Antiviral therapy for chronic hepatitis B: are we doing any good to patients?

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At the recent National Institutes of Health Consensus Development Conference, the value of antiviral therapy for chronic hepatitis B in improving clinical outcome was hotly debated. In patients with chronic hepatitis B, antiviral therapy has proved effective in viral load reduction, alanine aminotransferase normalization and histological improvements. However, its efficacy in reducing decompensated liver disease, hepatocellular carcinoma and liver-related death remains unclear. To date, animal studies and observational studies, but very few randomized controlled trials, have shown improved clinical outcomes after antiviral therapy. The difficulties of conducting clinical trials using clinical endpoints are highlighted. Before more clinical outcome data are available, it is important to validate the clinical implications of surrogate markers including biochemical, virological and histological responses.

Keywords: hepatocellular carcinoma, interferon alfa-2a, lamivudine, liver cirrhosis, viral DNA

Introduction

Chronic hepatitis B is one of the most common causes of hepatocellular carcinoma (HCC) and cirrhosis. At present, two immunomodulatory agents (conventional interferon α and peginterferon α-2a) and five oral nucleos(t)ide analogues (lamivudine, adefovir dipivoxil, entecavir, telbivudine and tenofovir) have been registered in the USA and Europe. In registration trials, these drugs have been shown to result in hepatitis B virus (HBV) DNA reduction, alanine aminotransferase (ALT) normalization and histological improvements. In hepatitis B e antigen (HBeAg)-positive patients, HBeAg seroconversion can be achieved in ~30% with peginterferon and in 20% with oral antiviral treatment for 1 year. In addition, up to 11% of HBeAg-negative patients developed hepatitis B surface antigen (HBsAg) seroclearance 4 years after peginterferon treatment. At a recent National Institutes of Health Consensus Development Conference, the value of antiviral therapy for chronic hepatitis B in improving clinical outcome was hotly debated. The bottom line is: do all these surrogate parameters that improve with antiviral therapy translate into improved survival of patients?

Since high levels of ALT, HBV DNA, HBeAg and cirrhosis are associated with the development of HCC, therapy with antiviral therapy for chronic hepatitis B in improving clinical outcome was hotly debated. In patients with HBV DNA ≥1 million copies/mL. If we randomize only patients with HBV DNA >1 million copies/mL and assume that all patients enrolled in the active treatment arm can have HBV DNA suppressed to an undetectable level, we still need to follow >600 patients for 5 years to detect a difference in HCC incidence.

Difficulties in hepatitis studies

To test whether antiviral therapy in chronic hepatitis B does any good, the best study should be an adequately powered placebo-controlled, double-blind, randomized controlled trial using HCC and/or liver-related mortality as the primary endpoint. The first hurdle is the sample size and duration of follow-up. Cirrhosis and its complications take years, if not decades, to develop. In the REVEAL Study, the incidence of HCC was only 108 per 100000 person-years in patients with undetectable HBV DNA, compared with 1152 per 100000 person-years in those with HBV DNA ≥1 million copies/mL. If we randomize only patients with HBV DNA >1 million copies/mL and assume that all patients enrolled in the active treatment arm can have HBV DNA suppressed to an undetectable level, we still need to follow >600 patients for 5 years to detect a difference in HCC incidence.
Even if sufficient resources can be gathered to run a large trial, one would face the ethical dilemma of putting some patients on placebo. For a clinical trial to be ethical, the usual design is to compare routine clinical treatment with supposedly better new treatment. At present, antiviral therapy for chronic hepatitis B has become standard practice. In other words, a placebo-controlled trial would mean comparing routine treatment with no treatment. It would be difficult to obtain ethical approval for such a trial, not to mention the more challenging task of getting patient consent, especially if they have cirrhosis or persistently abnormal ALT. Alternatively, potent antiviral drugs may be compared with less potent ones to partially resolve the ethical issues. However, the provision of treatment would likely lower the event rate in the comparison arm, further increasing the sample size to an astronomical level.

Animal studies

Alternatively, the efficacy of antiviral therapy in improving HCC-free mortality may be tested in animal models. The woodchuck and duck models are favourite animal models for the study of antiviral therapy. HBV belongs to the Hepadnaviridae family, which also includes other mammalian and avian viruses such as the woodchuck hepatitis virus (WHV), ground squirrel hepatitis virus, arctic squirrel hepatitis virus, woolly monkey hepatitis virus, duck hepatitis B virus, heron hepatitis virus and snow goose hepatitis virus. Woodchucks chronically infected with WHV often develop HCC within the first 2–4 years of life, and can serve as a good model to test the effect of antiviral therapy.12

In one study, woodchucks with chronic WHV infection received entecavir.13 Among animals that stopped treatment, three had sustained virological response and did not develop HCC for up to 28 months. In contrast, all animals with virological relapse died of HCC. Six other animals continued entecavir. Four of them had HBV DNA near the lower limit of detection and did not develop HCC for up to 22 months.

In another study, woodchucks chronically infected with WHV received clevudine and/or WHV surface antigen vaccine or placebo. Compared with placebo, clevudine and/or vaccine suppressed viraemia and hepatic viral load, reduced liver injury and delayed the onset of HCC.14 However, among animals with established HCC, clevudine did not prolong the tumour doubling time.

In contrast, another study using lamivudine failed to demonstrate a reduction in HCC or mortality in woodchucks.15 However, the difference might be explained by the use of a weaker antiviral agent, and the short duration and late administration of treatment. Overall, these studies support the notion that sustained viral suppression can limit liver injury and delay/prevent HCC, especially when the treatment is started before significant liver injury has occurred.

Current clinical evidence

At present, only one placebo-controlled, randomized controlled trial involving multiple centres in Asia exists in the literature using clinical outcomes as primary endpoints.16 In this study, 651 chronic hepatitis B patients with histologically confirmed cirrhosis or advanced fibrosis were randomized to receive lamivudine or placebo in a 2:1 ratio. The primary endpoint was disease progression, defined by the first occurrence of any of the following: an increase of at least 2 points in Child–Pugh score, spontaneous bacterial peritonitis, renal insufficiency, variceal bleeding, HCC or liver-related death. According to the original protocol, the follow-up duration was going to be 5 years. Owing to significant differences in endpoints at an interim analysis, the study was terminated prematurely after a median duration of treatment of 32 months.

Endpoints were reached by 7.8% of the patients receiving lamivudine and 17.7% of those receiving placebo [hazard ratio (HR) 0.45; confidence interval (CI) 0.28–0.73]. A close scrutiny of the results showed that the endpoints were almost entirely explained by an increase in Child–Pugh score (3.4% versus 8.8%; HR 0.45; 95% CI 0.22–0.90) and HCC (3.9% versus 7.4%; HR 0.49; 95% CI 0.25–0.99), both with borderline statistical significance. There was no difference in the incidence of renal insufficiency or variceal bleeding. No patient in either group developed spontaneous bacterial peritonitis or died from liver disease.

Although this study is arguably the best evidence in the current literature, major limitations remain. First, while it is generally accepted that studies should be monitored and stopped for safety reasons, premature termination of a study for efficacy is debatable. In fact, the difference in the incidence of HCC was of borderline significance (P=0.047). After adjusting for multiple testing due to repeated interim analyses, this difference should not be taken as significant. Moreover, the incidence of HCC did not differ between the two groups after excluding five patients who developed HCC in the first year of treatment (P=0.052). Second, a 2 point increase in Child–Pugh score has not been validated and should just be considered as another surrogate marker instead of a hard clinical outcome. Third, lamivudine is a drug with a low genetic barrier to resistance. In up to 70% of patients lamivudine resistance develops within 4 years.17 Drug resistance leads to virological and biochemical breakthrough and negation of histological improvements.18 Indeed, patients harbouring YMDD mutants experienced more clinical endpoints than those without mutants.16 It is possible that the study would have been negative if it had been continued to the end of 5 years.

A recent meta-analysis tested the hypothesis that antiviral therapy in chronic hepatitis B reduces the risk of HCC. Among 12 studies comparing interferon with placebo or no treatment (n=2742), the risk of HCC after treatment was reduced by 34% (relative risk 0.66; 95% CI, 0.48–0.89). Among five studies comparing lamivudine with placebo or no treatment (n=2289), the risk of HCC was reduced by 78% (relative risk 0.22; 95% CI 0.10–0.50). Like all meta-analyses, the conclusion is affected by publication bias and the quality of the original studies. Importantly, only two studies were randomized controlled trials, and most did not use HCC as the primary endpoint.

Liver fibrosis and cirrhosis

In the past, liver fibrosis and cirrhosis were thought to be largely irreversible. Since effective antiviral therapy has become available, this concept has been shown to be wrong. In 1 year randomized controlled trials, lamivudine, adefovir, entecavir, telbivudine and peginterferon improved liver fibrosis and reduced progression to cirrhosis.20 In a cohort of 63 patients treated with
lamivudine for 3 years, 12 of 19 patients with bridging fibrosis and 8 of 11 patients with cirrhosis at baseline had improvement in fibrosis stage by 1 point or more.31 In theory, liver cirrhosis is the single most important risk factor for HCC and other liver-related complications. The prevention of cirrhosis should translate into improved clinical outcomes.

Because the assessment of liver fibrosis requires liver biopsies, large studies on fibrosis progression require multiple serial biopsies and are difficult to conduct. In recent years, serum markers (e.g. FibroTest) and transient elastography have been validated as reasonable non-invasive tests to estimate liver fibrosis and cirrhosis in patients with various chronic liver diseases.22–24 If these tests are validated to be sensitive in detecting changes in fibrosis over time, they may become useful tools in the evaluation of the efficacy of antiviral therapy.

Validation of surrogate markers

Before a definitive clinical trial is available, it is important to validate the surrogate markers reported in clinical trials. Since natural evolution of surrogate markers may be different from the changes induced by treatment, the surrogate markers should be validated in patients on antiviral therapy. For example, HBeAg seroconversion after lamivudine treatment is less durable than spontaneous HBeAg seroconversion. In a Korean series of 34 patients who achieved HBeAg seroconversion after lamivudine treatment, 49% developed virological relapse at 2 years; accompanied by HBeAg reversion in 81% of cases.25

Common surrogate markers reported in hepatitis studies include biochemical response (normalization of ALT), virological response (HBV DNA suppression, HBeAg seroconversion and HBsAg seroclearance) and histological response (improvement in necroinflammation and fibrosis). To date, HBsAg seroclearance is closest to a cure of the disease. In patients with spontaneous HBsAg seroclearance before age 50 years, the risk of HCC is minimal.26 Up to 11% of HBeAg-negative patients treated with peginterferon have HBsAg seroclearance 4 years after treatment, and 3% of HBeAg-positive patients develop HBsAg seroclearance after 1 year of tenovir treatment.5,27 It is important to follow the long-term outcomes of these patients to know the benefit of HBsAg seroclearance in reducing the incidence of decompensated liver disease and HCC.

Oral antiviral drugs suppress HBV replication but not the production of other proteins such as HBsAg. Therefore, quantitative HBsAg has emerged as a potential test to reflect intrahepatic total HBV DNA and covalently closed circular DNA (cccDNA).28 Reduction in cccDNA has been demonstrated in patients treated with peginterferon and oral antiviral drugs.29,30 How changes in serum quantitative HBsAg and intrahepatic cccDNA correlate with long-term outcome warrants further investigation.

Recently, long-term follow-up data of 195 chronic hepatitis B patients enrolled in four clinical trials were reported.31 Since all of these patients had per-protocol surrogate endpoint assessment, the surrogate markers could be correlated with hard clinical outcomes. At a median follow-up of 86 months, 12 patients developed liver-related events (10 HCC and 2 cirrhotic complications). Liver-related events occurred in 1 of 100 (1%) patients with histological response (reduction of modified Knodell score by 2 points or more with no deterioration in fibrosis) versus 11 of 95 (12%) patients without histological response ($P=0.005$). No patient with regression of cirrhosis after treatment developed liver complications. This study lent support to the benefit of antiviral therapy in improving the clinical outcome of patients.

Conclusions

From a clinical perspective, liver-related complications arise as a result of viral replication and ongoing liver injury. It is likely that adequate control of HBV replication and limitation of liver injury can translate into improved clinical outcomes and survival. However, current evidence comes largely from animal studies, long-term observational studies and clinical trials reporting surrogate endpoints. Before more data are available, it is important to validate the clinical meaning of various surrogate markers. Non-invasive tests for liver fibrosis may revolutionize the evaluation of antiviral therapy in the future.

Transparency declarations

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