA levels. Immune tolerance is defined by HBeAg positivity and HBV DNA levels greater than 20,000 IU/mL, no evidence of inflammation (normal ALT/AST and benign biopsy). Chronic, active HBV infection is defined as HBsAg positivity for greater than 6 months, serum HBV DNA levels greater than 20,000 IU/mL (but lower levels 2000-20,000 IU/mL are often seen in chronic HBeAg-negative chronic HBV), persistent or intermittent elevations in (AST/ALT), and liver biopsy showing chronic hepatitis with moderate or severe necroinflammation.[10] All patients who meet these criteria for chronic, active HBV should be considered for treatment using the algorithm in Figure 1.

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Patients who are HBeAg positive with HBV DNA levels greater than 20,000 IU/mL or those who are HBeAg negative with HBV DNA levels greater than 2000 IU/mL should be actively considered for treatment if they have elevated ALT levels greater than 2 times the upper limit of normal for a 3- to 6-month period. Furthermore, immediate treatment should be considered in patients with decompensated liver function or jaundice.

The criteria for initiating therapy in patients with HBV are the same in patients with CKD compared with those with normal kidney function. However, patients with ESRD often have lower baseline aminotransferases for unclear reasons (possibly caused by hemodilution, pyridoxine deficiency, or homocysteine elevation).[11] In these patients, aminotransferase levels that are within the normal range may mask increased inflammatory activity. When aminotransferases are noted to increase from baseline, even if still within the normal range, liver biopsy may be needed to more accurately demonstrate the burden of inflammation. Therefore, instead, clinicians need to rely more heavily on liver biopsy (often difficult to obtain because of uremia-associated platelet dysfunction) and noninvasive markers of fibrosis, which, unfortunately, have not been studied extensively in this group. Additionally, the decision to treat should be based on the potential risks and benefits of treatment including life expectancy, candidacy for kidney transplantations, and comorbidities.[10]

CLINICAL SUMMARY

- There are several well-tolerated oral antiviral agents that are successfully controlling chronic hepatitis B infections and curing chronic hepatitis C infections.
- There is a shortage of data regarding the use of these therapies for chronic hepatitis B and hepatitis C infections in the kidney insufficiency or failure.
- More studies are needed to further elucidate dosages, safety, and efficacy of these therapies in patients with CKD and ESRD on HD.

Therapies

The goal of treatment of chronic HBV is to achieve sustained suppression of HBV replication to prevent cirrhosis, hepatic failure, and HCC.[10] Currently, there are 5 oral agents that have been approved for the treatment of chronic HBV infection: 3 nucleoside (lamivudine, telbivudine, and entecavir) and 2 nucleotide (adefovir dipivoxil and tenofovir disoproxil fumarate) analogues. Before their development, the only available therapeutic option was interferon-alpha (standard and pegylated), which was rarely used in patients with CKD because of relatively low efficacy, poor patient tolerability, and risk of adverse events (including the risk of acute rejection in kidney transplant recipients.)[12]

All 5 of these agents target the reverse transcriptase of HBV and inhibit HBV replication that can subsequently normalize aminotransferases, improve necroinflammation on liver biopsy, and prevent adverse outcomes, such as cirrhosis, liver failure, and HCC, in patients with chronic HBV.[10,12] The main advantages of nucleos(t)ide analogues (NA), compared with interferon, is that they have high antiviral potency and on-therapy efficacy, improved safety and tolerability profiles, and the convenience of oral administration. However, because they have poor off-therapy efficacy, there is a need for long-term, if not indefinite, therapy in many patients, which poses a risk of viral resistance, especially in the setting of nonadherence.[12,13]

Lamivudine was the first NA approved for treatment of chronic HBV infection and is still the most widely used NA worldwide. One year of monotherapy achieves virological remission in 36% to 44% of HBeAg-positive and 71% to 75% HBeAg-negative patients,[14-17] but long-term therapy results in progressively accumulating rates of viral resistance (14%-32% at Year 1 and 60%-70% at Year 5), which leads to virological and biochemical breakthroughs and subsequent clinical worsening of liver disease.[15,18-21]

Adefovir is the second NA that was approved for chronic HBV infection; it has activity against lamivudine-resistant strains and achieves virological remissions at the end of the first year in 13% to 21% of HBeAg-positive and 51% to 63% of HBeAg-negative patients.[22-24] However, its moderate antiviral potency, coupled with its high cost and its risk of resistance (20% and 29% at Year 5 for HBeAg positive and HBeAg negative, respectively),[25] quickly led to its replacement by newer agents.[12]

Telbivudine is a potent NA that achieves 1-year virological remission in 60% of HBeAg-positive and 88% of HBeAg-negative patients.[17] Furthermore, 4-year virological remission rates in patients who did not have resistance at 2 years was 76% for HBeAg-positive and 86% for HBeAg-negative patients.[26] However, it has a limited role in the treatment of chronic HBV because of its high rates of resistance (1- and 2-year resistance rates are 4.4% and 21.6% in HBeAg-positive and 2.7% and 8.6% in HBeAg-negative patients, respectively)[27] and because telbivudine-resistant mutations are cross-resistant with lamivudine.[10]

Entecavir and tenofovir are considered to be the first-line therapy for NA-naive patients with chronic HBV, based on their potency and minimal-to-no risk of resistance. They have demonstrated 1-year virological remission rates of 67% to 76% in HBeAg-positive and 90% to 93% of HBeAg-negative patients[14,16,24] and 3-, 5-, and 6-year accumulating/maintaining remission rates of greater than 90% with minimal risk of resistance (1.2% for entecavir and 0% for tenofovir at 5-6 years)[28-31] However, tenofovir alone is the preferred agent for patients with known lamivudine-resistant strains because entecavir has not been shown to be effective in treating these strains of HBV.[10]

Therapies and Kidney Risk

As per the European Association for the Study of the Liver Hepatitis B guidelines, all patients starting NA therapy need an estimation of creatinine clearance and a baseline assessment of kidney risk before the initiation of therapy. Patients at high risk of incurring kidney damage include those with decompensated cirrhosis, creatinine clearance less than 60 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, and solid organ