CLINICAL CHALLENGE

Lamivudine or Interferon alpha? this is the problem

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Introduction

More than 400 million people worldwide are chronically infected by the hepatitis B virus (HBV).[1] It is a common cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma, and more than a quarter of people with chronic hepatitis B (CHB) will die of liver disease.[1,2]

The optimal approach to antiviral therapy for CHB remains undefined and controversial. Currently, two antiviral drugs have been licensed to use in CHB worldwide. Recombinant interferon-alpha and Lamivudine have been approved for use in many countries, consisting Iran. Fortunately both of these drugs are manufactured locally in Iran. Unfortunately, there are no clear guidelines for using antiviral therapy, and investigators differ markedly in recommendations and approaches.[3]The task of developing a consensus of therapy for this disease is challenging.

Selection of Patients for Antiviral Therapy

An important distinction is the differentiation of chronic hepatitis B from inactive chronic HBsAg carrier state. Persons with HBsAg in serum and normal ALT and no detectable or only low levels of HBV DNA in serum (less than 100000 copies per ml) should not be treated.[4] Chronic hepatitis B is usually defined by the presence of hepatitis B Surface antigen (HBsAg) in serum and histological evidence of chronic necro-inflammatory disease on liver biopsy or persistently elevated serum alanine aminotransferase (ALT) activities. CHB based upon hepatitis B e antigen (HBeAg) is divided into two forms: HBeAg-positive; which is a typical form of CHB, characterized by stable, high levels of circulating HBV-DNA in serum and HBeAg-negative CHB is characterized by more modest and often fluctuating levels of HBV-DNA. Most patients with HBeAg-negative CHB harbor a variant of HBV with mutations in the pre-core region or the basic core promoter of the HBV genome. The goal of treatment of CHB with currently available agents is persistent suppression of HBV replication with conversion from the high to the low replicative phase (HBeAg to anti-HBe seroconversion with associated decline in HBV-DNA to less than 100 000 copies/ml).[5] In HBeAg-positive CHB, the endpoint of succeful treatment is sustained seroconversion of HBeAg to anti-HBe and decrease of HBV-DNA to below the level of detection by non-PCR methods (e.g. branched DNA assays). Indeed, HBeAg loss and seroconversion to anti-HBe have been shown to be associated with decrease in serum HBV- DNA levels to non-detectability by the branched DNA assays, biochemical remission, and HBsAg loss in some patients and eventually improved long-term outcome.[6, 7, 8] Loss of HBeAg as an endpoint of successful therapy has many limitations. In patients with HBeAg-negative CHB, who often have severe and progressive disease, these endpoints cannot be used. For these cases, suppression of HBV-DNA below the level that typically occurs after loss of HBeAg (below 100 000 copies per ml) has been used as an alternative endpoint.[3]

Treatment Options

Interferon alpha was the first agent shown to be effective in causing sustained suppression of HBV replication. The availability of lamivudine and the high

rate of response to this drug changed the approach to treatment of CHB, but high rate of relapse after discontinuation of drug made it complex. The advantages and disadvantages of the therapeutic agents for HBV infection are summarized in table 1 and reviewed in detail below.

Table 1
Advantages and Disadvantages of treatment of chronic hepatitis B with Antiviral Agents

	Interferon	Lamivudine
Route	subcutaneous	Oral
Side effects	Many	Negligible
Contraindications	Numerous	Uncommon
Drug resistance	none	20% in year 1 60% in year 4
Costs at 1 year	High	Low

Interferon-alpha

Interferon-alpha, an antiviral and immunomodulatory agent was the first effective therapeutic agent in both HBeAg-positive and HBeAg-negative CHB.[9,10] Recombinant interferon-alpha 2b was approved for treatment of chronic hepatitis B in the United States in 1992. Many controlled, randomized studies have shown that a 4-6 months course of interferon-alpha at a dose of 5 MU daily or 10 MU thrice weekly achieves loss of HBeAg, undetectable HBV-DNA, and loss of hepatitis B surface antigen in 33%, 37%, and 8% of patients, respectively.[11] Response to interferon is greatest in those with high serum ALT levels, low HBV-DNA levels, and more inflammatory activity on liver biopsy before treatment. The corresponding figures for 16-week course of either 5 MU daily or 10 MU three times weekly have been analysed. For white patients with chronic hepatitis B, up to 65% of patients who have HBeAg seroconversion will eventually also lose hepatitis B surface antigen. HBV-DNA is usually still detectable after HBeAg seroconversion, if the patients remain positive for hepatitis B surface antigen, but will become undetectable by PCR in 60–100% of those who lose the surface antigen. However, irrespective of whether or not they remain positive for hepatitis B surface antigen, patients who have HBeAg seroconversion have a lower risk of developing hepatitis B cirrhosis related complications than do those who remain positive for HBeAg. They also have longer survival rates and longer intervals free from clinical complications.[12] When interferon-alpha was found to induce loss of HBeAg in 33% of patients treated; this endpoint was taken as evidence of benefit.[11]

Interferon-alpha improves the probability of viral clearance and liver biochemistries in clinically well-compensated patients with CHB. A sustained virological response to interferon-alpha is associated with resolution of necroinflammatory activity, no change or improvement in fibrosis, a reduced risk of hepatic decompensation, and an improvement in long-term survival. The main disadvantage of interferon-alpha is its side-effects. Approximately one-third of interferon-alpha-treated patients may require dose reduction and 5% may discontinue the drug prematurely due to adverse events.[13] Dose and duration of treatment appear to have some effect on the response to interferon. Virological response is higher with doses of 9-10 MU thrice weekly (or 5 MU daily, or 6 MU/m2 thrice weekly) than with lower doses. Treatment for 4-6 months or longer is superior to 3 months of therapy. In patients who have a virological response within 1 year after start of 3-6 month course of interferon-alpha, the sustained virological response rate is 80-90% at 5 years. A complete response rate of 20-30% was found at 5 years in studies from Europe [12, 14, 15, 16] ; and 70% at 10 years in one United States study. [15] The complete response rate is less than 10% in studies from Asia .[17,18]

In conclusion, responses after interferon-alpha therapy are durable in majority of patients and even clearance of serum HBsAg may eventually develop in a proportion .[8]

Lamivudine

Lamivudine is a pyrimidine nucleoside analogue that is orally bioavailable and has excellent antiviral activity against both HBV and HIV. Many studies showed that 100 mg/day of lamivudine resulted in a median of 4-log fall in HBV-DNA level, with the virus being undetectable during treatment in all patients.[19] The arrival of nucleoside analogue treatment marks a new era in treatment of CHB. In most clinical trials, the standard therapeutic endpoints have been loss of HBeAg (with or without antibodies against HBeAg), together with undetectable HBV- DNA, as measured by branched DNA or hybrid capture assays. Lamivudine was approved for use in hepatitis B in the United State in 1998. Lamivudine has minimal side effects and results in marked suppression of HBV-DNA levels with accompanying improvements in ALT levels and liver histology; Lamivudine has been increasingly used as continuous, maintenance therapy.[20]

The most important problem of prolonged therapy with lamivudine has been the development of resistance in 20-25% of patients each year.[21, 22] Viral resistance is associated with rises in serum HBV-DNA levels in association with mutations in the HBV polymerase gene and often with increase in ALT levels and worsening of liver histology. Nevertheless, the risk and benefits of prolonged, continuous therapy with lamivudine have not been well defined. The endpoint for treatment of patients with antibodies against HBeAg is still controversial. For patients with high levels of serum alanine aminotransferase, long-term suppression of HBV-DNA is probably indicated. Total eradication of the virus is almost never achieved and is rarely used as a clinical trial or therapeutic endpoint .[23]

The percentage of responders who maintain HBeAg seroconversion after the cessation of lamivudine varies between studies. Maintenance of HBeAg seroconversion has been suggested to be associated with the extension of therapy after the development of anti-HBe seroconversion, the patients' origin and, perhaps, the duration of HBV infection. In particular, HBeAg seroconversion after the discontinuation of lamivudine has been reported to be maintained in 70–90% of patients from Western countries [31,32] and in 38–83% of

patients from South-East Asia [33] Overall, the sustained HBeAg seroconversion rate after lamivudine seems to be slightly lower than that after interferon-alpha therapy. The prolongation of lamivudine therapy for more than 2 years may gradually increase the HBeAg seroconversion rate, as a 2-year course has been found to achieve seroconversion in 27%, a 3-year course in 33% and a 4-year course in 47% of cases.[33,34,35]

In patients with HBeAg-negative CHB, unfortunately, sustained off therapy responses are rare; biochemical and virological relapses are observed in most patients after the cessation of a 12-month lamivudine course.[36,37] Given its excellent tolerability and safety profile, long-term treatment with lamivudine could be an acceptable maintenance therapy in patients with chronic hepatitis B. However, only one-third of patients with HBeAg-negative chronic hepatitis B may obtain long-term benefit from such an approach, because viral resistance develops in approximately two-thirds within the first 3 years of lamivudine monotherapy.[38]

The 1-year results from three large scale trials in Asian and white people who were HBeAg-positive and in those with precore HBV mutants showed that there are few side-effects. Results of a histological study [24] showed that 3 years' lamivudine treatment not only reduces necroinflammatory activity but also reverses fibrosis (including cirrhosis) in most patients. For patients who are HBeAg positive, therapy can be stopped 6–9 months after HBeAg seroconversion. The time for stopping treatment for patients with antibodies against HBeAg is difficult to determine and is still controversial. The major drawback of lamivudine monotherapy is emergence of resistant HBV with mutation of the tyrosine-methionine- aspartate-aspartate (YMDD) motif at the catalytic domain (C domain) of the viral reverse transcriptase/DNA polymerase. Incidence of YMDD mutants rises from 15–32% in the first year to 67–69% in the fifth year of treatment. Patients with the YMDD mutants tend to have alanine transaminase and HBV-DNA concentrations that are lower than concentrations before treatment, [25] probably because the YMDD mutants have less replication competence.[26] However, in some patients with YMDD mutants, the HBV-DNA concentrations can become higher than they were before treatment, which might result in varying degrees of hepatic decompensation. Lamivudine, unlike interferon-alfa, is safe and effective in patients with decompensated liver disease, significantly improving liver function and survival in many patients.[27, 28]

Interferon and Lamivudine Combination Therapy

The combination of interferon-alpha and lamivudine might, in theory, be more effective than either drug alone. High viral levels predict a poor response to interferon and therefore lamivudine might make patients more responsive to this immunomodulating drug.[29, 30] There is little data to support combination of interferon and lamivudine at this time, but the results of future studies will be of interest.Currently, this combination therapy is not recommended outside clinical trials.

Which of them are the first choices in treatment of CHB?

Long-term follow up of patients treated with interferon alpha showed that the loss of HBeAg and remission in disease was usually durable and, many patients went on to lose HBsAg and develop anti-HBs.[15, 16, 18] While a 1-year course of lamivudine leads to marked reduction in HBV-DNA and improvement in ALT levels and liver histology in the majority of patients, only a small proportion become HBeAg-negative with treatment .[19, 20, 39]

Indeed, discontinuation of lamivudine is almost always followed by a rise in HBV-DNA levels and relapse in disease in patients who remain HBeAg-positive on therapy (~ 80%).[19] Even in patients who become HBeAg-negative, this loss was not always durable once therapy was stopped, relapse being most frequent within the next 6 months .[33] Unfortunately there is not enough data about durability of improvements in serum ALT levels, HBV-DNA and HBeAg after discontinuation of lamivudine.

Based on some data, decrease in serum HBV-DNA appears to be more rapid with lamivudine than with interferon. On-treatment flares in aminotransferases are more common with interferon than with lamivudine. The results of the major clinical trials suggest that the rate of virological response is similar after a 4-6 month course of interferon-alpha or a 1-year course of lamivudine.[11, 14]

The loss of HBsAg with development of anti-HBs is a reliable marker for resolution of chronic hepatitis B and might be used as the definition of a complete response to therapy. In studies of interferon therapy, an average of 8% of patients cleared HBsAg with therapy.[11] In studies of lamivudine, loss of HBsAg occurred in only 1 to 2 % of patients.

In studies of continuous maintenance therapy, HBsAg loss with development of anti-HBs allowed for withdrawal of antiviral therapy and was reliably followed by long-term, durable remission in disease.[23] In patients with contraindications to interferon-alpha, such as decompensated cirrhosis, autoimmune disease and organ transplants, lamivudine is the drug of choice and in patients with co-infection of HBV and HCV or HBV and HDV infections, interferon-alpha is the drug of choice.Interferon-alpha is less successful as a treatment of HBV infection in patients with HIV co-infection ,and lamivudine is the treatment of choice in these patients. But it is important to know that lamivudine is also a potent antiretroviral agent in the setting of combination antiretroviral therapy. It should not be used as a single agent in patients with HIV infection, even if it is only being used to treat HBV, in order to avoid the rapid development of lamivudine-resistant quasispecies of HIV. Patients with HBV-HIV co-infection should be treated with triple-drug antiretroviral therapy, including a lamivudine daily dose of 300 mg.

Pre-treatment factors predictive of response are similar for both drugs, and include high serum aminotransferase (>5 ¥ upper limit of normal), high grade of necro-inflammatory activity, and low serum HBV-DNA level .[11, 14, 19]

The optimal approach to antiviral therapy of CHB remains

undefined. But interferons have the advantage over other treatment options because seroconversion is usually more durable, and loss of HBsAg eventually occurs in a large proportion of the responding subjects. However, interferon-alpha is subcutaneously administered, expensive, and sometimes poorly tolerated.

REFERENCES

1. Lee WM. Hepatitis B virus infection. N Engl J Med 1997; 337: 1733–45
2. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 1988; 61: 1942–56
3. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000-summary of a workshop. Gastroenterology 2001; 120: 1828-1853
4. Manesis EK, Papatheodoridis GV, Hadziyanis SJ, Serum HBV-DNA levels in inactive hepatitis B virus carriers. Gastroenterology 2002; 122: 2092-2093
5. Lok ASF,McMahon BJ. AASLD Practice Guidelines: Chronic hepatitis B. Hepatology 2001; 34: 1225-1241
6. Di Bisceglie AM, Waggoner JG, Hoofnagle JH. Hepatitis B virus deoxyribonucleic acid in liver of chronic carriers: correlation with serum markers and changes associated with loss of hepatitis B e antigen after antiviral therapy. Gastroenterology 1987; 93:1236-1241
7. Papatheodoridis GV, Hadziyanis SJ. Current management of chronic hepatitis B. Aliment Pharmacol Ther 2004; 19: 25-37
8. Korenmany J, Baker B, Waggoner J, Everhart JE, Di Bisceglie AM, Hoofnagle JH. Long-term remission of chronic hepatitis B after alpha-interferon therapy. Ann Intern Med 1991; 114: 629-34
9. Davis GL, Hoofnagle JH. Interferon in viral hepatitis: role in pathogenesis and treatment. Hepatology 1986; 6: 1038-1041
10. Hoofnagle JH, Di Bisceglie AM. The treatment of chronic viral hepatitis. N Engl J Med 1997; 336: 347-56
11. Wong DKH, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. Ann Intern Med 1993; 119:312-323
12. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med 1996; 334: 1422–27.
13. Vinayek R, Shakil O. Adverse events associated with interferon alfa therapy in patients with chronic viral hepatitis. Viral Hep Rev 1997; 3: 167-77
14. Tine F, Liberati A, Craxi A, Almasio P, Pagliaro L. Interferon treatment in patients with chronic hepatitis B: a meta-analysis of the published literature. J Hepatol 1993; 18: 154-162
15. Niederau C, Heintges T, Langes S, Goldmann G, Niederau CM, Mohr L, Haussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alpha for chronic hepatitis B. N Engl J Med 1996; 334: 1422-1427
16. Lau DT, Everthart J, Kleiner DE, Park Y, Vergalla J, Schmid P, Hoofnagle JH. Long-term follow-up of patients with chronic hepatitis B treated with interferon alpha. Gastroenterology 1997; 113: 1660-1667
17. 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.
18. Lok AS, Chung HT, Liu VW, Ma OC. Long-term follow-up of chronic hepatitis B patients treated with interferon alpha. Gastroenterology 1993; 105:1833–1838.
19. Dienstag JL, Perrillo RP, Shiff ER, et al. A preliminary trial of lamivudine for chronic hepatitis B infection. N Engl J Med 1995; 333: 1657-1661
20. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999; 341: 1256-1263
21. Tipples GA, Ma MM, Fischer KP, Bain VG, Kneteman NM, Tyrrell DLJ. Mutation in the HBV RNA dependent DNA polymerase confers resistance of lamivudine in vivo. Hepatology 1996; 24: 714-717
22. Lau DT-Y, Khokhar F, Doo E, Ghany MG, Herion D, Park Y, et al. Long-term therapy of chronic hepatitis B with lamivudine. Hepatology 2000; 32: 838-844
23. Hoofnagle JH. Challenges in therapy of chronic hepatitis B. J of Hepatol 2003; 39: S230-S235
24. Dienstag JL, Goldin RD, Healthcote EJ, et al. Histological outcome during long-term lamivudine therapy. Gastroenterology 2003; 124: 105–17.
25. Lai CL, Dienstag JL, Schiff E, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy of patients with chronic hepatitis B. Clin Infect Dis 2003; 36: 687–96.
26. Allen MI, Deslauriers M, Andrew CW, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Hepatology 1998; 27: 1670–77. 34: 785–91
27. Kapoor D, Guptan RC, Wakil SM, et al. Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. J Hepatol 2000; 33: 308–12.
28. Yao FY, Terrault NA, Freise C, Maslow L, Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. Hepatology 2001; 34: 411–16.
29. Shalm SW, Heathcote J, Gianciara J, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. Gut 2000; 46: 562-568
30. Schiff E, Karayalcin S, Grimm I, et al. A placebo controlled study of lamivudine and interferon alpha 2b in patients with chronic hepatitis B who previously failed interferon therapy [Abstract]. Hepatology 1998; 28: 388A
31. Schiff E, Cianciara J, Karayalcin S, et al. Durable HBeAg and HBsAg seroconversion after lamivudine for chronic hepatitis B. J Hepatol 2000; 32(Suppl. 2): 99.
32. Chang TT, Lai CL, Liaw YF, et al. Incremental increases in HBeAg seroconversion and continued ALT normalization in Asian chronic HBV (CHB) patients treated with lamivudine for four years. Antiviral Ther 2000; 5(Suppl. 1): 44
33. Song B-C, Suh DJ, Lee HC, Chung Y-H, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology 2000; 32: 803–6.
34. Leung NW, Liaw Y-F, Chang T-T, et al. Durable HBeAg response in Chinese patients treated with lamivudine. Hepatology 2001; 34: 348A.
35. Leung NWY, Lai CL, Chang TT, et al. Three year lamivudine therapy in chronic HBV. J Hepatol 1999; 30(Suppl. 1): 59.
36. Liaw Y-F, Leung NWY, Chang T-T, et al. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Gastroenterology 2000; 119: 172–80.
37. Tassopoulos NC, Volpes R, Pastore G, et al. Post lamivudine treatment follow up of patients with HBeAg negative chronic hepatitis B. J Hepatol 1999; 30(Suppl. 1): 117
38. Papatheodoridis GV, Dimou E, Laras A, Papadimitropoulos V, Hadziyannis SJ. Course of virologic breakthroughs under long-term lamivudine in HBeAg-negative precore mutant HBV liver disease. Hepatology 2002; 36: 219–26.
39. Lai C-L, Chien R-N, Leung NWY, Chang T-T, Guan R, Tai D-I, et al. A 1- year trial lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 1998; 339: 61-68