Six products are approved in the United States for the treatment of chronic hepatitis B (CHB) viral infection: interferon alfa-2b, recombinant (Intron-A); peginterferon alfa-2a (Pegasys); lamivudine (Epivir HBV); adefovir dipivoxil (Hepsera); entecavir (Baraclude); and telbivudine (Tyzeka). In clinical trials, oral products administered up to 1 year to treat this chronic condition have demonstrated similar rates of hepatitis B e antigen (HBeAg) seroconversion from HBeAg-negative status to HBeAg-positive status with the detection of hepatitis B e antibody (anti-HBe) ranging from 17% to 27% in adults. Costs, however, can vary widely. Factors affecting costs include the direct cost of the drug, length of treatment, and complications associated with continued therapy (e.g., development of resistance, intolerable adverse events). In addition, predictors and durability of response (pretreatment alanine aminotransferase [ALT] levels and serum hepatitis B virus [HBV] deoxyribonucleic acid [DNA] levels) may affect overall costs.

In this issue of JMCP, Yuan and colleagues attempt to estimate the long-term health and economic impact of treating patients with CHB from an overall cost perspective. The authors conclude that entecavir is more cost-effective than lamivudine in the long-term treatment of HBeAg-positive CHB virus patients. We applaud the efforts of the authors for the development and refinement of such a complicated and sophisticated model. However, the assumptions used for model development in this disease state (i.e., 10-year time horizon, difference in study populations, and epidemiology of the disease) create a double-edged sword. On one edge, using multiple variables allows an opportunity for greater accuracy for predictive modeling, and 10 years is an appropriate period to measure outcomes in a disease such as CHB since it typically takes 10 years or longer for the disease to manifest as adverse clinical outcomes. However, in a hypothetical population, if any of the assumptions used in creating the model are incorrect, the over- or underestimation of clinical utility will be magnified in proportion to the length of the time frame used in the model.

Lamivudine was the first oral nucleoside analog approved for the treatment of CHB and is now joined by 3 other oral agents. Since lamivudine’s entry into the marketplace, evidence of drug resistance to HBV has emerged, suggesting reduced susceptibility to lamivudine. Reported lamivudine resistance rates in CHB patients are 14% after 1 year of treatment and may increase to as high as 69% after 5 years of treatment. In light of lamivudine’s reported resistance patterns and the overall conclusion that entecavir given for up to 10 years is more cost-effective, the 10-year time horizon utilized in Yuan et al.’s comparison of lamivudine with entecavir appears impractical. According to American Association for the Study of Liver Disease (AASLD) guidelines, lamivudine is preferred for short (undefined) courses of treatment.

In addition, this pharmacoeconomic (PE) model proposed by Yuan et al. begins with a hypothetical population of lamivudine treatment-naïve individuals in the base-case model, and conclusions are drawn from the sensitivity analysis in which more than half of the patient population develops resistance to lamivudine within 10 years. This population is quite different from that of the Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) study in which 2% of patients in the entecavir study group and 18% of patients in the lamivudine study group experienced virologic rebound during the first year of therapy. In the BEHoLD study, virologic rebound was used as a determinant to identify if resistance, defined as an increase in HBV DNA by at least 1 log10 copies per mL from the nadir, occurred during the treatment period. The continued use of lamivudine in treating lamivudine-resistant individuals has been associated with a diminished treatment response (i.e., higher pretreatment HBV DNA and ALT levels). The clinical significance of this observation, however, has not been fully elucidated.

The incidence and clinical course of CHB are different in developing countries than in the United States. In the United States, the risk of adults developing CHB from acute exposure to HBV is <5% while the incidence of CHB in endemic areas (e.g., Southeast Asia) can range from 25% to 30% in infants and children under the age of 5 years to as high as 90% in newborns of HBeAg-positive mothers. Cohorts in studies describing the natural history of CHB can be categorized into 2 basic groups: (1) patients born in areas with high and intermediate prevalence rates for HBV and (2) patients in high-risk groups (e.g., intravenous drug users, homosexual men, inmates of correctional institutions, and individuals coinfected with hepatitis C virus or human immunodeficiency virus). This is an important consideration when evaluating drug therapy. Those who develop CHB early in life (i.e., acquired at birth from an infected mother or during early childhood) from an acute exposure experience disease progression and develop serious liver complications (i.e., compensated and decompensated cirrhosis and hepatocellular carcinoma) by the fourth decade of life due to the prolonged immune tolerance phase that is characterized by persistence of HBeAg, persistence of viremia for a longer duration, and normal ALT/aspartate aminotransferase (AST) levels. The prolonged immune tolerance phase is followed by a prolonged immune clearance phase (i.e., longer time to...
seroconversion of HBeAg and decrease in HBV DNA levels and more frequent bouts of disease activity constituted by hepatic flares.8,17-19

People of Asian descent born in areas endemic to hepatitis B typically acquire infections perinatally and thus fall into the immune tolerance phase. Conversely, adolescents and adults exposed to HBV that progresses to CHB immediately enter the immune clearance phase; the duration of the disease is usually shorter and becomes quiescent after seroconversion of HBeAg to anti-HBe. Individuals falling into this category are commonly referred to as healthy carriers of HBV and do not have active disease.8

Clinical trials have shown that clearance of HBeAg reduces the risk of hepatic decompensation and improves survival in patients with CHB.20,21 In the Risk Evaluation Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study, which was used by Yuan et al. to determine risks of complications for patients with differing levels of HBV viral load, most patients were from Taiwan and more likely to be in the immune tolerance phase; 85% of the REVEAL study patients were HBeAg-negative and 94% had normal (defined as <45 units per liter) ALT levels.22,23 In contrast, in the BEHoLD study, which was used by Yuan et al. to determine HBV DNA levels for patients treated with entecavir and lamivudine, 58% of the study subjects were of Asian descent and 40% were white. Also, at least 98% were HBeAg-positive in each BEHoLD study group, and 97% did not have antibodies to HBeAg. Hence, patients in the BEHoLD study group appeared to have active chronic disease, while individuals from the REVEAL study may have been carriers of HBV because the status of anti-HBe antibodies was not noted in the study.

In addition, the presence of HBeAg has been correlated with high levels of HBV DNA replication.24 In the REVEAL study, approximately 84% of HBeAg-positive individuals had HBV DNA levels >1 million while 4% had HBV DNA levels <10,000 copies per mL.2 Because of the differences observed in these populations and the different disease etiologies in the 2 studies, it is difficult to interpret the applicability of the REVEAL study findings for Yuan et al.’s PE model for the treatment of hepatitis B in the United States. It is noteworthy that 86% of the patients in BEHoLD were from outside North America and 48% were from Asia and Australia. This PE model implies that the clinical course and progression of disease are similar for individuals with chronic disease versus carriers of HBV, an assumption that may or may not be correct.

PE models have advantages compared with clinical trials. For example, changes to the assumptions in the design or population can be made easily, and the vast amounts of time and resources required for a clinical study are not needed. However, the most useful study for payers of health care services would include real patients, stratified and randomized appropriately. The REVEAL study was a prospective cohort population-based study that evaluated the risk of liver complications based on HBV DNA viral load in treatment-naïve individuals. Because there is no direct correlation with HBV DNA viral load and complications in treated subjects, the reader is left to assume that this PE model mirrors the natural progression of CHB.

The current PE model proposed by Yuan et al. leaves the following 2 questions unanswered: (1) Does chronic administration with entecavir significantly reduce the risk of complications compared with the natural progression of the disease? (2) Does the amount of reduction in the risk of complications justify the additional costs in drug expenditure for entecavir? It is difficult to determine if the assumptions of the outcomes (compensated cirrhosis, decompensated cirrhosis, and hepatocellular cancer) based on the REVEAL and BEHoLD trials would come to fruition in an actual, long-term clinical trial. Additionally, a clinical trial would allow for more detailed analyses of the effects of race, gender, age, and other factors than is possible in a hypothetical model.

Another point not directly addressed in the Yuan et al. analysis is specification of the optimal regimen for treating HBV. Although this determination was not an objective of the study, it would have been interesting to see the analysis of the outcomes for an arm in which lamivudine was used first and patients were either converted to another agent upon treatment failure or intolerance of the product, or continued with add-on therapy. The model incorporated costs associated with add-on therapy with adefovir dipivoxil for study subjects who experienced virologic rebound with lamivudine and also included a sensitivity analysis of switching subjects from lamivudine to adefovir dipivoxil monotherapy. Both treatment scenarios may have varying degrees of impact on at least the HBV DNA viral load, with consequent influence on the associated costs of the model.

A few studies have shown improved outcomes in lamivudine-resistant patients as measured by virologic and serologic markers (i.e., HBV DNA viral load and ALT) associated with either adding adefovir dipivoxil to lamivudine in lamivudine-resistant patients or switching patients to adefovir monotherapy.25-27 Therefore, costs for a lamivudine-resistant patient treated with adefovir, either in monotherapy or in combination with lamivudine, may actually be lower than calculated by Yuan et al.’s model due to additional HBV DNA suppression. The PE model projects event probabilities of liver complications based on HBV DNA levels but does not appear to account for HBV DNA suppression that may occur with the addition of adefovir in lamivudine-resistant patients. Conversely, the addition of adefovir dipivoxil to lamivudine in lamivudine-resistant treated patients has also been associated with a higher risk of adefovir resistance.27,28 Accounting for this risk would increase the costs calculated by the Yuan et al. model.

Also unknown are the resistance patterns or mutations for entecavir. In the BEHoLD study, 2% of patients in the entecavir group and 18% of patients in the lamivudine group experienced
viral rebound during the first year of therapy. Although the genotypic analysis from this study did not reveal any substitutions in the isolates of subjects taking entecavir, the reason for virologic rebound is unknown. The PE model proposed by Yuan et al. does not provide enough information on viral rebound beyond 1 year for entecavir; thus, the validity of the assumptions is not readily apparent.

In addition, the correlation between lamivudine resistance and progression of disease is not clearly understood. It has been demonstrated that some patients seroconvert even in the presence of lamivudine-resistant hepatitis B viral mutants. At the end of 4 years, seroconversion occurred in up to 50% of patients treated with lamivudine. Thus, some experts favor continued treatment with lamivudine even in the presence of resistant variants. Therefore, the use of combination therapies would also need to be addressed in a more complete PE model.

Another uncertainty arises from the potentially invalid assumption that HBeAg seroconversion is equivalent to a positive clinical endpoint outcome. Although seroconversion is a valid measure of active disease, it is not a guarantee of clinical success. In the BEHoLD study, the HBeAg seroconversion rates for entecavir and lamivudine were similar in the 2 treatment groups (21% for entecavir vs. 18% for lamivudine, \( P = 0.33 \)).

Current clinical trials of drug therapy to treat CHB use a variety of biochemical, virologic, and histologic markers to determine disease progression and efficacy of drug therapies. It is not uncommon to see effectiveness defined by histologic score (e.g., Knodell or Ishak index score), biochemical score (e.g., ALT), virologic response (e.g., HBV DNA viral load, loss of HBeAg), HBSAg seroconversion, or presence of HBe or HBs antibodies. Unlike HBeAg status, which can denote if individuals have an acute or chronic infection, the presence of HBSag indicates active infection.

Current diagnostic and treatment guidelines suggest that high-risk individuals and those living in areas with endemic HBV should be screened for HBSag and HBSAg antibodies. Although HBeAg is a common biological marker used in clinical trials, its absence does not denote a true virologic cure of CHB. True cure is defined as (1) loss of HBsAg, (2) absence of detectable HBV DNA, (3) formation of anti-HBs antibodies, and (4) normalization of ALT levels. During the natural course of the disease, HBsAg average loss is <2% per year, similar to that seen with treatment with nucleoside/nucleotide analogs and 3% to 10% after 1 year of interferon therapy. HBSAg loss increases to 11% to 32% after 24 to 26 weeks of follow-up in those who initially respond to interferon therapy. Because of the complexity of these issues, it is difficult to determine the accuracy of the assumptions used in the PE model proposed by Yuan et al.

Also, the authors seem to imply that the treatment would be continuous; patients with CHB should be treated long-term with oral antiviral agents (in those eligible according to treatment guidelines) to maintain suppression of HBV DNA viral load. In clinical practice and in the BEHoLD trial, not all patients continue with therapy after an initial success. Studies from Asian and non-Asian populations have reported a sustained response following initial treatment of at least 52 weeks with lamivudine or 52 weeks with entecavir. It is interesting to note that of the patients in the BEHoLD trial who experienced a protocol-defined response (HBV DNA level <0.7 MEq per mL and HBeAg loss), 82% in the entecavir group and 73% in the lamivudine group had a sustained response 24 weeks after discontinuation of therapy; however, 41% in each group had undetectable HBV DNA levels and normalization of ALT. Thus, the results of this study show that the durability of response appears similar for the 2 agents.

Approximately 95% of primary infections in immunocompetent adults with HBV are self-limiting, with clearance of virus from blood and liver and subsequent development of lasting immunity to reinfection. CHB follows a dynamic history of progression. Current practice guidelines from 3 associations concerned with liver disease suggest that once a person achieves a healthy hepatitis B carrier state (i.e., seroconversion of HBeAg, presence of anti-HBe antibodies, and HBV DNA levels <10^5 copies per mL and normal ALT levels), treatment can be terminated. The debate, however, continues regarding the most appropriate duration of treatment, depending upon how early the patient contracted the infection.

The amount of viral replication has been suggested to play an important role in the development of cirrhosis and hepatocellular carcinoma. The magnitude of HBV DNA viral load is increasingly becoming a recognized independent risk factor that can be used to determine the risk of developing complications associated with CHB and to evaluate the efficacy of treatment regimens in treatment-naïve patients and those who experience virologic rebound. Known factors affecting treatment outcome include viral load, ALT levels, and compliance with drug therapy.

More research is needed in tailoring therapy based on the diversity of disease progression and sustainability or durability of response, and determining the best treatment for failing regimens. Data are limited, and U.S. payers should be cautious in interpreting the results of this hypothetical model, particularly since the data inputs are not derived from populations in the United States. More studies are warranted to determine if long-term prophylaxis with entecavir will result in significant incremental cost savings and improved quality of life.

On the basis of current recommendations from the AASLD guidelines, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver, individuals with HBeAg for at least 3 to 6 months, HBV DNA >10^5 copies per mL (<20,000 IU per mL), and ALT levels >2 times the upper limits of normal (i.e., 45 units per liter, as defined in the REVEAL study) should be initiated on interferon alfa-2b for 16 weeks, or peginterferon alfa-2a for 48 weeks, or nucleoside/nucleotide therapy (lamivudine, adefovir, entecavir,
or telbivudine) for a minimum of 1 year, followed by 6 months of additional therapy after HBeAg seroconversion. Patients should be treated until HBeAg seroconversion to anti-HBe, HBV DNA <20,000 IU per mL, and normalization of ALT levels.

Although 6 drugs are approved in the United States for the treatment of CHB, the Centers for Disease Control and Prevention (CDC) is moving to eliminate transmission of hepatitis B in the United States. From a societal perspective, the best course of action to decrease the risk of complications associated with CHB virus is through vaccination of high-risk individuals. Preliminary data from the CDC indicate that approximately 50% to 60% of adolescents aged 13 to 15 years are vaccinated against hepatitis B and that from 1990 to 2005, the incidence of acute hepatitis B in the United States declined by 78%. Data are also emerging to suggest that vaccination of individuals entering the United States from high-endemic areas may be cost-effective. The successful implementation of vaccination programs may truly reduce the economic burden of treating CHB and its complications.

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