Journal of Hepatology 46 (2007) 6–8

Journal of Hepatology

www.elsevier.com/locate/jhep

Editorial

Does treatment with interferon-based therapy improve the natural history of chronic hepatitis B infection?

George K.K. Lau*

Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Rm 1838, Block K, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China

See Article, pages 45–52

Worldwide, approximately 400 million people are chronically infected with hepatitis B virus (HBV). Most of them reside in the Asia-Pacific region, such as Southern China and Taiwan, where chronic HBV infection is highly prevalent (>10%). Among them, around 25–40% will eventually die of liver disease (viz. cirrhosis with or without hepatocellular carcinoma), largely due to protracted hepatic necroinflammation (chronic active hepatitis). In greater China, it is estimated that more than half-a-million deaths were due to HBV-related liver complications annually [1]. For those patients with chronic active HBV infection, progression to cirrhosis occurs at an annual rate of 2–6% in hepatitis B e antigen (HBeAg) positive and 8–10% for HBeAg negative patients [2–4]. Once cirrhosis is established, the yearly incidence of hepatic decompensation is about 3% [5] and the annual incidence of hepatocellular carcinoma will be markedly increased from close to zero percent in inactive HBV carriers [6] to over 2%, with a cumulative 5-year incidence of 15–20% [2,7].

The diversity of clinical outcome of HBV infection in humans, either resolution (immunity) or persistence of infection with protracted hepatic necroinflammation (immunopathogenesis), is dependent on the host immune response to the virus [8]. For those with an impaired host immune control to the virus, there will be protracted hepatic necroinflammation. Therefore, it is not surprising that among the various risk factors identified for the progression to cirrhosis and hepatocellular carcinoma, a high level of HBV replication DNA level (a reflection of impaired host immune control on the virus) has been identified as the most important factor. The adjusted relative risk of cirrhosis was 2.3 (95% CI, 1.6–3.5) and 9.3 (95% CI, 6.5–13.1) for baseline serum HBV DNA $> 10^4$ and 10^6, respectively [9], and for hepatocellular carcinoma, the adjusted odds ratio for patients with the highest quintile (5.91–10.81 $\log_{10}$ copies/mL) versus those with lowest quantile (2.77–3.61 $\log_{10}$ copies/mL) of serum HBV DNA was 7.26 (95% CI = 3.54–14.89) [10]. Logically, most of the treatment guidelines emphasize the necessity of reducing hepatitis B viral load levels in those patients with active hepatic necroinflammation, as a measure of the effectiveness of therapy with a long-term goal to reduce the development of liver cirrhosis and hepatocellular carcinoma [8].

By the year 2006, there are seven agents registered for treatment of chronic HBV infection. Two are immunomodulatory agents, namely conventional interferon-α2b and pegylated interferon-α2a, which aim to restore host immune control on HBV and thus lead to sustained off-treatment disease remission. The other three agents are all nucleos(t)ide analogues (lamivudine, adefovir, entecavir and telbuvidine) with direct anti-viral activity. However, direct antiviral agents have little impact on host immune response, as reflected by a low rate of HBeAg seroconversion and negligible hepatitis B surface antigen (HBsAg) seroconversion, and thus most patients treated with these agents need prolonged or even life-long therapy. The major limitations of immunomodulatory therapy are: [1] lack of efficacy in 40–60% of patients treated and [2] side effect profile. This has limited its usage, especially in those patients with decompensated liver cirrhosis, immune incompetent, other immune-mediated diseases, marrow insufficiency and psychiatric

* Tel.: +852 28184300; fax: +852 28184030.
E-mail address: gkklau@netvigator.com

doi:10.1016/j.jhep.2006.10.008

disorders. On the other hand, the risk of development of viral resistance increases with prolonged therapy with pure anti-viral agents, running a risk of worsening of liver function [8].

A million-dollar question is whether these agents really transform the natural history of chronic HBV infection? Most importantly, does the use of these agents reduce the risk of liver complications, such as liver cirrhosis and hepatocellular carcinoma, and hence improve the survival of chronic HBV patients? These questions could only be answered by well-conducted long-term follow-up studies (Table 1) [11–14]. With the continued use of lamivudine, disease progression has been shown to be significantly reduced in chronic HBV patients with advanced fibrosis/cirrhosis. However, this beneficial effect was markedly diminished with the development of lamivudine resistance, which increased with prolonged therapy [14]. An alternative to avoid the use of prolonged maintenance therapy in chronic HBV patients with nucleos(t)ide analogues is to induce disease remission with the use of interferon-based therapy at an earlier stage. In keeping with this, sustained disease remission has been shown to be accelerated in chronic HBV patients with active hepatitis, treated with conventional interferon. In Caucasians, it has been demonstrated that treatment with a finite course of conventional interferon not only will hasten disease remission but those who have responded were shown to have a better long-term prognosis with a significant reduction of liver-related mortality [11,13]. In Asians, so far, the long-term follow-up data on the use of interferon-based therapy on chronic HBV patients with active hepatitis are limited [12].

In this important study by Lin et al., the long-term outcome of interferon-α therapy in HBeAg positive patients was examined [15]. Altogether, 233 Chinese patients with active hepatitis (baseline serum ALT is 175 IU/l) treated with a finite course of interferon-based therapy were followed up for a median of 6.8 years (range 1.1–16.8 years). All treated and untreated controls were followed up at intervals of at least 3–6 months. Compared to untreated controls ($n = 233$) with persistent HBeAg positivity, HBeAg seroconversion in untreated and interferon-treated patients had a significantly lower incidence of liver cirrhosis and cancer. This supports the use of HBeAg seroconversion as a measure of treatment efficacy for HBeAg positive chronic active hepatitis. An added value of HBeAg seroconversion is

Table 1
Long-term follow-up on chronic HBV patients with active hepatitis or advance fibrosis/cirrhosis treated with finite duration of conventional interferon or continuous lamivudine

Study	Follow-up (yrs)	Race	Number of patients		Cirrhosis (%)		HBsAg loss		Comments
			IFN	Control	IFN	Control	IFN	Control	
Niederau [11]	4.2	C	103	53	26	30	10	0	IFN-induced serological clearance of HBeAg has improved clinical outcome
Lin [12]	7.0	A	67	34	10	15	0	0	IFN increases HBV clearance, reduces HCC, and prolongs survival
Fattovich [13]	7.2	C	40	50	100	100	11	5	IFN-induced disease remission associated with improved survival in HBeAg-positive patients with compensated cirrhosis
			LAM	Control	LAM	Control	LAM	Control	
Liaw [14][a]	2.7	A/C	436[a]	215	436[a]	215	4[a]	0	Continuous LAM treatment delays clinical progression in HBV patients with advanced fibrosis or cirrhosis

Study	Follow-up (yrs)	Race	Decompensation		HCC		Death		Comments
			IFN	Control	IFN	Control	IFN	Control	
Niederau [11]	4.2	C	16	13	NR	NR	6	3	IFN-induced serological clearance of HBeAg has improved clinical outcome
Lin [12]	7.0	A	6	5	1	4	1	4	IFN increases HBV clearance, reduces HCC, and prolongs survival
Fattovich [13]	7.2	C	6	11	4	6	8	15	IFN-induced disease remission associated with improved survival in HBeAg-positive patients with compensated cirrhosis
			LAM	Control	LAM	Control	LAM	Control	
Liaw [14][a]	2.7	A/C	4[a]	3	17[a]	16	0[a]	0	Continuous LAM treatment delays clinical progression in HBV patients with advanced fibrosis or cirrhosis

C, Caucasian; A, Asians; IFN, conventional interferon; LAM, lamivudine.
[a] Treatment arm was lamivudine instead of interferon.

that it is a prerequisite for HBsAg seroconversion and it occurs in up to one-tenth of those patients treated with interferon-based therapy and experienced HBeAg seroconversion [16]. Serological clearance of HBsAg is of paramount importance in the natural history of chronic hepatitis B as its development will be close to a cure, provided the patient has not already developed liver cirrhosis or hepatocellular carcinoma [8].

As pointed out by Lin et al., the result of this retrospective study is in contrast with other reports which showed that interferon therapy has a minimal effect on reducing the risk of cirrhosis, hepatocellular carcinoma and liver-related mortality. Compared to the other studies, the present study has the superiority of studying more patients with appropriate disease characteristics (active hepatitis) and for a long-enough duration. This is reflected in the expected outcome of the untreated control group, with an incidence of liver-related mortality of 11% [15]. This supports the validity of the design and the conduct of this long-term follow-up study. From the scientific point of view, having a well-matched control group in a retrospective study is still only second to ideal design with a long-term prospective follow-up from the original randomised registration study. However, with the availability of effective agents for controlling the viral replication, it is perhaps difficult to keep patients untreated. Nonetheless, in collaboration with the industrial partners, longer term off-treatment follow-up study comparing patients treated with interferon-based therapy to those new and recent more potent nucleos(t)ide analogues will be awaited.

References

[1] He J, Gu D, Wu X, Reynolds K, Duan X, Yao C, et al. Major causes of death among men and women in China. N Engl J Med 2005;353:1124–1134.

[2] Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol 1998;28:930–938.

[3] Liaw YF, Tai DI, Chu CM, Chen T. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Hepatology 1988;8:493–496.

[4] Fattovich G, Brollo L, Giustina G, Noventa F, Pontisso P, Alberti A, et al. Natural history and prognostic factors for chronic hepatitis type B. Gut 1991;32:294–298.

[5] Realdi G, Fattovich G, Hadziyannis S, Schalm SW, Almasio P, Sanchez-Tapias J, et al. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). J Hepatol 1994;21:656–666.

[6] de Franchis R, Meucci G, Vecchi M, Tatarella M, Colombo M, Del Ninno E, et al. The natural history of asymptomatic hepatitis B surface antigen carriers. Ann Int Med. 1993;118:191–194.

[7] Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP study group on hepatitis B virus and cirrhosis. Hepatology 1995;21:77–82.

[8] Hui CK, Lau GK. Current issues and future directions in treatment. Semin Liver Dis 2006;26:192–197.

[9] Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Risk evaluation of viral load elevation and associated liver disease/cancer – In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678–686.

[10] Yu MW, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst 2005;97:265–272.

[11] Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med 1996;334:1422–1427.

[12] Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. Hepatology 1999;29:971–975.

[13] Fattovich G, Giustina G, Realdi G, Corrocher R, Schalm SW. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. European concerted action on viral hepatitis (EUROHEP). Hepatology 1997;26:1338–1342.

[14] Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521–1531.

[15] Lin S-M, Yu M-L, Lee C-M, Chien R-N, Sheen I-S, Chu C-M, Liaw Y-F. Interferon therapy in HBeAg positive chronic hepatitis reduce cirrhosis and hepatocellular carcinoma. J Hepatol 2007;46:45–52.

[16] Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, 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.