Therapy for hepatitis B: 'La nouvelle vague'

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PA: Before we discuss the future of hepatitis B, let us discuss the current playing field.

RG: Hepatitis B is a worldwide problem with more than four hundred million infected individuals and more than one million deaths occurring as a result of cirrhosis and liver cancer each year. Hepatitis B remains a serious problem in countries with a higher socioeconomic status due to the prevalence of hepatitis B in immigrant populations as well as high-risk individuals. The only way to break the infection cycle, long-term, is to provide vaccination to infants at birth with additional vaccinations for older children, young adults and high-risk individuals. The current treatment for hepatitis B focuses on profound hepatitis B virus (HBV) DNA suppression because hepatitis B is an incurable disease and HBV DNA is the driver of serious consequences of this global scourge. Because hepatitis B can be controlled and 'cleared', long-term suppression of HBV DNA is the ultimate goal, with some patients achieving hepatitis B surface antigen (HBsAg) seroconversion. Interferon has been relegated to a minor role because only a subset of patients

have persistent HBV DNA suppression (undetectable) after 24 to 48 weeks of

therapy. Reversal of cirrhosis has now been documented after or during therapy with all available agents. Some studies have indicated that there is a lower risk of liver failure in patients treated with sustained viral suppression. Furthermore, cases of liver failure reversal and of declines in patients' MELD (Model for End-Stage Liver Disease) scores have been published. A recent study has demonstrated that there are fewer HBV-infected patients with concomitant liver failure currently on the liver transplant list in the

United States UNOS (United Network for Organ Sharing) database than in the past. With less liver failure and fewer deaths or transplants due to liver failure, more patients are living long enough to develop liver cancer. Importantly, there is no evidence that any of the nucleosides or nucleotides approved for use in humans by the regulatory authorities are carcinogenic. I recognize that there is a substantial cost associated with the annual use of single- or dual-drug therapy for HBV. I would also emphasize that the cost of death and liver transplant is substantial. A review of the medical literature would stress that anti-HBV therapy has been shown in many models to be cost effective.

PA: In the new era, what is the ideal end point of hepatitis B therapy?

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RG: In this new era of hepatitis B treatment, with profound HBV DNA suppression, and with long-term resistance rates at 1% or less, I would advocate that the ideal new end point of treatment should be HBsAg loss. This, of course, needs to be in concert with HBV DNA negativity. Off medications, this HBsAg loss, with or without seroconversion, appears to be durable in a great number of patients. HBsAg loss and seroconversion portends the greatest clinical benefit and the most favourable clinical outcome with the lowest risk of cirrhosis and cancer.

PA: A concept from the past was the need for the patient's immune system to rise up and overcome the viral infection. If we vigorously suppress hepatitis B with oral medications, do we remove the stimulus for the immune system to fight off the virus?

RG: The immune system is both friend and foe in the patient due to the fact that the immune system, through an active inflammatory response, is the cause of the progressive liver injury and results in an increased risk of developing cirrhosis, as well as an increased risk of liver cancer. Conversely, the immune system is ultimately 'in charge' of profound viral suppression and seroconversion of the hepatitis B 'e' antigen (HBeAg) and the ultimate seroconversion of HBsAg. Although there is profound suppression of HBV DNA with nucleoside or nucleotide therapy, there appears to be modest effects on e antigen and s antigen production. Thus, the decline in HBeAg or HBsAg levels tends to be due to the reconstitution of the immune system. Interferon is useful for this reconstitution as well, although only approximately 30% to 40% of patients have long-term HBeAg seroconversion and more than one-half of those patients are HBV DNA-positive. I believe that with profound virus suppression, we will continue to have cumulative HBeAg and HBsAg seroconversion at a higher rate than in the 'natural' population. Although interferon is useful for immune system activation, it appears that only approximately 11% of patients can benefit from the immune stimulatory effects of interferon leading to profound viral suppression and subsequent HBeAg and HBsAg seroconversion.

PA: Another new concept is that we should be aggressively screening high-risk populations for HBV. Is this feasible and are there ethical concerns?

RG: Screening for hepatitis B in high-risk populations has now been deemed the standard of care by a variety of different national and international organizations including the American Association for the Study of Liver Diseases. In countries where there are substantial health care resources, I find that the screening and education process is feasible and ethical. I see distinct problems with cost issues and treatment applications of screening in areas of the world that have limited or no health care resources. One must question the benefit of broad-based screening if there are limits to medical care and resources. Thus, the ability to initiate antiviral therapy in those patients who are at risk of cirrhosis, cancer or death is an imperative part of any screening and surveillance program. The presence of an HBV infection also promulgates a social conflict in the form of social discrimination. In areas of the world such as China, there is a profound level of prejudice and discrimination that takes place daily. The loss of employment and the possibility of being ostracized from the family or social environment are substantial risks for individuals who 'come out of the closet' and admit that they are HBV infected.

PA: Are there conflicts of interest in population screening for hepatitis B?

RG: Indeed, pharmaceutical companies have typically supported this screening process, although through third parties such as public health departments and a variety of other stakeholders, thus having a secondary or tertiary involvement in the screening process. The pharmaceutical companies have yet to be involved with the primary screening events directly. Although there may be a perceived 'conflict of interest' or 'secondary gain', the grants have been handled through the appropriate channels and have withstood the scrutiny of many prestigious organizations. In San Francisco, we are screening patients within secure databases and reporting individuals who are HBsAg-positive to the Public Health Department. Unfortunately, with a lack of a robust public cross-referenced database, some patients are being screened multiple times and even getting vaccinations after a previous series of vaccinations have been applied. One of the controversies is where one initiates and completes the vaccination series. 'Incident to' vaccination at the screening event, or awaiting surface antigen antibody results before determining who actually should undergo hepatitis B vaccination, are two diametrically opposed options. 'Incident to' vaccination events often results in the wasting of vaccine doses in up to 50% of clinic clients.

PA: Do you think that with the newer treatments, experts and guidelines may recommend that all HBsAg carriers are treatment candidates?

RG: It is apparent that HBV DNA is the profound driver of risk for cirrhosis and cancer. These data are derived from a number of government-sponsored databases (which are not 'pharma-supported') from Taiwan and Hong Kong as well as Korea and other countries. HBV DNA data support that the risk of progressive disease in Europe, Africa and other parts of the world is also associated with higher levels of HBV DNA. This link to a risk of cirrhosis and cancer is separate from alanine aminotransferase levels or HBeAg status. Thus, one could consider any patient who is HBV DNA-positive to be a candidate for treatment. As HBV DNA assays become more sensitive, one may estimate that more than one-half of the infected individuals worldwide are candidates for treatment using these available data. As you can recognize, this new treatment paradigm would involve treating an extremely large number of patients with long-term or indefinite treatment. Because these costs are enormous, it is important for a clinician to sit and discuss with every patient who is HBV DNA-positive what the individual indications for treatment are, and reframe their treatment candidacy by looking not only at their positive DNA status. Other factors to include in treatment decisions are:

- age;
- sex;
- family history of liver cancer;
- genotype;
- presence of precore or core promoter mutations;
- duration of HBV DNA positivity;
- degree of HBV DNA elevation;
- duration and severity of alanine aminotransferase elevation;
- presence or absence of cirrhosis or advanced fibrosis (eg, considering a liver biopsy before initiating therapy);
- presence of coinfection with HIV and/or hepatitis C and/or delta hepatitis;

- patient motivation;
- estimated risk of infectivity; and
- the presence of biomarkers that may indicate an increased risk of hepatocellular carcinoma.

I believe that the patients who are HBsAg-positive are treatment candidates only if they are HBV DNA-positive. Once the two tests have been scrutinized, a liver specialist or an individual with profound expertise in managing hepatitis needs to balance benefits and risks of treatment as well as costs.

PA: What are the newest treatment developments?

RG: Currently, entecavir and tenofovir, along with interferon in selected patients, are the first-line therapies for chronic HBV infection. The future of managing hepatitis B, in my opinion, now needs to evolve into a new therapy that allows us to stop treatment and clear HBsAg early and profoundly. After considering all of the above described elements concerning initiating and continuing HBV DNA therapy, it becomes obvious that most patients are going to be taking an oral therapy indefinitely. Importantly, most patients are not candidates for interferon due to the lack of predictors of treatment response, either before or during therapy. One of the new possibilities for treating hepatitis B was clevudine. This is an oral medication that appears to reduce HBeAg and HBsAg levels more profoundly than the other oral nucleoside and nucleotide therapies that are available. This may allow shorter-term treatment and durable suppression of virus off therapy. The phase III studies will not be completed

due to the very high incidence of myopathy due to mitochondrial toxicity. One of the future steps is gene therapy such as interfering RNA. A trial has been initiated in the United States and three patients were treated with an interfering RNA that binds to and cleaves messenger RNA produced by HBV at 10 separate sites. This cleavage resulted in profound suppression of HBsAg, core antigen and HBV DNA in preclinical models.

Currently, the medical care system is spending billions of dollars managing patients with end-stage liver disease and liver cancer in hospitals and as outpatients. We are also expanding the domain of liver transplantation by transplanting patients with more advanced liver cancer, something that also involves substantial costs. We should model the costs and benefits of therapies. By advancing care for a variety of patients for whom hepatitis B infection could have profoundly serious consequences, we can both improve the quality of life and prolong life, while also potentially reducing long-term costs. The biggest questions posed to physicians, administrators and society are whether the health care system can afford not to treat hepatitis B, and how the health care system is going to allocate resources to this disease that results in profound morbidity and mortality, both locally and internationally, on an annual and long-term basis.

DISCLOSURE: Robert Gish is a consultant for Bristol-Myers Squibb, Gilead Sciences Inc, Roche Ltd and Pharmasset Inc.