Therapy for chronic hepatitis B : nucleoside analogues in adult and pediatric patients

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Introduction

Chronic viral hepatitis is a disease of global importance with a wide range of prevalence in various countries throughout the world and with considerable associated morbidity and mortality including cirrhosis and hepatocellular carcinoma . Hepatitis B is the most prevalent chronic viral infection affecting more than 300 million people worldwide (1). Acquisition of viral hepatitis B in children leads to chronicity more often than in adults. Approximately 30% of all deaths in patients with chronic hepatitis B are related to sequelae of underlying liver disease. More than 1 in 100 infants born around the world are expected to die due to hepatitis B virus (HBV) infection annually. Vaccination has been effective for prevention of hepatitis B and the introduction of interferon therapy has been an important step in trying to halt disease progression and prevent the long-term morbidity and mortality of viral hepatitis in children.

The therapeutic effectiveness of interferon has been well documented for adults with chronic hepatitis B with 30-40% of patients responding with loss of HBeAg and HBV DNA from serum and improvement in liver disease activity. Many patients go on to lose HBsAg from serum too. Trials done in several countries suggest that interferon may be equally effective in children (2). In general, alpha interferon appears to be well tolerated in children. Similar side effects to those seen in adults also occur in children but are usually less severe. Though interferon appears to be successful in achieving remission of active hepatitis B in both adults and children, this effect is not universal. Interferon is unlikely to be of benefit in patients with normal serum aminotransferases or those who are positive for HBsAg but negative for HBeAg. The role of interferon in immunosuppressed adults is uncertain and is probably best avoided in children.

Nucleoside analogues in hepatitis B

Nucleoside analogues have become the mainstay of therapy for several viral infections including herpesvirus, cytomegalovirus and the human immunodeficiency virus (HIV). Many of these agents have been tried in patients with HBV infection but are currently not used due to lack of efficacy or unacceptable toxicity. These included adenine arabinoside (vidarabine) and its monophosphate, acyclovir, didadinosine, zidovudine and ribavirin. Recently *in vitro* and *in vivo* models of chronic HBV infection have led to the identification of orally bioavailable agents with marked inhibitory activity against hepatitis B (3-5). These include the second generation nucleoside analogues fialuridine (1-(2-deoxy-2-fluoro-ß-D-arabinofuranosyl)-5-iodouracil, or FIAU), 3'-thiacytidine or 3-TC (lamivudine) and famciclovir. Though preliminary studies using fialuridine for two- and four-week courses showed that it led to marked suppression of serum HBV DNA levels and was well tolerated in patients with chronic hepatitis B, a recent phase 2 trial was terminated because of severe multisystem toxicity including hepatic failure, lactic acidosis, pancreatitis, neuropathy and myopathy (6). This toxic reaction was attributed to widespread mitochondrial damage which was not evident in previous *in vitro* studies.

Currently, the two most promising agents that appear to be effective against hepatitis B and also have a good safety profile are lamivudine and famciclovir. These drugs have not yet been evaluated in children but are currently undergoing large scale clinical studies in adults with hepatitis B. Other agents which are being tested in adult patients with HBV infection are adefovir and lobucavir. If proven to be effective in adults, these nucleoside analogues may offer an alternative to children with hepatitis B, especially those who fail interferon, relapse after interferon or those who are not candidates for interferon therapy.

Lamivudine (3'-thiacytidine or 3-TC)

Lamivudine, the negative enantiomer of 2'-deoxy-3'thiacytidine has been shown to markedly inhibit HBV replication both *in vitro* and *in vivo* (4,7). In previous phase I and phase II clinical trials in patients with HBV, lamivudine given for 1 to 3 months resulted in marked reduction of HBV DNA levels in serum but this effect

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was temporary. In the study by Dienstag and colleagues (8), lamivudine was given in doses of 25, 100 or 300 mg daily for 12 weeks to 32 patients. Levels of HBV DNA in serum became undetectable in 70% of patients receiving 25 mg and 100% of receiving either 100 or 300 mg. Discontinuation of the drug was associated with a reappearance of HBV DNA in serum in most patients. Six patients (19%) had sustained suppression of HBV DNA and four of these six (12%) lost HBeAg.

In a subsequent dose-ranging study by Nevens and colleagues (9), lamivudine was administered for 24 weeks at daily doses of 25, 100 and 300 mg to 51 patients with active HBV infection. At the end of treatment, serum HBV DNA was undetectable in 58%, 93% and 88% of patients receiving 25, 100 and 300 mg respectively. This effect was transitory and serum HBV DNA rose to pretreatment levels in the majority of patients. In addition to the fall in HBV DNA levels, quantitative decreases in both HBeAg and HBsAg were seen with all doses. Four patients (8%) lost HBeAg and developed anti-HBe during the study, however, only two (4%) maintained this response at the end of follow-up. In this study, 49% were of Asian origin and 29% had normal ALT prior to treatment. However, this did not appear to influence the responses seen between the different groups. Lai and colleagues reported on the use of lamivudine given for 4 weeks in 42 Chinese patients with active HBV infection (10). All patients receiving lamivudine had a decrease in serum HBV DNA values of $>$ 90% at daily doses of 25, 100 and 300 mg compared to placebo. All patients remained HBeAg positive through the study period. These studies show that lamivudine is effective in suppressing HBV DNA even in Asian patients who are usually considered difficult to treat because of high levels of viremia and normal or near normal levels of serum ALT which makes them poor candidates for interferon therapy. In general, all studies have shown that a single dose of 100 mg is effective in inducing viral suppression and higher daily doses (300 or 600 mg) or twice daily dosing did not lead to significantly different results.

Though most studies to date have shown that lamivudine produces a rapid and profound decrease in serum HBV DNA levels, the effect was not sustained and very few have lost HBeAg. In a recent report of 24 patients who received extended duration of lamivudine for a median of 52 weeks (range, 4-60 weeks), 39% lost HBeAg and 9% lost HBsAg (11). These results are very encouraging and show that longer duration of treatment may be needed to achieve sustained loss of viral replication.

Similar to interferon, histological improvement has been seen with lamivudine treatment. In the study by Honkoop and colleagues (12), of the 13 patients who were treated for 24 weeks and who became HBV DNA negative during treatment, histology improved in 7 (54%). Improvement was seen in portal and periportal inflammation, but the most significant was a reduction in piecemeal necrosis. These results suggest that prolonged viral suppression can induce histological improvement possibly by reducing the immunological damage to the liver even in the absence of HBeAg seroconversion. In addition, these investigators have also shown that treatment with lamivudine does not induce any signs of mitochondrial toxicity in the livers of these patients. The combination of viral suppression along with improvement in histological activity seen with lamivudine may have a major impact in reducing the long-term sequelae of chronic HBV infection, including the development of cirrhosis and hepatocellular carcinoma. Larger controlled trials for longer periods are currently underway in the United States, Europe and Asia which will give us a better understanding about the rates of HBeAg seroconversion and histological improvement with lamivudine in patients with HBV infection.

Lamivudine is generally well tolerated when given up to 24 weeks to patients with HBV infection (8-10). In HIV-infected patients, lamivudine has been given in doses up to 20 mg/kg per day for 6 months or more with minimal toxicity. Most common side effects reported with the use of lamivudine are nausea and vomiting, headaches, abdominal discomfort, diarrhea, dizziness and fatigue. Usually, these symptoms are mild and transient. Asymptomatic elevations of amylase and lipase have been reported but symptomatic pancreatitis is rare. Peripheral neuropathy, arthralgias, myalgias and skin rash have also rarely been reported. In addition, elevations of serum aminotransferases have been seen with lamivudine but they appear to usually resolve in spite of continuing the drug. Unlike FIAU, lamivudine and most other antiviral nucleoside analogues lack a 3'-hydroxyl group and therefore are not incorporated into nascent DNA, which prevents serious hepatotoxicity.

Though clinical experience using lamivudine is very limited in children with HBV infection, phase I/II dose-ranging studies have been performed in children with symptomatic HIV infection (7). In general, the tolerability of lamivudine in children and adolescents appears to be similar to that seen in adults with either HIV or HBV infection. Currently, a multi-center dose-ranging study using lamivudine in children with chronic hepatitis B is underway in Europe.

Reactivation of hepatitis B with elevations in serum aminotransferases has been reported following discontinuation of lamivudine (9,13). These elevations accompany the return of measurable serum HBV DNA. Most patients remain asymptomatic and spontaneous resolution is usual. However, decompensation of underlying liver disease has been noted with elevations of serum bilirubin and prolongation of prothrombin time. This should be an important consideration especially when one uses lamivudine in patients with marginally compensated or decompensated cirrhosis.

In patients undergoing orthotopic liver transplantation (OLT) for end-stage liver disease due to hepatitis B,

recurrence of disease in the allograft is common especially if the patient has evidence of active viral replication at the time of transplant. The severity of the recurrent infection is variable and can lead to rapidly progressive liver injury with development of cirrhosis. As prophylaxis to prevent reinfection of the allograft after OLT, the most successful approach has been the use of high dose hepatitis B immune globulin (HBIG) to passively neutralize the virus. Despite this progress, the administration of HBIG is cumbersome, expensive and the supply is limited in most countries where liver transplantation is performed. The efficacy of lamivudine is currently being studied in several settings. These include patients with decompensated cirrhosis who are undergoing OLT, prophylaxis against reinfection of the liver allograft and in patients with recurrent disease post-OLT. Early reports have shown that lamivudine can suppress HBV DNA to undetectable levels is patients pre- and post-OLT and prevent reinfection of the allograft (14-18). Prophylactic therapy has been shown to result in HBsAg loss post-OLT even in the absence of HBIG. However, this has not always been successful because of the emergence of mutants and reactivation of hepatitis B which has been associated with prolonged therapy under high dose immunosuppression (19-21). The mutations involve the DNA polymerase gene which are associated with a delayed rise in serum HBV DNA levels and elevation of serum aminotransferases but are not always associated with clinical deterioration. Once lamivudine is discontinued, the wild type (WT) HBV may re-emerge as the dominant species. The most common mutation involves the highly conserved YMDD motif of the active site of the DNA polymerase with a valine or isoleucine substitution of methionine at position 552 (M552V or M552I). These mutations are similar to those seen with lamivudine in patients with HIV infection. Another mutation involves a leucine to methionine substitution at position 528 (L528M) of the DNA polymerase gene. Unfortunately, such mutations have also been reported in immunocompetent patients with chronic HBV infection when lamivudine is administered for prolonged periods (11,22). This suggests that the selection of these mutations is probably a result of selective pressure due to immunosuppression and or long-term therapy on lamivudine.

Famciclovir

Famciclovir is a well absorbed oral form of penciclovir which has potent activity against herpes simplex virus. Famciclovir at doses of 5-25 mg/kg has been shown to inhibit viral DNA in ducks chronically infected with the duck HBV (23). In a double-blind controlled study of famciclovir given for 10 days, HBV DNA levels fell by $< 90\%$ in patients receiving 1,500 mg daily (24). Large scale multi-center studies are currently underway using famciclovir for longer duration in adult patients with chronic HBV infection.

Similar to lamivudine, famciclovir has been used as prophylaxis in patients undergoing OLT and in patients with recurrent hepatitis B post-OLT (25,26). Once again, the results have been encouraging and famciclovir appears to be well tolerated even with prolonged administration. As with lamivudine, mutations involving the DNA polymerase gene have also been described with the use of famciclovir. Additional studies which are needed to assess the efficacy of famciclovir pre- and post-OLT, in patients with end-stage liver disease due to HBV infection, have been initiated.

Combination Therapy

As in the case of HIV therapy, there has been interest in combining therapeutic agents for the management of HBV infection. Possible combinations include combining two or more antiviral agents *or* an antiviral agent and an immunomodulator such as interferon. A recent report has shown a synergistic inhibition of hepadnaviral replication by lamivudine in combination with penciclovir *in vitro* (27). Currently, a phase III study on long-term combination therapy with lamivudine and interferon alpha 2b is underway. Further studies are needed to determine the efficacy, toxicity and the incidence of drug-resistant mutants when these agents are given in combination for prolonged periods in patients with chronic HBV infection.

Conclusion

We are entering a new and exciting era in the management of HBV infection both in immunocompetent patients and in patients undergoing liver transplantation. Several new nucleoside analogues have been identified and large multi-center studies are currently under way to study the efficacy and toxicity of prolonged therapy with these agents. In addition, the role of combination therapy using two or more nucleoside analogues or nucleoside analogues and immunomodulators on the long-term course of chronic HBV infection remains to be determined.

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