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# Monotherapy vs multiple-drug therapy: The experts debate

## Monotherapy for treatment-naïve patients

By Robert G. Gish, MD

Powerful antiviral medicines with activity against hepatitis B virus (HBV) have long-term records of potency and safety, supporting the case for monotherapy in treatment-naïve patients. Combination therapy has a limited role in the management of HBV infection; if the approach to treatment is rational from the start, then combination therapy can be reserved for cases of treatment failure or resistance.

### ■ THE CASE FOR MONOTHERAPY

Three arguments that favor monotherapy with potent medications are cost, low risk of resistance, and unproven benefit of combination therapy.

#### Cost

The cost of dual-medication therapy is nearly double that of single-drug therapy, while the benefit is unknown in treatment-naïve patients. My choices for first-line therapy are tenofovir or entecavir, highly potent nucleoside/nucleotide analogues that can cost up to \$5,500 and \$8,000, respectively, per year of treatment.<sup>1</sup> The two in combination would cost nearly \$14,000 per year, and benefits have not been proven in the treatment-naïve population.

#### Low risk of resistance

Potent medications have low rates of resistance, in the range of 1% over 2 to 5 years.<sup>2-4</sup> If one starts therapy with the highly potent entecavir, discussions about switching or adding on therapy would be superfluous because of the low rates of resistance and failure associated with entecavir monotherapy. At 5 years, the cumulative rate of entecavir resistance in patients with positive HBV DNA at baseline is 1.2%.<sup>5</sup> Tenofovir also produces potent inhibition of HBV DNA and is associated with

low rates of resistance,<sup>6</sup> although follow-up data with tenofovir extend only to 2 years. Starting therapy with the less potent adefovir, followed by the development of resistance, decreases the probability that tenofovir will achieve HBV DNA suppression during treatment.<sup>7</sup> The main driver of resistance is nonadherence with therapy, not treatment failure.

Resistance to pegylated interferon has not been encountered. The therapy is limited in duration (24 to 48 weeks), with durable suppression of HBV DNA and

high rates of seroconversion from hepatitis B e antigen (HBeAg)-positive to HBeAg-negative status. Parameters for the use of pegylated interferon as first-line therapy have been established, and include patients with genotype A or B who are young, have HBV DNA levels less than  $10^7$  copies/mL, have serum alanine aminotransferase (ALT) levels two to three times the upper limit of normal, and lack significant comorbidities.<sup>3,4</sup>

#### Unproven benefit of combination therapy

Perhaps the most convincing argument against combination therapy is that numerous studies of combinations have failed to demonstrate a benefit compared with monotherapy in treatment-naïve patients:

- Interferon in combination with lamivudine has not been shown to be significantly more effective than lamivudine monotherapy.<sup>8,9</sup> Further, because of limited information on the safety of interferon in combination with nucleoside or nucleotide analogues, use of the combination is not recommended.<sup>4</sup> Neuropathy has been reported with the combination of interferon and telbivudine,<sup>4</sup> leading to the release of a warning about its use.<sup>10</sup>

- A 1-year trial by Lai et al failed to show an improvement in virologic and biochemical responses with the combination of telbivudine and lamivudine

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compared with telbivudine alone.<sup>11</sup>

- In patients with lamivudine-resistant chronic HBV infection, adefovir reduced serum HBV DNA levels by 4 weeks whether or not lamivudine therapy was ongoing.<sup>12</sup>

- Although more patients taking a combination of adefovir and the nucleoside reverse transcriptase inhibitor emtricitabine had normalization of ALT and suppression of HBV DNA to less than 300 copies compared with adefovir monotherapy, rates of HBeAg seroconversion were comparable in the two arms.<sup>13</sup>

- A recent study that compared tenofovir monotherapy with tenofovir and emtricitabine in combination showed comparable effectiveness for both regimens; the authors concluded that further study is necessary before either choice can be recommended as superior to the other.<sup>14</sup>

### ■ RESISTANCE: IDENTIFY EARLY, ADD ON

To minimize the likelihood of resistance and its impact, HBV DNA levels should be monitored every 3 months; at the first sign of a virologic breakthrough, therapy

should be added or switched. Resistance to lamivudine is apparent early; models of treatment response indicate that resistance to lamivudine is likely if HBV DNA does not become undetectable by week 4.

In cases of lamivudine failure, adding adefovir early, when the viral load is less than  $10^7$  copies/mL, increases the probability of a virologic response.<sup>15</sup> In the situation of lamivudine failure, I prefer adding on to switching to reduce the risk of resistance—a practice supported by the study just cited.<sup>15</sup> In lamivudine-resistant patients, adefovir monotherapy was associated with virologic breakthrough and resistance to adefovir in 21% of patients, whereas no patient experienced virologic breakthrough or resistance when adefovir was added to lamivudine.

Successful management involves choosing the best medication up front and educating patients about the importance of taking their medication as instructed. For example, entecavir should be taken without food to maximize its bioavailability. With tenofovir, the risk of renal toxicity is low (1%),<sup>16</sup> and can be reduced even further with a pretreatment assessment of the patient.

## Multiple-drug therapy is the wave of the future

By Pierre M. Gholam, MD

A concise rationale for multiple-drug therapy is that resistance to monotherapy will occur eventually, with serious consequences in some patients and grave public health implications over the long term. Data from France and Australia indicate that multidrug-resistant HBV is a reality in individual cases. Resistance may be less likely when combinations are used, although little evidence exists at present to support this contention.

### ■ COMBINATION THERAPY IS COMMON SENSE

Much of the evidence supporting combination therapy for HBV is common sense:

- Most patients with HBV infection require treatment indefinitely, and duration of therapy that is not finite will inevitably lead to resistance.

- Your first shot is your best shot. Once resistance develops, treatment response will eventually decline.

- Sometimes the stakes are too high to risk breakthroughs. In particular, in patients who have cirrhosis and in those awaiting or following liver transplant, flares and recurrences can have disastrous consequences.

### Treatment duration and resistance

As Dr. Gish demonstrated, tenofovir and entecavir

are highly potent drugs that suppress viral loads effectively and have high genetic barriers to resistance. On an intent-to-treat basis, HBV DNA levels below the threshold level of detection are achieved at impressive rates with tenofovir and entecavir at 2 years in patients who are either HBeAg negative or positive.<sup>5,6,17</sup> When the analyses are limited to patients who actually received the drugs, suppression of HBV DNA to undetectable levels exceeds 90%. Resistance to tenofovir is 0% at 2 years,<sup>3</sup> and resistance to entecavir is 1.2% at 5 years.<sup>5</sup>

Although such data appear to favor monotherapy, most HBV-infected patients who commit to treatment will be treated indefinitely; this applies to patients who are HBeAg negative, who constitute most HBV-infected individuals in the United States and worldwide, or HBeAg positive. There are no established end points for treatment termination in HBeAg-negative patients. The only treatment termination end point that is deemed acceptable in HBeAg-positive patients is a period 6 to 12 months after the loss of HBeAg and the development of antibody to HBeAg, or e antigen seroconversion. Even after many years of treatment that includes the first-line agents tenofovir and entecavir, the likelihood of achieving this end point is fairly low.<sup>2,5,18</sup>

**In patients who have cirrhosis and in those awaiting or who have undergone liver transplant, flares and recurrences can have disastrous consequences.**

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Adherence is also a consideration. Studies of patients with hypertension, heart disease, and other chronic diseases have shown that strict adherence to therapy over decades is unlikely. The same adherence pattern probably applies to the treatment of chronic HBV infection.

Antiviral drugs used in the treatment of chronic HBV infection are associated with certain resistance mutations that confer additional risk of developing resistance to a subsequent drug. Furthermore, with indefinite duration of therapy, it is realistic to expect that resistance will develop.

Other factors play roles in the development of resistance:

- **Mutant viruses.** We do not fully understand the potential problem of transmission of mutant viruses. This phenomenon is becoming apparent in endemic areas where treatment-naïve patients harbor mutant viruses acquired through sexual contact with HBV-infected patients who have been treated and in whom the virus has subsequently mutated.

- **Barriers to resistance.** The genetic barrier to resistance for a single drug will eventually be overcome. It may take longer than it took for adefovir, which is associated with a 30% rate of resistance at 5 years.<sup>3</sup> It may take a much longer time for entecavir or tenofovir, but resistance is a biological certainty and we need to contend with it. With human immunodeficiency virus (HIV) infection, we are able to genotype for mutations and tailor treatment accordingly. This strategy is not currently recommended for HBV infection, partly because it is expensive and not routinely available.

- **Misuse of therapy.** Finally, wider use of antiviral agents for the treatment of HBV may lead to wider misuse, and therefore more resistance. Realistically, not every practitioner will start therapy with entecavir or tenofovir; many of the less potent agents have associated rates of resistance, and these in turn may confer an additional risk of resistance if tenofovir or entecavir is eventually used.

### Declining response

Colonna et al<sup>19</sup> studied the likelihood of entecavir resistance developing in patients with existing lamivudine resistance. The likelihood of resistance to entecavir at 3 years was 1.2% among patients who had never been exposed to lamivudine. Among patients in whom lamivudine resistance had developed and who were subsequently started on entecavir, resistance to entecavir was 32% at 3 years.<sup>19</sup> Resistance has consequences; 25% of lamivudine-resistant patients develop viral breakthrough.

Dr. Gish and I agree that the addition of adefovir to

lamivudine is better than switching to adefovir monotherapy in the case of lamivudine failure. Compared with switching, the adefovir-lamivudine combination leads to a lower incidence of virologic breakthrough, a lower likelihood of adefovir resistance over time, a greater probability of achieving undetectable levels of HBV DNA (< 35 copies/mL), and a lower cumulative rate of resistance.<sup>20</sup> The superiority of combination therapy in achieving undetectable levels of HBV DNA confers a lower risk of developing resistance over time; by year 4, the likelihood of adefovir resistance is only 4% among lamivudine-resistant patients treated with the combination of adefovir and lamivudine.<sup>20</sup>

In a study of nucleoside analogue-experienced patients who did not achieve viral suppression, response to tenofovir, defined as HBV DNA less than 400 copies/mL at month 12, was 85% overall and only 30% in adefovir-resistant patients.<sup>7</sup> These data demonstrate that, if not starting with combination therapy, it is preferable to initiate treatment with a potent drug that is highly successful at HBV DNA suppression. A second monotherapy will be less successful than the initial attempt.

### Consequences of resistance

The consequences of resistance in patients with cirrhosis are significant, prompting strong consideration of combination therapy as a potential means to avoid resistance.

One consequence is a well-documented potential for decompensation in the setting of new-onset resistance as a result of flares. Another is post-transplantation recurrence of HBV, leading to poor outcomes. These risks converge in the patient who is awaiting liver transplantation, in whom combination therapy seems to make the most sense to prevent the development of a flare and a recurrence of HBV infection after transplantation.

### WHO SHOULD RECEIVE MULTIPLE-DRUG THERAPY?

The American Association for the Study of Liver Diseases recommends combination therapy as the preferred rescue therapy for primary failure of a first-line agent, citing the possibility of resistance with switching in some circumstances and the superiority of adding on as opposed to switching.<sup>2</sup> No data clearly support de novo multiple-drug therapy. Although a number of studies have failed to show an advantage of combination therapy over monotherapy, they were of relatively short duration and focused primarily on viral suppression rather than the occurrence of resistance over time. Long-term studies are needed to determine whether combination therapy is an option de novo.

De novo multiple-drug therapy might be reasonable

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if a patient is at high risk for resistance—for example, for patients with extraordinarily high levels of HBV DNA or in whom resistance can lead to dire consequences, such as patients with cirrhosis or pretransplant patients.

The HIV pandemic serves as a paradigm for combination therapy. Many agents used to treat HBV infection also have anti-HIV effects; their use as monotherapy

## Discussion

**William D. Carey, MD:** I hear more agreement than not between the debaters. Are there any comments from the panel?

**Morris Sherman, MD, PhD:** I'll comment on the guidelines for the treatment of HBV infection. Tong et al<sup>21</sup> recently examined whether a group of HBV-infected patients who developed cirrhosis and hepatoma would have qualified for treatment under four current sets of guidelines. A startlingly large proportion of patients who developed adverse consequences from their liver disease would not have met the criteria for treatment under any of these major guidelines. As many as one-fourth of patients with chronic HBV infection die as a consequence of their liver disease, and in order to prevent these deaths up to one-half of the patients have to be treated. In the long run, overtreatment may be preferable to undertreatment to reduce the incidence of hepatitis-related deaths. My point is that the treatment guidelines probably exclude many patients who should be treated.

The factors I consider important in my decision to treat are a high viral load, which is indicative of active viral replication, and evidence of liver injury. Patients who have a high viral load and no liver injury won't experience complications. What do I consider evidence of liver injury? Prolonged elevation of ALT is suggestive, although not necessarily as high as 200 or 300 U/L; it could be in the range of 50 to 80 U/L if fibrosis is significant, which I define as stage 2 or greater on the biopsy. If a high viral load and evidence of significant liver injury are present, I treat the patient regardless of the precise level of the viral load or the ALT.

**Dr. Carey:** Can you clarify your position? Some of our earlier discussion emphasized the importance of treating when the viral load is high, regardless of other factors. A high viral load by itself may be associated with increased risk of cirrhosis or hepatocellular carcinoma without cirrhosis, so why would a biopsy make a difference?

**Dr. Sherman:** We can't predict which younger HBeAg-positive patients with a very high viral load are going to run into trouble down the road. Many will seroconvert spontaneously and never have problems thereafter. In

contrast, a patient in his 40s with a high viral load, even if HBeAg positive, and without major fibrosis should be considered for therapy. I tell my patients and the physicians who refer them that once I'm finished with the evaluation, it's not good-bye. They have to be followed for life because things change.

I agree with Dr. Gish that cost and potential toxicity, especially renal toxicity, may limit the widespread use of combination therapies.

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**Tram T. Tran, MD:** In the paper by Tong et al,<sup>21</sup> all of the patients who subsequently had poor outcomes had low platelet counts. I therefore recommend considering the entire picture in the decision to treat. If physicians followed the treatment guidelines strictly, they would not have treated those patients, but had they noticed thrombocytopenia they would have considered the possibility of advanced fibrosis and considered screening or a biopsy.

## DISCLOSURES

Dr. Gish reported that he has received consulting fees, honoraria for speaker programs, and research grants from Bristol-Myers Squibb Company, Gilead Sciences, Inc., GlaxoSmithKline, Idenix/Novartis, Innogenetics, Merck, Metabasis Therapeutics, Pharmasset, Roche Laboratories, Inc., Schering-Plough, and SciClone Pharmaceuticals. Dr. Gholam reported that he has received grant/research support from Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals, Inc., Gilead Sciences, Inc., Roche Pharmaceuticals, and Sanofi-Aventis; and consulting fees and honoraria for teaching and speaking from Gilead Sciences, Inc., Onyx Pharmaceuticals, and Vertex Pharmaceuticals.

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