

LEADING ARTICLE

Combination therapy for hepatitis B

A M Di Bisceglie

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Hepatitis B virus is a major cause of morbidity and mortality worldwide. Effective therapies were first introduced in the mid-1980s but frequent and sometimes severe side effects limit their use. Combination therapy represents the future of treatment for chronic hepatitis B, probably consisting of two or more nucleoside analogues although interferon may form part of some combinations. New drugs acting by different antiviral mechanisms may be particularly potent in combination.

Infection with the hepatitis B virus (HBV) remains a major cause of morbidity and mortality worldwide. Although safe and effective vaccines have been in use for nearly two decades and have begun to have measurable impact, their full effect will take decades to be evident. Effective therapies against hepatitis B were first introduced in the mid-1980s when it became apparent that prolonged therapy with alpha interferon resulted in clearance of active HBV infection in 30–40% of treated patients compared with only 10–12% of controls.¹ However, the use of interferon is associated with frequent and sometimes severe side effects which may limit its use.

The development of second generation nucleoside analogues represented the next major step in the control of hepatitis B and lamivudine is now commonly used in the treatment of this chronic viral infection.² Unfortunately, it appears that many individuals require prolonged therapy for 12 months or more with lamivudine for control of HBV infection and this prolonged use of a single nucleoside analogue is associated with development of viral resistance in about 15% of patients per year.³ The basis for becoming resistant to lamivudine is mutations within the YMDD amino acid domain of the HBV DNA polymerase. Although this viral resistance is usually only associated with mild reactivation of hepatitis, the resulting liver disease may occasionally be very severe.

COMBINATION THERAPY: HISTORICAL PERSPECTIVE

Several antiviral and immunomodulatory agents have been tested in combination as therapy for chronic hepatitis B. Some of these combinations included alpha and gamma interferon, alpha interferon and acyclovir, prednisone and interferon, and so on. Some appeared to offer marginal benefit but others had no benefit and even appeared to have additive toxicity.⁴ However, these early studies illustrated many of the pitfalls to be encountered later in subsequent studies of

two or more drugs in combination for the treatment of chronic hepatitis B. Firstly, each drug should ideally be proven to have therapeutic benefit when used individually. This tenet was somewhat undermined in the case of chronic hepatitis C where ribavirin was found to clearly add significantly to the antiviral effect of alpha interferon but had little effect by itself. The timing of combination therapy is also problematic. Should both drugs be used simultaneously or should their use be staggered? If staggered, which drug should come first? Should both be given for the same period of time? For example, the combination of prednisone and interferon appears to work best when prednisone is given first and then interferon. Perrillo *et al* found that prednisone given for six weeks prior to starting interferon was more effective than interferon alone in a subgroup of patients with low serum aminotransferases.⁵ Here it may have been the effect of withdrawal of prednisone which was critical, resulting in a mild flare of hepatitis and therefore optimising the action of interferon.

RECENT STUDIES OF COMBINATION THERAPY

Perhaps the most appealing of possible current combinations is lamivudine and alpha interferon. Both of these agents, separately, are potent antivirals. Both agents have been widely used and physicians have experience in their administration. But there have been very few adequate studies of this combination. In one of the largest of such studies, Schalm *et al* investigated 230 patients with chronic hepatitis B who were randomised to interferon alone, lamivudine alone, or the combination.⁶ They found that the rate of seroconversion (loss of hepatitis B e antigen (HBeAg) and development of anti-hepatitis B e antibodies (anti-HBe)) was not significantly different between the three groups (19% with interferon alone, 18% with lamivudine alone, and 29% with the combination). However, the fact that the response rate was somewhat greater in the combination group led the authors to speculate that a larger study might prove that the combination was superior.

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The timing of administration of the two drugs in combination in this trial may not have been

Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HIV, human immunodeficiency virus.

See end of article for author's affiliation

Correspondence to: Dr Di Bisceglie, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Saint Louis University School of Medicine, 3635 Vista Ave, St Louis, Mo 63110, USA; dibiscam@slu.edu

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ideal. Lamivudine was given for 52 weeks by itself, interferon was given for 16 weeks by itself, and in the combination group, lamivudine was given for 24 weeks with interferon being administered in the latter 16 weeks of therapy. Thus the treatment periods were uneven but the response to therapy in all groups was measured at 52 weeks from the start of treatment.

The role of interferon in combination with a nucleoside analogue has by no means been completely explored. Interferon has the ability to eliminate active HBV infection, evidenced by clearance of HBeAg and high levels of HBV DNA while with nucleoside analogues the focus is more on suppression of HBV replication. Interferon presumably exerts part of its action through the immune system. The concept of reducing HBV replication to very low levels with nucleoside analogues and then delivering a "death blow" to the virus with the addition of interferon is very appealing. Similarly, it could be argued that a drug such as lamivudine might be used first as it has been found to restore immune reactivity to HBV antigens. Once that has been accomplished, interferon might be more effectively applied.

A recent study of the combination of famciclovir and lamivudine was interesting as it revealed a synergistic effect of the two drugs. Famciclovir has been known for some time to have an antiviral effect against HBV although this effect is not considered particularly potent. None the less, studies of viral kinetics allowed the study of synergy in antiviral effect. Thus Lau *et al* studied 21 patients with chronic HBeAg positive hepatitis B.⁷ Nine were randomised to receive lamivudine alone at a dose of 150 mg/day while the other 12 received both lamivudine and famciclovir 500 mg three times a day for a total of 12 weeks. Although only one subject in the first group and two in the second experienced HBeAg seroconversion, studies of viral dynamics revealed that the fraction of baseline viral production persisting during therapy was 1.2% for the combination versus 6% with lamivudine alone, a fivefold difference in viral suppression. It is unlikely that this combination will become commonly used as other more potent drugs will replace famciclovir. However, this study illustrates some of the potential of combination therapy.

THE FUTURE OF COMBINATION THERAPY

Clearly however combination antiviral therapy represents the future for treatment of chronic HBV. There are several nucleoside analogue agents under development which have potent antiviral activity against HBV, including adefovir dipivoxil, entecavir, L-dT, L-dC, FTC, L-FMAU, and DAPD, among others.⁸ It is likely that combinations of these drugs could be used to control HBV infection, just as is done for human immunodeficiency virus (HIV) infection. Not only are combinations likely to be more effective (several have slightly different mechanisms of action) in inhibiting HBV infection but they are also likely to minimise the risk of development of drug resistant viral mutants, again analogous to combination therapy for HIV infection.

"Combination antiviral therapy represents the future for treatment of chronic HBV"

Combinations may also allow minimisation of the toxicity of nucleoside analogues. For example, adefovir is well known as causing nephrotoxicity, in particular a Fanconi-like syndrome with phosphate wasting and reversible renal insufficiency. This toxicity is very much dose dependent and occurs relatively commonly at doses of 60 mg/day for periods of more than six months but is rare at smaller doses. Combinations of adefovir with other antiviral agents may allow very low doses of adefovir to be used with minimal risk of renal toxicity.

The recent development of cell culture and animal models of HBV infection has proved to be critical in assessing anti-

viral drugs in combination. Specifically, the 2.2.15 cell line based on hepG2 cells transfected with HBV DNA and woodchucks infected with woodchuck hepatitis virus have allowed both in vitro and in vivo assessment of antiviral activity of new antiviral agents against hepatitis B prior to their administration to humans.^{9,10}

Antiviral drugs that have different mechanisms of action will be very interesting to test in combination. Non-nucleoside reverse transcriptase inhibitors and polymerase antagonists, as used to treat HIV infection, have not yet been developed against hepatitis B although drugs depending on an entirely new mechanism of action may appear.

"Antiviral drugs that have different mechanisms of action will be of great interest to test in combination"

For example, Block *et al* have recently described agents that inhibit folding and trafficking of HBV proteins.¹¹ These alpha glucosidase inhibitors may lack potency against HBV by themselves but may be very effective when used in combination with a nucleoside analogue reverse transcriptase inhibitor.

One of the major obstacles to the development of combination therapy is the current regulatory environment. Manufacturers feel the need to develop each new agent separately. Certainly there is little or no incentive for two manufacturers to test their new drugs in combination. In the USA at least, the Food and Drug Administration has not proved very receptive to the study of drug combinations and yet the potential safety advantages of combinations in decreasing the risk of viral resistance should be obvious to regulatory authorities. They should encourage manufacturers to work with each other to study their drugs in combination. Funding agencies such as the National Institutes of Health should consider sponsoring studies of combinations of new drugs, as their support would go a long way towards clearing regulatory obstacles and would facilitate drug manufacturers working with each other. Patient advocacy was instrumental in accelerating the development of combination therapy for HIV infection and acquired immunodeficiency syndrome. This approach may also be useful or even required for hepatitis B.

SUMMARY AND CONCLUSIONS

It seems inevitable that combination therapy will eventually be used for chronic hepatitis B. This therapy will probably consist of two or more nucleoside analogues although interferon may form part of some combinations. New drugs acting by different antiviral mechanisms may be particularly potent in combination. The problem is, how do we get from here to there? How do we overcome the regulatory and other obstacles to testing antiviral drugs in combination? This may require a combination of advocacy by researchers and patients, and goodwill by drug manufacturers. Drug companies that have more than one drug in their "stable" will be at an advantage as they will at least have access to the compounds to be tested in combination. Study designs will have to be very carefully thought out to test whether combinations work better than individual drugs alone. The sooner we all recognise that combination therapy represents the future of treatment for chronic hepatitis B, the sooner we can get there.

Author's affiliation

A M Di Bisceglie, Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St Louis, Mo, USA

Conflict of interest:

Dr Di Bisceglie has been a consultant for SciClone Pharmaceuticals (alpha thymosin) and InterMune (gamma interferon), provided research support for Schering Plough (interferon, ribavirin, PEGylated interferon), Roche (PEGylated interferon, ribavirin), and Gilead Sciences (adefovir

dipivoxil), and been part of the scientific advisory board for Roche, CMI (Center for Medical Innovation), Novirio (L-dT, L-dC), and MDS Nordion (Therasphere).

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