

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Management of Viral Resistance in the Therapy of Chronic Hepatitis B

Anna Lok, MD, FRCP  
Professor, Department of Internal Medicine  
Director, Clinical Hepatology  
University of Michigan Health System

**G&H** Could you describe the process of random viral mutation in treatment-naïve patients with chronic hepatitis B?

**AL** Although the hepatitis B virus (HBV) is a DNA-containing virus, it replicates through an RNA intermediate. Therefore, it does not have proofreading mechanisms. As the virus replicates, it makes errors that cannot be deleted, resulting in subpopulations of mutated virus with the potential for drug resistance, even in patients who have not yet been treated.

In many patients with hepatitis B, particularly those who are candidates for treatment, as much as  $10^{12}$  viral particles may be generated daily. Therefore, the possibility of multiple mutations and combination mutations due to random error is very high. However, in the case of random error, the mutation would be present as only a tiny fraction of the entire viral population. Further, many random mutations negatively impact the ability of the virus to survive and may not be propagated.

**G&H** Was the presence of these random mutations an issue in treatment during the era of interferon-based therapies?

**AL** Interferon works by a very different mechanism from that of the current direct antivirals. It does not attack or block a specific part of the viral replication process. Therefore, it does not select for specific mutations and its efficacy is not affected by specific antiviral drug-resistant mutations. Interferon has broad antiviral activity, working

on multiple steps in the HBV replication cycle. Interferon also stimulates host-immune response. Although many patients do not respond well to interferon, development of resistance mutations is not a factor in treatment failure.

**G&H** Why have resistance mutations become a treatment issue with the use of direct antivirals?

**AL** Most of the drugs that we currently use to treat hepatitis B block the reverse transcription of the virus at a specific enzyme. When a patient is exposed to an antiviral drug, the wild-type virus, without the resistant mutations, is successfully suppressed. However, the resistant mutations allow the mutant virus to survive and because the mutant can now replicate much more effectively, the entire dynamic of the viral population is changed. Wild-type virus remains suppressed and the drug-resistant mutation becomes dominant over time, leading to an eventual rise in HBV DNA levels and what is known as viral breakthrough.

**G&H** Can you describe the historic evolution of monotherapy versus combination drug therapy strategies with the oral direct antivirals?

**AL** After years with interferon as the only treatment option for HBV, physicians were encouraged by the introduction of the first direct antiviral, lamivudine, which has potent antiviral properties and an excellent side-effect profile. However, we soon realized that the virus could acquire mutations and become resistant to lamivudine. In

the absence of rescue therapy, liver enzymes may increase suddenly at the time of viral breakthrough. In patients with advanced liver disease, the sudden burst of viral replication and hepatitis activity could push the patient into liver failure and possible death.

Lamivudine resistance is common due to its very low barrier to genetic resistance (ie, a single mutation dramatically decreases response to the drug). With some of the newer antivirals, such as entecavir, 2 or 3 mutations must be present in the virus before the efficacy of the drug is diminished.

Three of the approved HBV drugs, adefovir, and, more recently, entecavir and tenofovir, are effective against lamivudine-resistant virus. The initial thought was that if the early signs of lamivudine resistance were detected and the patient was switched to the other agent, the virus would be suppressed. At the time, we saw no advantage in continuing a drug that was clearly not working (ie, lamivudine). However, with more experience, we quickly realized that this was not a good idea because patients switched from one drug to another were more likely to develop eventual resistance to the second agent. At any given time, the viral pool remains heterogeneous. Even when there are signs of clinical resistance, there is still wild-type as well as drug-resistant virus present. Ultimately, we realized that by using 2 drugs that are not cross-resistant, we could obtain better results and prevent resistance to the second drug. This has led to the practice of adding on a drug rather than switching from one agent to another.

### **G&H** Is there a role for de novo combination therapy in hepatitis B treatment?

**AL** For the past several years, many virologists and infectious disease specialists have indicated that we should learn from the mistakes made in the initial treatment of HIV, where monotherapy and switching among agents did not work. However, therapy for HBV is very different from that for HIV because we do not have drugs with different targets. So far, no study has demonstrated additional antiviral activity with de novo combination of 2 drugs versus 1 drug in HBV.

Several studies have shown reduced rates of drug resistance with de novo combinations, but all of these studies have utilized lamivudine, which, as monotherapy, is associated with a very high resistance rate (approximately 20% after 1 year of treatment, escalating to 30–40% after 2 years). When de novo combination of lamivudine plus another drug (eg, adefovir) is utilized, resistance rates at 2 years of treatment can be reduced to approximately 15%. However, we are no longer advocating the use of lamivudine monotherapy in treatment-

naïve patients, in countries where cost is not a limiting factor. The newest HBV drugs, entecavir and tenofovir, have 1-year resistance rates of approximately 1%. Even after 4–5 years, resistance rates with these drugs remain at 1–2%. If a single drug is associated with 1–2% drug resistance after 4 or 5 years of treatment, how much better can de novo combination be? Reducing resistance from 2% to approximately 0.2% represents a very small difference. Patients are required to take 2 pills daily instead of 1 and pay for the cost of 2 medications, which could have an adverse effect on compliance. Even in real-world practice, where resistance rates with the newer agents could be as high as 5%, it is not clear that de novo combination would be advantageous.

### **G&H** How do you approach therapy in HBV patients who have developed multidrug resistance?

**AL** Multidrug resistance is a growing problem among HBV patients in the United States. Unfortunately, patients with resistance to 2 drugs have few choices because, although we currently have 5 oral agents, some of them are cross-resistant. Lamivudine and telbivudine are entirely cross-resistant, and both are partially cross-resistant with entecavir. Adefovir and tenofovir are partially cross-resistant as well.

My first step in treating multidrug-resistant patients would be to characterize the sequence of the virus and identify the pattern of mutation because I want to make an informed decision as to the next step in treatment. It is unwise to assume that because a patient has failed a specific drug, and then a second specific drug, the virus must have acquired resistance mutations because treatment failure can also be due to medication noncompliance. I have had patients whom I thought had multidrug resistance, but when their virus was characterized, no resistant mutation was found. These patients may simply be noncompliant, in which case a change of drug is not needed.

### **G&H** What are the other important issues in the successful treatment of HBV with direct antiviral therapies?

**AL** The most important issue to carefully consider is when to commence treatment. Often, we are referred patients who have been put on treatment before it was necessary. The decision to start treatment depends on a variety of factors: the age of the patient, levels of viral activity, and disease activity based on liver enzymes and histology. For patients in whom we know the time of onset of infection, the duration of infection may also play a role. The same virus and liver enzyme levels in a patient who

has been infected for only 3 years may have a different connotation from that in someone who has been infected for 30 years. When HBV has had 30 years to cause damage, even low-level virus may be clinically important and should be addressed therapeutically.

### G&H What are the next steps in HBV drug development and treatment?

**AL** It would be helpful to have drugs available to target different steps in the viral replication cycle. These drugs would provide the potential to suppress the virus more quickly and to avoid cross-resistance.

We also need to make sure that physicians who treat patients are actually monitoring patients closely. Because of the need for very long durations of therapy, it is important to appropriately counsel patients upfront and manage their expectations. Patients may think that they will only need 1 year of treatment. When treatment stretches to 2 years, 3 years, and beyond, patients may become frustrated and stop taking therapy. I tell patients that therapy will be for at least 4–5 years and possibly for life. If they understand this initially and are

committed to it, they are less likely to be noncompliant. Regular meetings with patients to re-inforce the concept of compliance will also play a role. We cannot assume that patients understand the serious nature of hepatitis B and the need to continually take medicine. Having more drugs and better drugs is good, but if we do not take care of our patients and monitor them properly, drugs will not solve their problems.

### Suggested Reading

Degertekin B, Lok AS. Monitoring antiviral resistance in patients receiving nucleos(t)ide analog therapies for hepatitis B: which method should be used? *J Hepatol.* 2008;48:892-894.

Keeffe EB, Dieterich DT, Pawlotsky JM, Benhamou Y. Chronic hepatitis B: preventing, detecting, and managing viral resistance. *Clin Gastroenterol Hepatol.* 2008;6:268-274.

Nguyen T, Locarnini S, Desmond P. Changing landscape of antiviral resistance management in chronic hepatitis B. *J Gastroenterol Hepatol.* 2008;23:1314-1317.

Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology.* 2007;45:507-539.

Lok AS, Zoulim F, Locarnini S, Bartholomeusz A, Ghany MG, et al; Hepatitis B Virus Drug Resistance Working Group. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology.* 2007;46:254-265.

Gish RG, Perrillo RP, Jacobson IM. Customizing the management of chronic hepatitis B virus infection. *Semin Liver Dis.* 2007;27(Suppl 1):9-17.