

Combination Nucleoside Analogue Therapy

Robert P. Perrillo, M.D.

Director of Academic Affairs, Section of Gastroenterology and Hepatology, Ochsner Clinic Foundation

Rationale: There are two proposed advantages to the use of combination nucleoside therapy:

- More rapid and quantitatively greater suppression of HBV replication
- Deferred or decreased rates of resistance to antiviral drug therapy

The current discussion will focus on the evidence for both.

Preclinical Experiences: How Close Is the Correlation With *In Vivo* Effects of Drug Therapy?

Several *in vitro* systems have been used to measure drug-drug interactions to see if antagonistic, additive, or synergistic benefits can be demonstrated. While additive or synergistic effects have been observed with a number of compounds, one problem is that these artificial systems do not accurately reflect the *in vivo* condition since cultured hepatocytes (e.g., duck hepatocytes or human hepatoma cell lines) use different cellular enzymatic pathways for drug activation and disposal when compared to healthy human hepatocytes. Moreover, these systems necessarily do not involve short-term exposure to antiviral agents so that selection of drug-resistant HBV does not occur. Using mathematical drug interaction models such as Bliss independence or Lowe additivity to assess additive or synergistic effects has uncertain relevance to the human condition. Also, it is unknown if human genetic polymorphisms for drug-activating intracellular kinases exist or if different levels are achieved in infected versus non-infected patients as has been seen with HIV. These potentially important questions can not be addressed using *in vitro* systems.

Early Clinical Experiences in Humans

More rapid clearance of HBV DNA was observed in a 12-week course of treatment when famciclovir combined with lamivudine was compared to lamivudine monotherapy. This study included only 21 HBeAg-positive patients and did not use conventional endpoints. Instead, a mathematical model was applied to determine the dynamics of viral clearance. A subsequent study compared the combination of emtricitabine and adefovir to adefovir alone in 30 patients. Thus far, the 96-week data have yet to be published, but loss of HBV DNA by PCR (LLOD 300 copies) at week 12 occurred significantly more frequently in the combination group, and this was associated with enhanced CD4+ T cell responses. PCR became negative by week 48 in roughly 80% of combination-treated patients versus approximately 40% of adefovir-treated patients. However, rates of HBeAg seroconversion were disappointingly low in both groups (10% and 5%, respectively). In general, limited conclusions can be derived from these early studies due to short drug-exposure periods and small sample sizes. The results may reflect the weaker potency of adefovir when compared to emtricitabine rather than any inherent synergistic benefit for this particular combination.

Phase II Studies

Several studies have evaluated combination therapy given for 48 weeks or longer. In one clinical trial involving 113 previously untreated HBeAg-positive HBV carriers, nearly identical curves for HBV DNA suppression were demonstrated during the first year of treatment when a combination of lamivudine and adefovir was compared to lamivudine alone. The slight differences observed toward the end of the first 52 weeks of treatment were explainable by a greater rate of lamivudine resistance in the monotherapy limb (18% vs 2%). When on-treatment observations were carried out to week 104, 14% of the monotherapy group and 26% of the combination group were found to be negative for HBV DNA by PCR (LLD: 200 copies/mL). The rates of HBeAg seroconversion were equivalent at weeks 52 and 104 (lam alone: 17% and 20%, respectively vs. 10% and 13% for combination, Glaxo SmithKline, data on file). Surprisingly, there was a high rate of sustained virologic breakthrough (> 1 log increase over nadir on two successive

visits and at final on-treatment observation) when evaluated at week 104 in both groups (40% with lam alone; 17% with combination).

A second study evaluated the combination of telbivudine with lamivudine to either agent alone in 104 HBeAg-positive carriers. There was a trend for the rates of HBeAg loss and nondetectable HBV DNA (LLOD 200 copies) at treatment week 48 to be higher in the group treated with telbivudine or lamivudine monotherapy when compared to combination (HBeAg loss: 17% with combination vs. 33% with LdT and 28% with lamivudine; HBV DNA negativity: 49% with combination vs. 61% for telbivudine and 32% for lamivudine). These data suggest a possible negative interaction when these drugs are used in combination.

Viral Resistance

At the current time, it appears that nucleoside analog combinations provide a major advantage in reducing the rate of genotypic and phenotypic resistance. Cross resistance between the two drugs must not be possible for this to be achievable. Combinations that have been associated with a lower rate of viral resistance are adefovir and lamivudine, tenofovir and lamivudine, and tenofovir and emtricitabine. To date, the combination of adefovir and lamivudine has been best studied, but properly designed, randomized, controlled, long-term studies (4-5 years) are lacking to see whether drug resistance ultimately will develop. Adefovir switchover has been shown to be associated with adefovir resistance in transplant and non-transplant patient populations, and this can be prevented with lamivudine maintenance. The use of emtricitabine and tenofovir appears to be a promising combination but thus far has only been studied in HIV coinfecting patients. Due to cross resistance, combinations of entecavir and lamivudine and entecavir and emtricitabine will hold far less promise.

Other Considerations

Proponents of combination therapy for hepatitis B underscore the importance of multi-nucleoside analog therapy in HIV infection. Several of the currently available nucleoside analogs used to treat HBV, however, have excellent resistant profiles and can be given for prolonged periods without the emergence of drug resistance. A question then arises as to whether agents like tenofovir and entecavir, which have excellent antiviral activity and low resistance profiles, will obviate the need for multi-drug therapy as a first-line approach in patients who initially are at lower risk for drug resistance (e.g., low serum HBV DNA at baseline). Instead, will combination therapy be reserved for patients where resistance would occur quickly (e.g., immunosuppressed) or where it would be poorly tolerated (e.g., decompensated cirrhosis)?

Summary

At the current time, data on combination nucleoside analog therapy is very limited. Convincing data are lacking to show that combination therapy leads to greater rates of virologic response during treatment when compared to monotherapy, and off-treatment responses have not been described. What has been shown is that resistance to adefovir is reduced with concomitant lamivudine, and the converse also holds; remaining to be clarified is whether alternate combinations with more potent antiviral agents might not be more effective. There are data to suggest that certain combinations may actually lead to impaired virologic responses (e.g., telbivudine and lamivudine). It is presently uncertain if this is due to competition for binding to HBV DNA polymerase, competition for phosphorylating enzymes, or other negative drug interactions. Thus, some of the key questions moving forward are:

- What are the long-term clinical advantages of using combination therapy in regards to virologic response and reduction in viral resistance?
- Is it possible to achieve a clinically meaningful additive or synergistic antiviral effect with drugs that block viral replication by the same basic mechanism?
- Do drugs acting on a particular part of the replication cycle (e.g., minus HBV DNA strand synthesis) add anything to drugs working on a different part of the cycle (e.g., plus strand)?
- Is it possible to maintain low rates of viral resistance indefinitely with combination therapy?

- Does combination therapy prevent the emergence of genotypic resistance or does it just suppress resistant HBV from becoming the dominant form?
- Can the clinical effectiveness of one nucleoside be inhibited by the presence of a second, either through an effect on cellular drug disposal, competition for binding sites, or competition for activating phosphorylating enzymes? This important question requires that the biopharmacology of these agents be better understood.
- What, if any, impact does combination treatment have on intracellular cccDNA?
- Is combination therapy a better first-line therapy for all patients or just individuals more likely to develop resistance or those likely to suffer greater clinical consequences from drug resistance?

References

Delaney WE IV, Yang H, Miller MD, Gibbs CS, Xiong S. Combinations of adefovir with nucleoside analogs produce additive antiviral effects against hepatitis B virus *in vitro*. *Antimicrob Agents Chemother* 2004; 4*:3702-3710.

Fung SK, Chae HB, Fontana RJ, Conjeevaram H, Marrero J, Oberhelman K, Hussain A, Lok ASF. Virologic response and resistance to adefovir in patients with chronic hepatitis B. *J Hepatol* 2006; 44:283-290.

Lau GK, Ribeiro RM, Powers KA, Bowden S, Mommeja-Marin H, Mondou E, Lewin S, Rousseau F, Perelson A, Locarnini S, Naoumov N. Randomized, double-blind study comparing adefovir dipivoxil (ADV) plus emtricitabine (FTC) combination therapy versus ADV alone in HBeAg (+) chronic hepatitis B: efficacy and mechanisms of treatment response. *Hepatology* 40: 272A (abstract 245).

Lai C-L, Leung N, Teo E-K, Tong M, Wong F, Hann H-W, Han S, Poynard T, Myers M, Chao G, Lloyd D, Brown NA, and the telbivudine phase II investigator group. A 1-year trial of telbivudine, lamivudine, and the combination in hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; 129:528-536.

Lau G K-K K, Tsiang M, Hou J, Yuen S-T, Carman WF, Zhang L, Gibbs CS, Lam S-K. Combination therapy with lamivudine and famciclovir for chronic hepatitis B-infected Chinese patients: a viral dynamics study. *Hepatology* 2000; 32:394-399.

Locarnini S, Qi X, Arterburn S, Snow A, Brosgart CL, Currie G, Wulfsohn M, Miller MD, Xiong S. Incidence and predictors of emergence of adefovir resistant HBV during four years of adefovir dipivoxil (ADV) therapy for patients with chronic hepatitis B (CHB). *J Hepatol* 2005; 42:17 (abstract 36).

Turriziani O, Butera O, Gianotti N, Parisi S, Mazzi R, Girardi E, Iaiani G, Antonelli L, Lazzarin A, Antonelli G. Thymidine kinase and deoxycytidine kinase activity in mononuclear cells from antiretroviral-naïve HIV-infected patients. *AIDS* 2005; 19:473-479.

Sung JJYY, Lai JY, Zeuzem S, Chow WC, Heathcote E, Perrillo R, Brosgart C, Woessner M, Scott SA, Campbell FM. A randomized double-blind phase II study of lamivudine (LAM) compared to lamivudine plus adefovir dipivoxil (ADV) for treatment naïve patients with chronic hepatitis B (CHB): week 52 analysis. *J Hepatol* 2003; 38: 25 (abstract 69).