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Is it better to treat chronic hepatitis B as early as possible?—Con

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Abstract Ideally, treatment of chronic hepatitis B in its early stage prior to irreversible liver damage should be most effective in preventing adverse clinical outcome. However, currently available treatments have low efficacy in achieving sustained response among patients in the early phase of chronic hepatitis B infection when the immune response to hepatitis B virus is weak. This review will provide evidence why a 'wait and monitor' approach is appropriate for chronic hepatitis B patients who are in the immune tolerant phase.

Key words: adefovir dipivoxil, hepatitis B e antigen, immune tolerance, interferon, lamivudine.

INTRODUCTION

Remarkable progress has been made in the treatment of chronic hepatitis B in the past decade. Treatment options have expanded from a single approved treatment that has to be administered parenterally, has many unpleasant side-effects, is expensive, and has limited efficacy and applicability to three approved treatments including two orally administered antiviral compounds which have very few side-effects. Nevertheless, current treatments are far from satisfactory. Sustained off-treatment response is achieved in a very small percent of patients. Maintenance of on-treatment response requires long-term therapy with increasing costs, and risks of drug-resistance and adverse effects. Thus, decision to initiate treatment must carefully balance long-term benefits against long-term costs and risks, as well as patient preference, age, comorbid conditions and severity of liver disease. The natural history of chronic HBV infection can be depicted as consisting of four phases: immune tolerant phase, immune clearance phase (HBeAg positive chronic hepatitis), inactive carrier state, and reactivation (HBeAg negative chronic hepatitis). Treatment guidelines recommend that patients with HBeAg positive chronic hepatitis and those with HBeAg negative chronic hepatitis be treated because antiviral therapy can decrease hepatic necroinflammation and risk of progression of liver disease.[1–4] Treatment is not recommended for inactive carriers who have low or undetectable serum HBV DNA ($< 10^3$ copies/mL) and normal alanine aminotransferase (ALT) levels. Current treatment will not bring about further improvement and is unlikely to eradicate HBV, clear hepatitis B surface antigen (HBsAg) or prevent future reactivation. These carriers should be monitored and treatment instituted if they should progress to HBeAg negative chronic hepatitis. Much of the controversy regarding hepatitis B treatment is focused on patients in the first phase—immune tolerant phase.

WHAT IS THE IMMUNE TOLERANT PHASE?

The 'immune tolerant' phase of chronic HBV infection is characterized by the presence of HBsAg, HBeAg, high serum HBV DNA levels (10^7–10^{10} copies/mL), persistently normal ALT levels, and minimal or no hepatic inflammation and fibrosis if a liver biopsy is performed.[1] The classical patient in the 'immune tolerant' phase is a young (< 30 years) Asian patient with perinatally acquired HBV infection.

Evidence of immune tolerance was provided by studies of peripheral blood mononuclear cells in HBeAg-positive Chinese children with normal ALT levels and cord blood mononuclear cells from neonates of HBsAg and HBeAg-positive carrier mothers showing lack of proliferative response to HBcAg that was not reversed by depleting CD8+ suppressor T cells.[5] However, it should be noted that tolerance is not permanent because HBe/HBcAg-specific T cell proliferative responses have been demonstrated to increase during acute exacerbations of chronic hepatitis B and in HBeAg-positive Chinese children with elevated ALT.[5,6]

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Longitudinal follow-up studies also showed that elevated ALT and acute exacerbations of chronic hepatitis B can be observed indicating that 'immune tolerance' is a reversible state.[7]

WHAT ARE THE GOALS OF TREATMENT OF HEPATITIS B?

The primary goal of treatment of hepatitis B is to prevent adverse clinical outcome: cirrhosis, liver failure and HCC. The end-point of treatment of HBeAg-positive patients is HBeAg to anti-HBe seroconversion with associated suppression of serum HBV DNA to <100 000 copies/mL and normalization of ALT.[8] Several long-term follow-up studies have demonstrated that responders have improved clinical outcome. Intuitively, maximum benefit would be derived if treatment can be initiated early and response achieved before there is irreversible liver damage. Thus, hepatitis B patients in the immune tolerant phase are ideal candidates for treatment provided effective treatment is available.

WHAT IS THE EFFICACY OF CURRENTLY APPROVED TREATMENTS?

Three treatments have been approved for chronic hepatitis B: standard interferon alpha (IFNα), lamivudine (Epivir), and adefovir dipivoxil (Hepsera).

IFNα

Clinical trials showed that compared to untreated controls, a 4–6 month course of IFNα treatment results in HBeAg clearance in an additional 24% (95% CI 8%–30%) patients.[9] The strongest predictor of response is pretreatment ALT level.[10,11] This explains why studies in Asian patients that included patients with normal or minimally elevated ALT levels reported very poor response to IFNα therapy (Table 1).[12–15] Subsequent studies found that Asian patients with elevated ALT had similar response rates as Caucasian patients[15,16] indicating that host immune response at the time treatment is initiated and not genetic factors led to the low response rates in the early studies of Asian patients. These data showed that IFNα has very limited efficacy in HBeAg clearance—a surrogate marker for sustained viral suppression, in hepatitis B patients who are in the immune tolerant phase. However, Asian patients who have entered the immune clearance phase (HBeAg positive, elevated ALT levels) may benefit from IFNα therapy.

A phase II clinical trial of pegylated IFNα2a reported that among patients with pretreatment ALT <2 times upper limit of normal (ULN), a combined response (HBeAg loss, serum HBV DNA <500 000 copies/mL and ALT normalization) was achieved in six of 22 patients who received pegylated IFNα2a and in only one of 9 who received standard IFNα2a suggesting that pegylated IFN may have a role in hepatitis B patients who are in the immune tolerant phase.[17] However, the number of patients was small and the exact number of patients with normal pretreatment ALT was not specified. Given the costs and the associated side-effects, further studies are needed to determine if pegylated IFNα has any role in hepatitis B patients who are in the immune tolerant phase.

Lamivudine

Clinical trials showed that a 1-year course of lamivudine results in HBeAg seroconversion in 16–18% compared to 4–6% of those who received placebo.[18–20] As with IFNα, pretreatment ALT is the strongest predictor of response to lamivudine. This is true for adults as well as children (Table 2)[21] and Caucasians as well as Asians (Table 3).[22] While increasing rates of HBeAg serocon-

Table 1 Efficacy of IFNα therapy in controlled trials in HBeAg-positive Chinese patients

Author [ref]	Treatment	No. of patients	Pretreatment ALT (× ULN)	No. (%) patients lost HBeAg
Lai[12,†]	IFNα	12	0.3	0
	Control	12	0.3	0
Lai[13,†]	IFNα ± Pred	60	0.3	5 (8)
	Control	30	0.3	0
Lok[14,†]	IFNα	54	1.5	9 (17)
	Control	18	1.5	0
Lok[15,†]	IFNα ± Pred	40	0.5	1 (2.5)
	Control	20	0.5	0
	IFNα ± Pred	39	3.5	14 (36)
	Control	16	3.0	3 (19)
Liaw[16,†]	IFNα ± Pred	76	6.0	27 (36)
	Control	40	6.0	10 (25)

[†]Studies in children.
Pred, prednisone/prednisolone priming.

Table 2 HBeAg seroconversion rates after 1 year of lamivudine treatment in relation to pretreatment ALT level[19,21]

Pretreatment ALT (× ULN)	HBeAg Seroconversion Adults Lamivudine *N* (%)	Placebo *N* (%)	Children Lamivudine *n* (%)	Placebo *n* (%)
<1	1/53 (2)	0/25 (0)	1/8 (12)	1/7 (14)
1–2	8/114 (7)	3/59 (5)	10/86 (12)	2/30 (7)
2–5	32/164 (20)	7/82 (9)	25/81 (31)	5/41 (12)
>5	25/60 (42)	4/26 (15)	8/16 (50)	4/17 (24)

Table 3 HBeAg loss in relation to pretreatment ALT and ethnic origin after 1 year of lamivudine treatment[22]

Pretreatment ALT (× ULN)	HBeAg loss Asians	Caucasians
1–2	9%	19%
2–5	26%	30%
>5	59%	54%

version can be achieved by extending the duration of lamivudine treatment, only 25% patients with normal pretreatment ALT had HBeAg seroconversion after 5 years of lamivudine treatment.[23] The low response rate in relation to a 5-year rate of lamivudine-resistant mutation of 69%[23] cannot justify the use of long-term lamivudine treatment for hepatitis B patients who are in the immune tolerant phase. The importance of pretreatment ALT in spontaneous and antiviral therapy related HBeAg seroconversion was highlighted in an analysis of 805 adults who were treated with lamivudine, IFNα, combination of IFNα and lamivudine, and placebo tablets (Table 4).[22]

Adefovir dipivoxil

Phase III clinical trial of adefovir dipivoxil reported that HBeAg seroconversion was observed in 12% and 6% of patients after 1 year of adefovir dipivoxil 10 mg and placebo, respectively.[24] A combined analysis of patients in this trial and patients in a parallel trial conducted in patients with HBeAg negative chronic hepatitis showed that histologic response and HBV DNA suppression was comparable in Asian and Caucasian patients.[25] However, only 2% of patients in the trial of HBeAg-positive hepatitis had normal pretreatment ALT levels.[24] Thus, the efficacy of adefovir dipivoxil in hepatitis B patients in the immune tolerant phase remains to be determined.

WHY IS TREATMENT NOT RECOMMENDED FOR HEPATITIS B PATIENTS IN THE 'IMMUNE TOLERANT' PHASE?

The primary goal of hepatitis B treatment is to prevent adverse clinical outcome. Accomplishment of this goal necessitates that treatment can result in sustained off-treatment virologic response, or maintenance of response through continuous therapy. The latter approach is practical only if the therapy is safe, affordable, and has a negligible risk of adverse effects with long-term use. Such therapy is not yet available. Thus, treatment is not recommended for hepatitis B patients in the 'immune tolerant' phase because the long-term benefits of currently available treatments do not outweigh the long-term costs; and risks of adverse effects and drug resistance. Treatment is recommended when 'immune tolerance' is broken and these patients remain HBeAg positive after ALT levels have been elevated for longer than 6 months. Treatment at this stage is more likely to be effective, and to benefit the patients by shortening the period of active liver damage. In conclusion, hepatitis B patients in the immune tolerant phase are ideal candidates for treatment provided effective treatment is available. Until then, the 'immune tolerant' patient should be monitored so treatment can be initiated promptly when the time is ripe.

Table 4 HBeAg seroconversion rates in randomized controlled trials of lamivudine, IFNα, and lamivudine + IFNα in relation to pretreatment ALT level[22]

Pretreatment ALT (× ULN)	HBeAg seroconversion (%) Placebo	Lamivudine	IFNα	Lamivudine + IFNα
= 1	0	2	50†	0
1–2	5	7	9	10
2–5	9	20	20	24
>5	15	42	30	45

†1 of 2 patients.

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