Treatment of chronic hepatitis B remains challenging due to medication-resistant viral mutations, unanswered questions for initiation and duration of treatment, and risk for chronic liver complications. More than 400 million people worldwide are chronically infected with hepatitis B virus (HBV). Of those, an estimated 1 million die annually of HBV-related liver diseases. In the past decade, HBV-related hospitalizations, cancers, and deaths have more than doubled in the United States. Cirrhosis develops in 15%-20% of actively infected HBV patients within 5 years. For those patients, the incidence of hepatocellular carcinoma (HCC) is increased, with 70%-90% of HCC cases occurring in cirrhotics.

With the advent of telbivudine, the sixth medication approved for treatment of chronic hepatitis B by the U.S. Food and Drug Administration (FDA) in October 2006, treatment regimen complexity is predicted to increase due to HBV mutations leading to antiviral resistance. Combination therapies are being further explored, especially for treatment-experienced patients who face issues of resistance and adverse effects. Although vaccination to prevent hepatitis B became available in 1982, continued unawareness of modes of transmission and immigration from endemic areas are concerns for potential new exposures and development of costly chronic complications. Prevention is crucial to halt the increasing health care costs for hepatitis B, but current therapies have efficacy limitations for treatment-experienced patients. Further research to determine appropriate starting and ending treatment criteria is needed.

Hepatitis B treatment could reach the complexity of treatment of human immunodeficiency virus (HIV) with multiple medications in multiple classes. However, an increased ability to detect mutations may permit selection of the medication most likely to be effective for individual patients. For example, knowledge of the tyrosine-methionine-aspartate-aspartate (YMDD) mutation resulting from lamivudine therapy led to investigation of addition of therapy such as adefovir to decrease viral load and reduce resistance. Hepatitis B e antigen (HBeAg)-negative patients with lamivudine resistance who were treated for 3.5 years with adefovir plus lamivudine had less adefovir resistance (4.4%) than did patients treated with adefovir alone (33.3%).

The approval of tenofovir for treatment of chronic hepatitis B is expected within the next year, and other nucleoside analogues such as clevudine and emtricitabine remain in phase 3 trials. New advancements offer additional hope for treatment options for nonresponsive or resistant hepatitis B. A key to controlling the virus may lie in combination drug therapy.

To date, 8 genotypes for hepatitis B are known but are not routinely determined in patients outside of academic or clinical trial settings. Genotype determination may become standard in the near future and could increase the cost-effectiveness of treatment. One study demonstrated the positive predictive value for response in genotype A patients treated with interferon compared with genotypes B, C, and D. Another study showed that genotype B was more responsive than genotype C to interferon in HBeAg-positive patients. Knowledge of a patient’s genotype could also influence initial treatment decisions. Treating a patient with interferon injections for 16 to 32 weeks instead of prescrib- ing lifelong oral medication could be cost saving, especially considering that immunomodulators such as peginterferon alfa-2a carry no risk for viral resistance. More data on the correct medication choice based on genotype are needed.

FDA approval of entecavir in 2005 substantially increased the ability to manage chronic hepatitis B. Lamivudine is no longer recommended as a first-line choice in treatment-naïve patients. With a reportedly low incidence of adverse effects, entecavir therapy is well tolerated. Lamivudine’s reported resistance rate of 14% to 32% in the first year, increasing up to 20% each year thereafter, cannot compare with entecavir’s 0% reported resistance at 1 and 2 years for nucleoside-naïve patients. Although the long-term resistance profile of entecavir is still unknown, 4-year data in a cohort of 120 nucleoside-naïve patients showed that virologic rebound occurred in only 1 subject without evidence of genotypic or phenotypic resistance. As treatment benefits are obsolete once resistance develops and HBV DNA levels increase, maintenance of viral suppression is critical.

Telbivudine, the most recently approved oral medication for treatment of chronic hepatitis B, has a lower reported resistance compared with lamivudine, 21.6% for HBeAg-positive and 8.6% for HBeAg-negative patients at 92 weeks of treatment. Because of the higher rate of resistance for telbivudine compared with entecavir, telbivudine may eventually play the greater role in combination therapy. Adefovir and tenofovir are treatment options for telbivudine resistance. The PROACTIV Study is underway to evaluate continued therapy with (1) adefovir alone versus (2) telbivudine plus adefovir versus (3) telbivudine plus tenofovir.

Release of the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) trial results in 2006 precipitated the revision of national guidelines for the treatment of HBV to focus on viral levels versus the previous focus on alanine aminotransferase (ALT) elevations. More emphasis is now placed on suppressing viral loads. Data showed an increased risk of cirrhosis with HBV-DNA levels ≥ 10^4 copies per mL. Although an increased risk of progression to cirrhosis was associated with HBeAg-positive status and serum ALT elevations, the strongest predictor of future cirrhosis risk was elevated viral levels, providing evidence...
to heavily weight reduction of viral levels in making treatment decisions. The previous viral load cutoff for expected hepatitis B complications—100,000 copies per mL (20,000 IU per mL)—was decreased in the American Association for the Study of Liver Diseases (AASLD) practice guidelines in 2007 to 10,000 copies per mL (2,000 IU per mL) for HBeAg-negative patients with the goal of suppression to the lowest possible level.

While there are minor differences between the published treatment guidelines in AASLD versus Keeffe et al., there are substantial guideline changes common to both publications including (1) viral levels ≥20,000 IU per mL, (2) the measure of ALT elevated 2 times the upper limit of normal (ULN) for HBeAg-positive patients and viral levels ≥2,000 IU per mL for HBeAg-negative patients, and (3) the measure of ALT elevated 2 times ULN.13-20 Previous guideline criteria included (1) ALT levels alone to guide treatment for HBeAg-positive patients and (2) the degree of necroinflammatory changes and fibrosis on liver biopsy to guide treatment for HBeAg-negative patients, without mention of viral levels.21

A potential cost-savings approach is to ensure that patients who meet recommendations for treatment receive proper medication and monitoring according to evidence-based guidelines. For example, initiation of antiviral therapy would be inappropriate for an HBeAg-negative patient with ALT 1.5 times ULN, HBV DNA 1,000 IU per mL, and a Metavir fibrosis score (an algorithm used to evaluate liver biopsy inflammation and fibrosis) of 0, the lowest possible score.22 Treatment outside of recommendations could result in patients starting costly therapy and potentially developing viral resistance sooner compared with monitoring and waiting until the evidence-supported starting point for treatment. Although guidelines do not always directly evaluate the cost-effectiveness of treatment, more evidence is building to guide initiation of hepatitis B treatment.

In the present issue of JMCP, Yuan et al. explore the cost-effectiveness of the previous first-line treatment, lamivudine, versus the newer therapy, entecavir.23 Although first-line use of entecavir is supported by national guidelines, third-party payers could be reluctant to cover entecavir as first-line treatment when a lower-cost alternative ($4,671 less per patient per year for lamivudine) is available. The REVEAL-HBV trial provides data to support a focus on decreasing viral levels by documenting prospectively a progression to cirrhosis ranging from 4.5% to 36.2% with increasing HBV-DNA levels in the absence of treatment.19 Despite applying mainly HBeAg-negative data to an HBeAg-positive population in the cost-effectiveness analysis, Yuan et al. proposed a model that is still useful in the overall picture of chronic hepatitis B treatment, considering that a 6.5 increased relative risk of cirrhosis was seen in REVEAL-HBV for the entire study population, including both HBeAg-positive and HBeAg-negative patients.19 However, more than 75% of cirrhosis complications, as well as HCC, occur after seroconversion from HBeAg-positive to anti-HBe.24 Therefore, the use of complication rates from a population in which 85% is HBeAg-negative may overestimate complication rates for an HBeAg-positive population. On the other hand, the cost savings of entecavir may be underestimated because the cost of liver transplantation for cases of HCC decompensation was not included in the model.

Also, it is unknown if extrapolation of results over a 10-year period is valid, given the unknown resistance pattern for entecavir. However, compared with lamivudine, entecavir is more attractive from the perspective of efficacy and prevention of hepatic complications. Additionally, there is the potential to discontinue treatment in HBeAg-positive patients as early as 6 months after seroconversion, possibly resulting in lower treatment costs compared with an HBeAg-negative population.13 As entecavir seroconversion rates range from 12% to 39% with increasing ALT levels, a number of HBeAg-positive patients may discontinue treatment before HBeAg-negative patients do.25

A prior cost-utility analysis by Kanwal et al. in 2005 found that lamivudine and adefovir monotherapy strategies were more expensive and less effective than alternative treatment with interferon or step therapy with adefovir for patients who experience resistance to lamivudine.26 The authors concluded that this “salvage therapy,” in which adefovir is reserved for lamivudine-associated viral resistance, is likely to be highly cost-effective across most health care settings, regardless of HBeAg status of patients. However, interferon may still be preferred in health systems that focus on managing limited resources, particularly for populations with a high prevalence of HBeAg-negative HBV patients. In contrast to the analysis by Kanwal et al., the analysis by Yuan et al. did not consider the outcomes in HBeAg-positive versus HBeAg-negative patients.

However, using entecavir in lamivudine-resistant patients may increase the risk of resistance to entecavir, since genotypic HBV resistance to entecavir is 14% at year 2 of treatment in lamivudine-refractory patients.27 Using entecavir second line after lamivudine increases rates of resistance by 14% at 2 years of treatment. Although data from a Chinese population in the REVEAL-HBV trial may not be entirely applicable to a U.S. population that acquires hepatitis B mainly later in life, there is a direct correlation between increased viral level and risk of cirrhosis. Lowering HBV-DNA and therefore decreasing the risk for cirrhosis can prevent multiple complications, especially considering that the relative risk of developing HCC increases more than 100-fold in HBV-infected patients than in noninfected patients.27-29 However, use of lamivudine as a comparator with entecavir for estimating cost-effectiveness may not be the best choice when other comparators such as adefovir are available.

Medication cost may be a factor for nonadherence, especially for patients with Medicare Part D who reach the coverage gap or who lack medication coverage altogether. As the annual direct drug costs calculated by Yuan et al. based on annual wholesale acquisition cost (WAC) in 2006 were $7,365 for entecavir and $2,604 for lamivudine, postponing initiation of therapy might
be a reasonable option until medication coverage is obtained, as an alternative to initiating therapy and then facing resistance associated with interruption of therapy.

One area in need of investigation is the cost-effectiveness of entecavir compared with adefovir for nucleos(t)ide treatment-naive patients. The costs of adefovir and entecavir are significant, with the average wholesale price (AWP) in 2007 of $8,720 for adefovir therapy and $9,742 for entecavir annually. Adefovir resistance is another factor to consider, with a reported incidence of approximately 30% at 5 years of treatment. Initial viral suppression is less potent with adefovir than with entecavir. However, adefovir is more closely matched with entecavir in efficacy compared with lamivudine.

As in so many areas in medicine, our need for information to guide decision making in patient care far outweighs the evidence available. Clinical trials of the complex array of treatment options in different patient subgroups (e.g., across different serum ALT and viral load levels, and HBeAg-positive vs. HBeAg-negative status) are needed. Chronic hepatitis B is the cause of 10%-20% of liver transplants.

Our ability to treat HBV in a cost-effective way will depend on the quality of information available about prevention of complications in the array of patient subtypes seen in clinical practice. Only with such high-quality information can we decrease overall health care costs and increase quality of life in this complex patient population. The importance of HBV vaccination and screening in cost-effectiveness strategies should not be forgotten, especially considering that up to two thirds of the HBV chronically infected United States: should the other virus be forgotten? [abstract] Hepatology. 2002;36:222A.

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