Impact of hepatitis B therapy on the long-term outcome of liver disease

Yun-Fan Liaw
Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan

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Abstract
Chronic hepatitis B virus (HBV) infection is a dynamic series of interactions between HBV, hepatocytes and the patient’s immune system. HBV replication is the key motor of disease progression, including the development of cirrhosis and hepatocellular carcinoma (HCC). HBV elimination or suppression can reduce the risk of or slow the progression of liver disease. Studies have shown that a finite course of conventional interferon-α (IFN) therapy provides long-term benefit for achieving a cumulative response as well as reducing the progression of fibrosis and the development of cirrhosis and/or HCC. Long-term therapy with nucleos(t)ide analogues (NUCs) may also improve fibrosis or reverse advanced fibrosis as well as reduce disease progression and the development of HCC. The problems associated with drug resistance can be overcome by the timely use of rescue NUCs without cross-resistance. The outcome with pegylated IFN (PEG-IFN) and newer NUCs may be even better because of more effective treatment and/or a low risk of resistance. However, the treatment outcomes still need to be improved, and more effective, safe and affordable anti-HBV agents/strategies are needed.

Chronic hepatitis B virus (HBV) infection is a serious worldwide clinical problem because of its potential adverse sequelae such as liver decompensation and the development of cirrhosis or hepatocellular carcinoma (HCC). In the past few decades, tremendous progress has been made in the understanding of the virus and the natural history and immunopathogenesis of chronic HBV infection (1). Studies have shown that several viral (viral load, genotype, genomic mutations), host (age, sex, immune status) and environmental or lifestyle factors contribute to the progression of liver disease (2). Active HBV replication is the key driving force of subsequent HBV-related immune clearance events that determine the clinical outcome of the disease (3). Therefore, HBV elimination or permanent HBV suppression should theoretically reduce the risk or slow the progression of liver disease. The development of effective antiviral agents with different mechanisms of action and the accumulation of significant experience with these drugs have made it possible to achieve these goals (4). Evidence has shown that anti-HBV therapy can improve the long-term outcome of chronic HBV infection.

Antiviral therapy for chronic hepatitis B virus infection
Currently, conventional interferon-α (IFN), pegylated interferon (PEG-IFN)-α2a, lamivudine, adefovir, entecavir, telbivudine and tenofovir have been approved for the treatment of chronic HBV infection. Short-term studies have shown that IFN-based therapy is moderately effective in inducing HBeAg loss or seroconversion (30–40%) in HBeAg-positive patients (5–9) and in producing sustained HBV DNA suppression (20–30%) in HBeAg-negative patients (9–12). Therapy with direct antiviral agents may suppress HBV replication and contribute to a significant improvement in liver disease, including fibrosis (13–19). A critical review of 26 therapeutic trials including 3428 patients showed that treatment-induced HBV DNA reduction was significantly and consistently correlated with histological, biochemical and serological responses, especially in studies using direct antiviral agents and in HBeAg-positive patients (20).

Long-term outcomes during therapy
The most extensive and longest experience in controlling disease progression have been gained with the first approved agents IFN and lamivudine.

Interferon-based therapy
Long-term follow-up studies after a 4- to 6-month course of IFN therapy in HBeAg-positive patients showed a reduction in the progression of fibrosis, especially in patients with sustained HBeAg seroconversion (5–7). Furthermore, a recent large study comparing 233 IFN-treated HBeAg-positive patients with 233 well-matched [age, gender, alanine aminotransferase (ALT), HBeAg status, histology and length of follow-up] untreated patients showed a reduced cumulative incidence of cirrhosis (17.8 vs 33.7% in the controls; P = 0.041) after a median follow-up period of 6.8 (1.1–15.5) years.
Studies have also shown that the sustained elimination of HBeAg is associated with a significant increase in survival (5–7, 21) and a reduction in the occurrence of severe cirrhotic complications and the need for liver transplantation (5). An earlier randomized control study showed that IFN therapy in HBeAg-positive active chronic hepatitis (mean ALT 175 U/L) reduced the incidence of HCC (6). In contrast, the response rate to IFN therapy in a study in young HBeAg-positive patients (89 were children) with normal (64%) or near-normal ALT (mean 46 U/L) was very low (15%) and there was no reduction of HCC in IFN-treated patients compared with historical controls, as described earlier (2). It should be noted that most of the patients in that study had no indication for therapy according to current guidelines (22, 23). More importantly, the above-mentioned recent large matched-control study in HBeAg-positive patients with active chronic hepatitis B confirmed that IFN therapy reduced the development of HCC (2.7 vs 12.5% in the controls; P = 0.011) (21).

In HBeAg-negative European patients treated with IFN for 6–24 months, sustained responders also showed a decrease in the progression of the Ishak fibrosis score (9, 10) or a decreased risk of cirrhosis (24). Sustained responders also had significantly improved long-term outcomes, including less severe cirrhosis-related complications, a reduced incidence of HCC (1.8 vs 10.5% in relapers; P = 0.027 and 7.7% in untreated; P = 0.048), less need for liver transplantation and lower mortality, although the sustained response rate in HBeAg-negative patients was usually < 30% (9, 10, 24). The clearance of HBsAg in serum occurred more frequently in IFN-treated patients with a sustained response (7, 9–11) and was associated with a lower rate of hepatic decompensation, HCC and with a longer survival (11).

The reduction of HCC by IFN therapy in patients with cirrhosis is less conclusive. It has been shown that IFN therapy in patients with compensated cirrhosis is safe and even more effective than that in patients without cirrhosis (25, 26). This suggests that HCC may be reduced in IFN-treated patients with cirrhosis after a longer follow-up. A subgroup analysis in a recent long-term follow-up study showed that the incidence of HCC was significantly reduced in patients with cirrhosis treated with IFN (21). A recent meta-analysis including 12 trials (1292 IFN-treated and 1450 untreated patients) showed that the risk of HCC was significantly reduced by 34% [risk ratio (RR): 0.66, 95% confidence interval (CI): 0.48–0.89; P = 0.006] after treatment with IFN and even more (47% reduction; RR 0.53, 95% CI: 0.36–0.78; P = 0.001) in patients with cirrhosis (27). Another meta-analysis including 11 trials showed that IFN therapy reduced cirrhosis and HCC (28). The pooled estimation in another meta-analysis of two randomized control trials and five non-RCT trials (553 IFN treated vs 750 no treatment) showed that IFN therapy significantly prevented the development of HCC especially in HBeAg-positive patients, Asian patients or in populations with a high incidence of HCC (29).

### Direct antiviral therapy: reversal of fibrosis

Long-term data on the effect of direct antiviral nucleos(t)ide analogues (NUCs) on the risk of developing cirrhosis and disease progression have been published recently. Long-term (>3 years) lamivudine or adefovir therapy showed the improvement of fibrosis or the reversal of advanced fibrosis (13–15). Fibrosis improved (≥1 point on the Ishak fibrosis score) in 57 and 88% of patients treated with entecavir for 3 and 6 years respectively (18, 19) (Table 1). There was a significantly lower cumulative rate of cirrhosis and/or the development of HCC (P = 0.005) with long-term lamivudine therapy (median 89.9 months; range 26.5–128.3 months) in 142 HBeAg-positive, non-cirrhotic patients from Hong Kong compared with 124 HBeAg-positive untreated controls (30). A double-blind, randomized-controlled trial showed that maintenance lamivudine therapy for a median of 32.4 months in 436 patients with cirrhosis or advanced fibrosis (Ishak fibrosis score ≥4) significantly reduced overall disease progression compared with 215 untreated controls (31). Long-term lamivudine therapy in 303 HBeAg-negative patients with cirrhosis also showed that liver disease was less likely to worsen in patients with a sustained virological response (SVR) than in those with a viral breakthrough (32).

### Direct antiviral therapy: decreased incidence of hepatocellular carcinoma

In the above-mentioned randomized control trial, the incidence of HCC was also significantly reduced (3.9 vs 7.4% in the placebo group, P = 0.048) in lamivudine-treated patients with advanced fibrosis or cirrhosis (31).
A study of 377 patients (51% HBeAg negative, 17% with cirrhosis) treated with lamivudine for up to 96 months (23.1–19.0 months) in Japan also showed a marked reduction in the incidence of HCC compared with a historical control group matched for age, sex, hepatic fibrosis score, albumin level and platelet count (0.4 vs 2.5% per year; \( P < 0.001 \)) (33). A retrospective multicentre study involving 656 HBeAg-negative patients (353 with chronic hepatitis, 303 with cirrhosis) treated with lamivudine for 1–66 months (median, 22 months) showed that HBV suppression reduced the development of HCC even in patients with cirrhosis (32). A recent Korean study showed a reduced incidence of HCC in patients with compensated cirrhosis who achieved sustained viral suppression compared with untreated patients or treated patients with a viral breakthrough or a suboptimal response to lamivudine. However, this beneficial effect was not observed in patients with chronic hepatitis B without cirrhosis or in those with decompensated cirrhosis (34). A meta-analysis in 1267 lamivudine-treated and 1022 untreated patients showed that HCC was reduced by 78% (RR: 0.22, 95% CI: 0.10–0.50; \( P = 0.0003 \)) on maintained lamivudine therapy and a greater benefit was observed in patients with cirrhosis (RR: 0.17 vs 0.21) and HBeAg-positive patients (RR: 0.21 vs 0.25) (27). In the most recent systematic review of 21 studies in 3881 NUC-treated and 534 untreated patients, HCC developed less frequently in NUC-treated patients (2.8 vs 6.4%; \( P < 0.003 \)) (35). However, long-term lamivudine therapy was associated with a high rate of drug-resistant mutations. Patients with drug resistance were more likely to experience disease progression and die from causes related to the worsening of liver function (31). In HBeAg-negative patients, the chance of developing HCC was significantly greater in patients with a virological breakthrough than in those who maintained viral suppression (32).

These results confirm that the suppression of HBV reduces the risk of or slows the progression of liver disease, and that renewed HBV replication may restore the potential for disease progression. The adverse effect of lamivudine mutations can now be overcome by the timely use of rescue therapy (36). This has been well demonstrated in a trial of long-term therapy started with lamivudine and rescued by adefovir (37). Long-term therapy with newer antiviral agents is expected to result in similar or better long-term outcomes because of their increased genetic barrier to drug resistance.

Summary and perspectives

Clinical and epidemiological studies have shown that HBV replication is the key driver of hepatitis activity and subsequent disease progression in patients with chronic HBV infection. Overall long-term data show that IFN therapy in HBeAg-positive patients results in cumulative HBeAg seroconversion, reduction of fibrosis, an increase in HBsAg seroclearance and a reduction in cirrhosis and/or the development of HCC, especially in patients with SVR. However, this long-term efficacy is less conclusive in HBeAg-negative chronic hepatitis B patients, especially those with cirrhosis, although sustained responders or those who lose HBsAg have better outcomes. Because PEG-IFN is more effective than conventional IFN in the treatment of chronic hepatitis B (38) and may result in a complete response with HBsAg seroconversion (8, 12), long-term follow-up studies will probably show that PEG-IFNs have similar or even better effects.

Data also suggest that maintained suppression of HBV replication using NUCs may reduce the worsening of liver fibrosis, reverse advanced fibrosis, reduce the development of cirrhosis and prevent further disease progression including HCC in patients with advanced fibrosis or cirrhosis. The main problem is the emergence of drug resistances and recurrent HBV replication, which may reduce the therapeutic benefit of these regimens. This problem can now be overcome by the timely use of rescue drug(s) (36). Long-term studies will probably confirm that the beneficial effects of newer antiviral agents in reducing disease progression are similar to or better than those of lamivudine because of a much lower risk of drug resistance.

However, current therapies only reduce the risk of or slow disease progression; they do not prevent all adverse sequelae. Monitoring for HCC with ultrasound and \( \alpha \)-fetoprotein assays is necessary to improve outcomes by increasing early detection and the chance of curative treatment (39). The development of safe and affordable agents and the development of management strategies to improve sustained or maintained HBV suppression without inducing drug resistance should be the ultimate goal in the management of chronic HBV infection.

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Conflicts of interest

Y. F. Liaw has been involved in clinical trials and served as a global advisory board member of Roche, BMS, Novartis, Gilead Sciences.

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