Why do we not yet have combination chemotherapy for chronic hepatitis B?

Joseph J Sasadeusz, Stephen L Locarnini and Graeme Macdonald

ABSTRACT

- Despite the emergence of multidrug-resistant strains of hepatitis B virus (HBV) and previous success with combination therapy for other chronic viral infections, we are still using sequential monotherapy for chronic HBV infection.
- Antiviral-resistant HBV can result in major life-threatening complications.
- We now have complementary drugs, such as lamivudine and adefovir dipivoxil, with fundamentally different structures and associated with different signature resistance mutations, with adefovir dipivoxil showing antiviral activity against most lamivudine-resistant strains.
- Studies of combination therapy to date have used traditional endpoints — short-term reduction of HBV DNA levels and HBeAg seroconversion — rather than evolution of resistance.
- There is now an emerging body of data suggesting that combination therapy can decrease antiviral resistance in HBV infection, the endpoint likely to be of greatest long-term importance, and, rather than adding or replacing an antiviral agent after resistance develops, it is likely to be more effective in treatment-naïve patients

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It is estimated that in excess of 400 million people have chronic infection with hepatitis B virus (HBV), resulting in about 1 million deaths per year globally and an attributable lifetime mortality of about 25%.[1] Data in Australia are incomplete; however, it is estimated that between 90 000 and 160 000 Australians are infected with HBV,[2] which is considerably more than the number infected with HIV and comparable to the estimated 240 000 people infected with hepatitis C virus. Thus, potentially, the burden on the Australian health care system caused by HBV infection will be considerable, and effective therapies are desperately needed.

Towards the end of 2003, a case report of a patient with HBV infection and antiviral resistance to adefovir dipivoxil, after failure of initial therapy with lamivudine, heralded the era of HBV multidrug resistance.[3] Many similar cases have emerged subsequently. It is remarkable that, in the face of these emergent multidrug-resistant strains and previous experience with other chronic viral infections, we are still using sequential monotherapy for the treatment of chronic HBV infection. Physicians with an infectious diseases perspective find this particularly difficult to understand.

The concept of combination therapy has long been established as the paradigm of therapy for a number of chronic infections. In the late 1940s, it was first shown that combination therapy with streptomycin and *p*-aminosalicylic acid could prevent the rapid emergence of streptomycin resistance during therapy for tuberculosis.[4] More recently, the HIV pandemic has given us greater insights into the management of chronic viral diseases. Studies such as the Delta trial using hard clinical endpoints (eg, mortality) unequivocally demonstrated the superiority of combination dual antiviral therapy over monotherapy. Moreover, these early studies showed that initiating dual therapy in treatment-naïve patients gave a superior outcome compared with using a second drug in treatment-experienced patients, proving that an upfront combination that prevented resistance was superior to sequential monotherapy.[5] More recently, it has been shown that triple therapy for HIV infection (ie, adding a protease inhibitor) is superior to dual therapy, thereby further strengthening the case for combination therapy.[6] By contrast, current Australian (Section 100) and international prescribing guidelines for HBV infection either mandate or recommend lamivudine monotherapy for HBV in treatment-naïve patients, resulting in the almost inevitable development of antiviral resistance and setting the scene for the emergence of multidrug resistance.

There are several reasons why combination therapy has not been introduced. Firstly, HBV has a significantly slower rate of evolution of antiviral resistance,[7] with lamivudine resistance occurring in about 20% of patients after a year of therapy, while in HIV resistance has been reported as early as a week after commencing lamivudine.[8] Secondly, unlike HIV, HBV takes much longer after diagnosis to result in death or serious morbidity in most infected patients; hence, there is not the same pressing need to control viral replication and its damaging effects on end organs. Thirdly, the affected populations and communities with HBV infection are not as politically organised or vocally active as those in the HIV community; and, finally, there are more limited classes of drugs available for HBV therapy. As a consequence, the pharmaceutical industry has not been as motivated to work across company barriers and design combination studies.

Despite the above, antiviral-resistant HBV can result in adverse clinical outcomes, such as hepatic decompensation and death.[9-11] More recently, it has been shown that long-term viral replication, even at relatively low levels (previously thought to be insignificant), is associated with the two major life-threatening complications of chronic HBV infection: end-stage liver disease and hepatocellular carcinoma.[12,13] Accordingly, even low levels of viral replication in patients who develop lamivudine resistance have the potential to result in significant adverse clinical outcomes.

There are a number of theoretical reasons why combination therapy should be effective in HBV infection. We now have complementary drugs, such as lamivudine and adefovir dipivoxil, that have fundamentally different structures and are associated with different signature resistance mutations, with adefovir dipivoxil demonstrating antiviral activity against most lamivudine-resistant strains tested.[14] Together, the two drugs have at least additive if not synergistic in-vitro activity,[15] with no overlapping toxicity.[16]

A number of investigators have studied combination therapy in clinical trials with mixed results. Studies of interferons combined with lamivudine have failed to show a consistent benefit in treat-

ment outcome.[17,18] Studies combining nucleotide/nucleoside analogues (eg, lamivudine and adefovir dipivoxil) have primarily been conducted in patients with established lamivudine resistance, rather than in treatment-naïve patients, and shown equivalent efficacy whether adefovir dipivoxil was used as a single agent or combined with lamivudine.[19,20] These data resulted in the strategy adopted in Australia, as well as in many international jurisdictions, of sequential monotherapy with a 3-month overlap during which both drugs are taken, after which lamivudine must be discontinued.

The real issue, however, is the nature of the therapeutic endpoints that have been used in these studies and, specifically, which are the most significant clinical endpoints in the long term. The studies of combination therapy to date have used traditional endpoints — reduction of HBV DNA levels and HBeAg seroconversion — which are undoubtedly important, but the issue of prevention of resistance has been largely overlooked. Resistance is particularly important, as many patients will need long-term, if not indefinite, therapy with the almost inevitable development of lamivudine resistance.

There is now an emerging and consistent body of data suggesting that combination therapy can decrease antiviral resistance, the endpoint likely to be of greatest long-term importance. A major issue here, as in HIV infection, is that it is likely to be more effective using combination therapy in treatment-naïve patients, rather than adding or replacing an antiviral agent after resistance develops. Three separate studies have shown that combination therapy used as initial therapy markedly reduced the emergence of lamivudine resistance. Sung et al showed that the rate of lamivudine resistance in patients treated with a combination of lamivudine and adefovir dipivoxil was only 2%, compared with 20% in patients treated with lamivudine monotherapy.[21] This finding was subsequently supported by two studies of pegylated interferon, which showed significantly reduced rates of lamivudine resistance of 4% and 1% for the combination arms, compared with 27% and 18% for lamivudine monotherapy, in patients with HBeAg-positive and -negative disease, respectively.[17,18]

While the impact of a second agent on lamivudine resistance has become clear, the other issue is whether adefovir dipivoxil resistance can also be reduced using a second agent. A major impediment to answering this question is that adefovir dipivoxil resistance in HBV infection takes even longer to emerge than resistance to lamivudine, suggesting that it would take many years to detect an effect on adefovir dipivoxil resistance. While there was no resistance seen early on in the registration studies of adefovir dipivoxil monotherapy over a relatively short duration of use (eg, 12 months),[22,23] more recent data have shown that adefovir dipivoxil resistance in treatment-naïve patients increases to 29% after 5 years of use.[24] Given the increasing use of adefovir dipivoxil for lamivudine-resistant HBV infection, there is likely to be an exponential rise in resistance, resulting in a potential epidemic of multidrug-resistant HBV. In the face of this, a recent study of 738 patients treated with adefovir dipivoxil for lamivudine-resistant HBV infection documented a significant difference in resistance in patients no longer taking lamivudine, compared with those in whom it was continued and no adefovir dipivoxil resistance was seen.[25] This suggested that lamivudine could protect against adefovir dipivoxil resistance even in a treatment-experienced population.

Recently, pegylated interferons have shown considerable promise in the treatment of HBV infection.[17,18] These agents have not been shown to be associated with the emergence of antiviral resistance; however, only 32% of HBeAg-positive patients achieve seroconversion.[17] In the case of HBeAg-negative patients, only 59% and 43% achieved the endpoints of an HBV DNA level of fewer than 20 000 copies and a normal alanine aminotransferase level, respectively, 24 weeks after cessation of therapy.[18] The durability of this response, in particular in a condition notorious for high relapse rates, is still questionable. While immune modulators can be used as first-line therapy, most patients will still not achieve a response, resulting in a continuing need for long-term nucleotide/nucleoside therapy in those who do not respond, or in those in whom immune modulators are contraindicated or who are intolerant of them.

These data strongly suggest that, as with HIV infection, combination therapy is the way to effectively manage chronic HBV infection in the long term. Even though HBV is a different virus, the emerging data are consistent with what established virological principles would have predicted, as also seen in HIV. Further studies examining the role of de-novo combination therapy are warranted, but now is the time to move to combination therapy for patients who require long-term nucleoside analogue therapy for HBV, rather than waiting for this epidemic to evolve.

Competing interests

See Box.

Author details

Joseph J Sasadeusz, FRCPC, FRACP, PhD, Infectious Diseases Physician[1]
Stephen L Locarnini, PhD, FRC(Path), Divisional Head[2]

Competing interests

Name	Consultant fees	Honoraria/fees for service	Advisory/steering committee fees	Research grants/ clinical trials	Shareholder
Joseph J Sasadeusz		Roche Pharmaceuticals, Gilead Sciences	Roche Pharmaceuticals, Gilead Sciences, Bristol-Myers Squibb	Roche Pharmaceuticals, Gilead Sciences, Bristol-Myers Squibb	
Stephen L Locarnini	Evivar Medical, Gilead Sciences, Pharmasset, Bristol-Myers Squibb	Innogenetics, Bristol-Myers Squibb		Gilead Sciences	Pharmasset
Graeme Macdonald		Roche Pharmaceuticals		Roche Pharmaceuticals, Gilead Sciences, Idenix Pharmaceuticals	

Graeme Macdonald, FRACP, PhD, Director, Department of Gastroenterology and Hepatology[3]

1 Victorian Infectious Diseases Service, and Centre for Clinical Research Excellence in Infectious Diseases, Royal Melbourne Hospital, Melbourne, VIC.

2 Research and Molecular Development, Victorian Infectious Diseases Reference Laboratory, Melbourne, VIC.

3 Princess Alexandra Hospital, and Centre for Diabetes and Endocrine Research, University of Queensland, Brisbane, QLD.

Correspondence: Joe.Sasadeusz@mh.org.au

References

1 Lai C, Ratziu V, Yuen M-F, Poynard T. Viral hepatitis B. *Lancet* 2003; 362: 2089-2094.

2 O'Sullivan B, Gidding H, Law M, et al. Estimates of chronic hepatitis B virus infection in Australia, 2000. *Aust N Z J Public Health* 2004; 28: 212-216.

3 Angus P, Vaughan R, Xiong S, et al. Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. *Gastroenterology* 2003; 125: 292-297.

4 Kucers A. Evolution of antituberculous therapy. In: Kucers A, Crowe S, Grayson M, Hoy J, editors. The use of antibiotics. 5th ed. Oxford: Butterworth-Heinemann, 1997: 1194.

5 Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996; 348: 283-291.

6 Hammer S, Squires K, Hughes M, et al; AIDS Clinical Trials Group 320 Study Team. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997; 337: 725-733.

7 Delaney WI, Locarnini S, Shaw T. Resistance of hepatitis B virus to antiviral drugs: current aspects and directions for future investigation. *Antivir Chem Chemother* 2001; 12: 1-35.

8 Wainberg M, Salomon H, Gu Z, et al. Development of HIV-1 resistance to (-)2'-deoxy-3'-thiacytidine in patients with AIDS or advanced AIDS-related complex. *AIDS* 1995; 9: 351-357.

9 Liaw YF, Chien R, Yeh C, et al. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999; 30: 567-572.

10 Locarnini S, Hatzakis A, Heathcote J, et al. Management of antiviral resistance in patients with chronic hepatitis B. *Antivir Ther* 2004; 9: 679-693.

11 Liaw Y, Sung J, Chow W, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; 351: 1521-1531.

12 Chen C, Yang H, Su J, et al. Viral load is a strong predictor of liver cirrhosis risk in people chronically infected with hepatitis B virus regardless of hepatitis B e antigen status. *J Hepatol* 2005; 42 Suppl 2: 172.

13 Chen G, Lin W, Shen F, et al. Viral load as a predictor of mortality from hepatocellular carcinoma and chronic liver disease in chronic hepatitis B infection. *J Hepatol* 2005; 42 Suppl 2: 173.

14 Westland C, Yang H, Delaney WE 4th, et al. Activity of adefovir dipivoxil against all patterns of lamivudine-resistant hepatitis B viruses in patients. *J Viral Hepat* 2005; 12: 67-73.

15 Colledge D, Civitico G, Locarnini S, Shaw T. In vitro antihepadnaviral activities of combinations of penciclovir, lamivudine, and adefovir. *Antimicrob Agents Chemother* 2000; 44: 551-560.

16 Dando T, Plosker G. Adefovir dipivoxil. A review of its use in chronic hepatitis B. *Drugs* 2003; 63: 2215-2234.

17 Lau G, Piratvisuth T, Luo K, et al; Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; 352: 2682-2695.

18 Marcellin P, Lau G, Bonino F, et al; Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004; 351: 1206-1217.

19 Perrillo R, Hann H, Mutimer D, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004; 126: 81-90.

20 Peters M, Hann HH, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B *Gastroenterology* 2004; 126: 91-101.

21 Sung JJY, Lai JY, Zeuzem S, et al. A randomised double-blind phase II study of lamivudine (LAM) compared with lamivudine plus adefovir dipovoxil (ADV) for treatment naïve patients with chronic hepatitis B (CHB): week 52 analysis. Abstract 69. *J Hepatol* 2003; 38 Suppl 2: 25-26.

22 Marcellin P, Chang T, Lim S, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; 348: 808-816.

23 Hadziyannis S, Tassopoulos N, Heathcote E, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; 348: 800-807.

24 Locarnini S, Qi X, Arterburn S, et al. 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 Suppl 2: 17.

25 Lampertico P, Marzano A, Levrero M, et al. A multicenter Italian study of rescue adefovir dipivoxil therapy in lamivudine resistant patients: a 2-year analysis of 650 patients. 41st Annual Meeting of the European Association for the Study of the Liver; 2006 Apr 26–30; Vienna, Austria. Abstract 116.

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