

Chronic Hepatitis B Virus Infection: Treatment Strategies for the Next Millennium

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Chronic hepatitis B virus (HBV) infection is a leading cause of cirrhosis and hepatocellular carcinoma worldwide. Its prevalence approaches 10% in hyperendemic areas, such as southeast Asia, China, and Africa. Although chronic HBV infection is seen less frequently in North America and Europe, an estimated 1.25 million persons in the United States are infected. In the past decade, revolutionary strides have been made toward the treatment of chronic HBV infection. Interferon- α was once the only available therapy but has recently been joined by the nucleoside analogues, the most extensively studied of which is lamivudine. Interferon therapy continues to have a role in the treatment of a carefully selected group of patients. Lamivudine therapy, which has less stringent selection criteria, suppresses HBV DNA in almost all treated patients: Seventeen percent to 33% experience loss of hepatitis B e antigen, and 53% to 56% have a histologic response. Extended lamivudine treatment leads to the development of a specific lamivudine-resistant virus with base-pair substitutions at the YMDD locus of the DNA polymerase. Newer nucleoside analogues and other immunomodulator therapies are being investigated. In the future, combination therapy with different classes of agents may yield improved response rates and delay the development of resistance.

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Chronic hepatitis B virus (HBV) infection accounts for 5% to 10% of chronic liver disease and cirrhosis in the United States (1, 2). Worldwide, the number of infected persons is predicted to reach 400 million during 2000 (3). Fulminant HBV infection is an important cause of acute liver failure and is responsible for approximately 100 to 200 deaths per year in the United States. The distribution of HBV varies throughout the world. Areas with high prevalence include southeast Asia, China, and Africa, where approximately 10% of the population are chronic carriers. North America, western Europe, and Australia have low levels of endemicity (4). In persons infected with HBV, major morbidity and mortality result when inflammatory liver disease progresses to cirrhosis and hepatocellular carcinoma.

Effective vaccines for HBV have been available since 1981. The initial strategy for vaccination, which targeted such high-risk groups as intravenous drug users, attendees of sexually transmitted disease

clinics, inmates of correctional institutions, homosexual men, patients undergoing hemodialysis, and health care workers, was ineffective. More recently, a broader approach has begun to dramatically reduce the prevalence of infection, the development of HBV carrier state, and the incidence of hepatocellular carcinoma (5). Universal infant immunization was recommended in the United States in 1991 (6).

Insights into the molecular biology of HBV have led to exciting advances in its treatment. This review focuses on the specific treatments available (Table 1) and discusses the replication of HBV to facilitate understanding of the mechanism of the nucleoside analogues.

Virologic Characteristics

Hepatitis B virus belongs to a family of DNA viruses called hepadnaviruses. It is a partially double-stranded circular DNA that is approximately 3200 base pairs in length and has four overlapping reading frames. These encode several viral products: S for surface gene, C for core, X for the x gene, and P for DNA polymerase. The DNA polymerase is a large reading frame of approximately 2500 base pairs that acts as a conventional DNA polymerase but also serves a reverse transcription function for RNA intermediates (Figure 1).

When HBV enters the hepatocytes, the genome moves to the nucleus and is converted to covalently closed circular DNA. This is transcribed to form an RNA intermediate that can move to the cytoplasm, where the virus polymerase uses reverse transcription to convert it to a new circular DNA. The virus polymerase is the site of action of the new reverse transcriptase inhibitors that are used to treat chronic HBV infection (Figure 2).

Goals of Treatment

The objective of treating chronic HBV infection is to halt progression of liver injury by suppressing viral replication or eliminating infection. Sustained loss of the markers of active viral replication (hepatitis B e antigen [HBeAg] and HBV DNA) results in biochemical, clinical, and histologic remission. In

Table 1. Treatment of Chronic Hepatitis B Virus Infection*

Interferon- α
Antiviral agents or nucleoside analogues
Immunomodulator therapy
Non-HBV-specific
Thymosin
Interleukin-2
Interleukin-12
Levamisole
HBV-specific
PreS or S peptide vaccination
Cytotoxic lymphocyte epitope vaccination
DNA vaccination

* HBV = hepatitis B virus; S = surface.

general, seroconversion from HBeAg to hepatitis B e antibody (anti-HBe) is associated with disappearance of HBV DNA in serum and remission of liver disease (7). However, because of mutation in the precore region of the HBV genome, which prevents production of HBeAg, some patients with anti-HBe still have active liver disease and persistent viral replication with serum levels of HBV DNA that are detectable by non-polymerase chain reaction-based assays (8).

Liver injury leading to cirrhosis occurs in patients with active replication but is minimal in those whose HBV DNA levels are negative despite persistence of HBsAg. Therefore, patients with active replication are most in need of treatment. Although many of these patients will have minimal evidence of liver inflammation, the presence of persistent viremia portends liver disease—if not now, then at a later date. Therapy is aimed at eradicating viral replication.

Indications for therapy include evidence of ongoing viral replication: presence of HBeAg and HBV DNA for at least 6 months, persistent elevation of aminotransferase levels, and evidence of chronic HBV infection on liver biopsy (9). Although not absolutely necessary, it is useful to perform a liver biopsy before treatment to assess the extent of disease and to rule out other causes. Monitoring should include monthly evaluations of serum levels of HBV DNA, HBeAg, anti-HBe, and alanine aminotransferase (ALT).

Interferon- α

In 1992, interferon- α 2b was approved by the U.S. Food and Drug Administration (FDA) for use in persons with chronic HBV infection. Until recently, it was the only approved treatment. The current recommended dose of interferon is 5 million U injected subcutaneously each day or 10 million U injected subcutaneously three times per week, for a period of 16 weeks. Possible patterns of response include a sustained response, in which DNA levels, as measured by conventional hybridization assays,

decrease and become negative. In two thirds of persons who develop a sustained response, aminotransferase levels increase transiently; in addition, HBeAg is lost and anti-HBe develops (Figure 3) (10). This aminotransferase flare is believed to be a result of immune-mediated clearance of HBV-infected hepatocytes. Although flares usually occur during treatment, they may be seen after treatment has been discontinued. Alternately, a partial response may occur in which a transient decrease in levels of aminotransferases and serum HBV DNA is associated with persistence of HBeAg (Figure 3) (10).

Interferon's principal mechanism of action is thought to include both antiviral and immunomodulatory effects (11–15). Interferons are effective for the treatment of chronic HBV infection, particularly when patients are carefully selected (16–20). Sixteen weeks of treatment with interferon resulted in clearance of HBeAg in approximately one third of patients in a small trial (17). In the largest U.S. trial (20), the efficacy of a 16-week course of interferon at a dosage of 5 million U/d was compared with that of a 6-week course of prednisone as “priming” before initiation of interferon treatment (21, 22). Both HBeAg and HBV DNA disappeared from serum in 37% of patients treated with interferon alone and 36% of those who received both prednisone and interferon. This represented a significant improvement compared with controls, of whom only 7% achieved the same result ($P < 0.001$). Loss of hepatitis B surface antigen (HBsAg) was seen in 12% and 11% of patients, respectively, and in 0% in

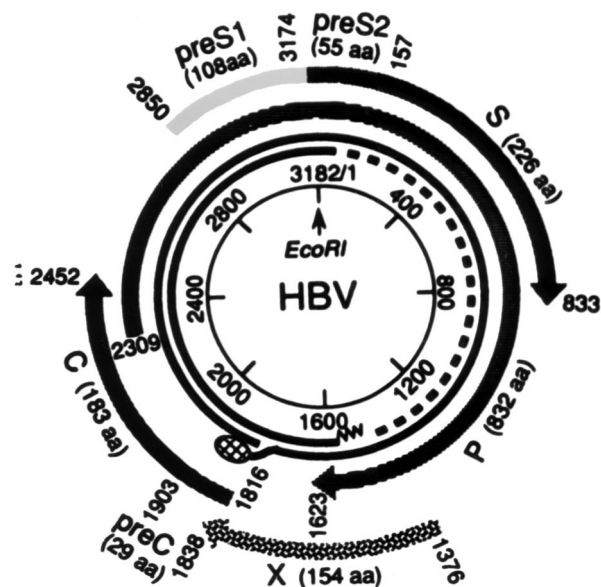


Figure 1. Genome of hepatitis B virus (HBV). The viral genome is partially double stranded. Four overlapping reading frames (surface [S], core [C], polymerase [P], and the x gene [X]) encode for the viral proteins. Three upstream regions (preC, preS1, and preS2) are also shown. The size of each segment is shown in parentheses. aa = amino acids. Adapted with permission from reference 3.

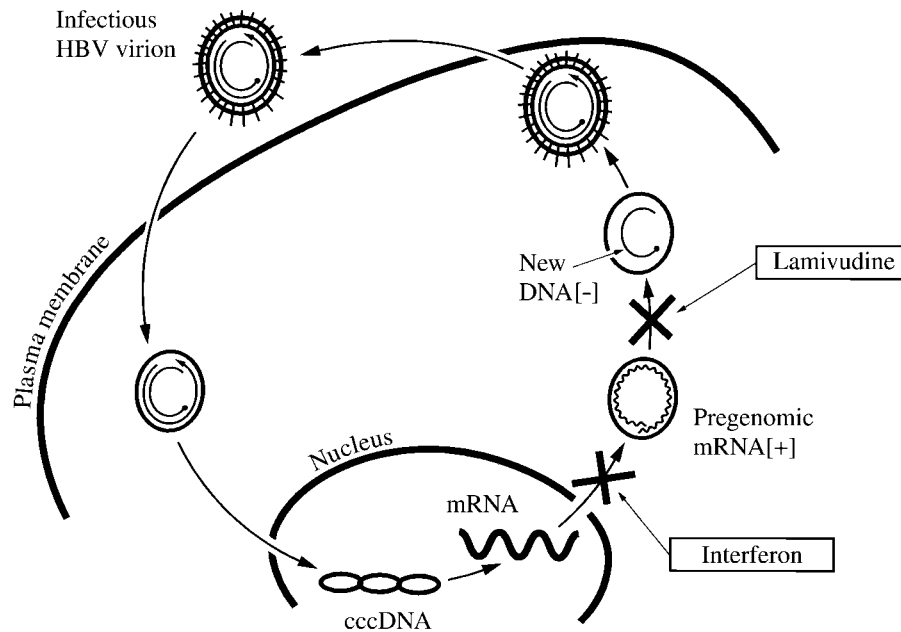


Figure 2. Mechanism of hepatitis B virus (HBV) replication and the site of action of different treatment methods. After HBV endocytosis into hepatocytes, the genome is translocated to the nucleus and converted to covalently closed circular DNA (cccDNA), which is transcribed and translated to form an RNA intermediate. Translocation of pregenomic RNA can be inhibited by interferon- α , and reverse transcription of the pregenomic RNA by polymerase to HBV DNA can be inhibited by nucleoside analogues. Association of the partially double-stranded DNA with envelope proteins leads to the formation of mature HBV particles that are then released from the hepatocyte. mRNA = messenger RNA. Adapted with permission from Glaxo-Wellcome Pharmaceuticals.

controls ($P = 0.024$). Aminotransferase levels normalized more frequently in the treated groups. Overall, histologic improvement was seen more often in treated patients, in association with serologic responses (loss of HBeAg and HBV DNA). A meta-analysis of seven additional studies showed a similar lack of efficacy of prednisone priming (23).

A meta-analysis of 16 randomized, controlled trials (19) found that loss of HBeAg and HBV DNA occurred in 33% and 37% of interferon-treated patients compared with only 12% and 17% of controls, respectively ($P < 0.001$). The number needed to treat (NNT) to observe loss of HBeAg and HBV DNA was 5. When compared with the background rate of seroconversion, loss of HBsAg in serum occurred in an additional 6% of patients. The NNT to observe loss of HBsAg was 18.

Long-term follow-up studies to demonstrate improvement in survival or prevention of cirrhosis have been limited. In 103 patients treated with interferon (24), the 5-year survival rate without complications was approximately 95% among those who became seronegative for HBeAg and less than 50% among those who did not.

Interferons have significant side effects, including flulike symptoms; fever; myalgia; mild bone marrow suppression; thyroid abnormalities in 2% to 5% of patients; and psychiatric side effects, such as depression, in approximately 15% of patients (25). Thrombocytopenia or granulocytopenia, serious mood changes, or debilitating fatigue may lead to dose adjustment or discontinuation. Interferon therapy

must be used with caution in patients with cirrhosis because it may exacerbate hepatitis and lead to decompensation. Very low doses of interferon have been used with some success in this setting (26).

Interferon is not effective in all patients. Despite patient selection, only 30% to 40% have achieved sustained responses. Factors that predict a favorable response include low pretreatment levels of HBV DNA (<200 pg/mL), high levels of serum aminotransferases (>100 U/L), and evidence of active necroinflammation in the liver (17, 18, 27). Other factors sometimes associated with an improved response include absence of immunosuppression, female sex, history of acute icteric hepatitis, short known duration of hepatitis, wild-type (HBeAg-positive) virus, and horizontal rather than perinatal acquisition of the virus. For patients who do not meet these criteria, response rates are less than 5% (28).

For patients who do not respond to interferon or are not appropriate candidates for such treatment, other methods are required. This group of patients also includes those who are immunosuppressed, those with normal aminotransferase levels (and viral replication), those with decompensated cirrhosis (29), and those infected with HBeAg-negative pre-core mutations.

Nucleoside Analogues

Nucleoside analogues were first tested two decades ago (Table 2). However, these first-generation

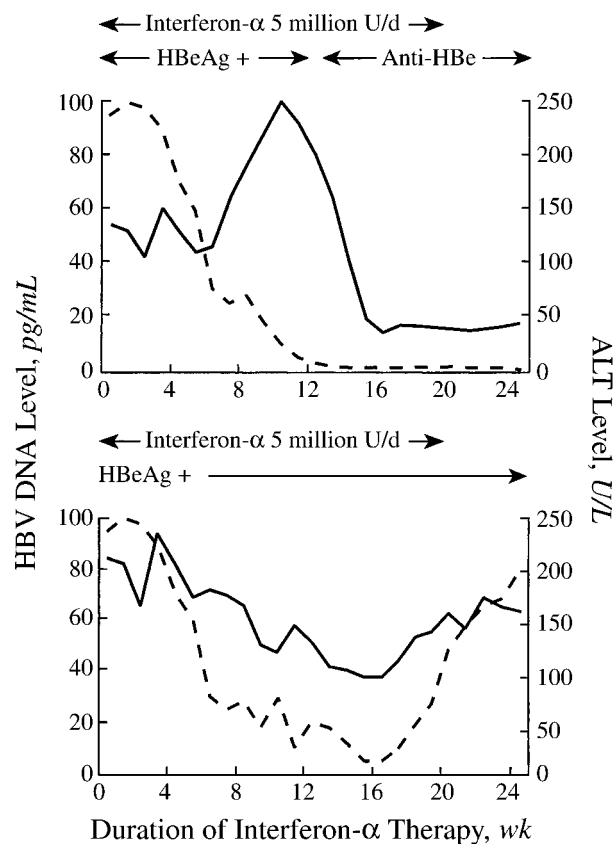


Figure 3. Interferon for chronic hepatitis B virus (HBV) infection. **Top.** Sustained response. A “flare” of alanine aminotransferase (ALT) activity is associated with the loss of hepatitis B e antigen (HBeAg). **Bottom.** Transient response. Serum levels of ALT (solid lines) and HBV DNA (dashed lines) return to pretreatment levels after interferon therapy is discontinued. Hepatitis B e antigen remains positive (+). Anti-HBe = hepatitis B e antibody. Adapted with permission from reference 10.

agents did not effectively suppress viral replication and had serious side effects. More recently, fialuridine, a fluoro-iodo-arabino-furanosyl-uracil nucleoside, markedly suppressed HBV DNA (30, 31) but caused severe multisystem toxicity due to mitochondrial dysfunction in patients treated for more than 2 months (32). Because of this tragic experience, more intensive preclinical investigation was done on the effect of the new nucleoside analogues on mitochondrial function.

Lamivudine

Lamivudine (Epivir-HBV, Glaxo Wellcome, Research Triangle Park, North Carolina) is the first nucleoside analogue to be approved by the FDA (December 1998) for use in chronic HBV infection (33) and is the only nucleoside analogue that has been studied in long-term clinical trials. Lamivudine competitively inhibits viral reverse transcriptase and terminates proviral DNA chain extension (34, 35). Unlike interferon, lamivudine and the other newer nucleoside analogues, such as famciclovir, lobucavir, and adefovir, do not affect the host immune response. Lamivudine decreases HBV replication by

approximately 3 to 4 log copies in most patients (36). It is rapidly absorbed after oral administration (37) and is excreted largely unchanged by the kidneys. In persons with substantial renal impairment, reduced doses should be administered.

In preliminary trials, few side effects were seen during 12 or 24 weeks of treatment with an optimal dosage of lamivudine (100 mg/d) (38, 39). Serum levels of HBV DNA decreased to undetectable levels in 93% to 100% of patients. After therapy was stopped, HBV DNA reappeared in most patients.

Three large placebo-controlled phase III clinical trials of lamivudine (100 mg/d for 1 year) have been performed. These trials included approximately 700 patients, both those who were treatment-naïve (40, 41) and those who had not responded to previous interferon therapy (42). The primary efficacy end point was histologic response; this was defined as a greater than 2-point reduction in the Histologic Activity Index, which assesses periportal and bridging necrosis, intralobular degeneration and focal necrosis, portal inflammation, and fibrosis or cirrhosis (43).

Histologic responses occurred in 52% to 56% of lamivudine recipients and 23% to 25% of placebo recipients ($P < 0.001$ for all studies; NNT, 3 for treatment-naïve patients and 4 for nonresponders). The median reduction in Histologic Activity Index score was 3 to 4 in the lamivudine group and 0 in the placebo group. Progression of hepatic fibrosis decreased in all lamivudine recipients regardless of serologic response. Loss of HBeAg by week 52 occurred in 17% to 33% of lamivudine-treated patients and 11% to 13% of controls ($P < 0.05$; NNT, 5 for treatment-naïve patients and nonresponders). Lamivudine recipients were more likely to seroconvert to anti-HBe by week 52 (16% to 18% compared with 4% to 6% in controls [$P < 0.05$]; NNT, 8 to 9 for treatment-naïve patients and 20 for nonresponders). Sustained normalization of ALT levels occurred in 41% to 72% of patients in the lamivudine group and in 7% to 24% of placebo recipients ($P < 0.001$ for all studies). Alanine aminotransferase responses occurred as early as 2 weeks after the start of treatment but were maximal only at 6 months.

Lamivudine induces a more rapid pattern of re-

Table 2. Nucleoside Analogues

First-generation	Second-generation
Vidarabine	Fialuridine
Acyclovir	Lamivudine
Ganciclovir	Famciclovir
Zidovudine	Lobucavir
Ribavirin	Adefovir (nucleotide analogue)
Didanosine	BMS 200475
Zalcitabine	Emtricitabine

sponse than interferon: Levels of HBV DNA showed a median reduction of 97% after 2 weeks and 98% by 1 year. Suppression of HBV DNA was well maintained during treatment. In a U.S. multicenter study (41), serum HBV DNA levels generally returned toward pretreatment values when treatment was stopped, although they continued to remain below baseline. Compared with patients treated for 3 or 6 months, who experienced a rapid relapse to baseline HBV DNA levels within 2 months after treatment, patients treated for 12 months had a slower return of detectable HBV DNA. In addition, their median HBV DNA levels remained approximately 55% below baseline levels for 4 months after treatment. The favorable responses seen with lamivudine in the Asian multicenter trial are particularly meaningful because they were obtained in a population that is unlikely to respond to interferon (44).

In the Asian multicenter study, therapy was continued after 1 year and resulted in continued improvement in liver necroinflammation (45). The sustained seroconversion rate of HBeAg to anti-HBe increased during the second year from 17% to 27% (46). However, the presence of detectable HBV DNA increased to 48% among lamivudine-treated patients after 2 years of therapy, suggesting lamivudine resistance. Histologic characteristics continued to improve despite the development of resistance.

Regarding durability of response after treatment, 70% to 90% of lamivudine-treated patients who had achieved HBeAg seroconversion or HBeAg loss by week 52 maintained their HBeAg responses 16 to 24 weeks after discontinuation of treatment (41, 47). Therefore, for immunocompetent patients with chronic HBV infection, it seems reasonable to continue treatment with lamivudine until HBeAg seroconversion is documented; lifelong treatment may not be needed.

Clinical trials of interferon have been unsuccessful for patients infected with precore mutant strains of HBV (48, 49), but lamivudine therapy suppresses HBV replication in these patients (50). Responses to lamivudine among these patients are similar to those reported in HBeAg-positive patients. Unlike interferon, lamivudine is equally effective in suppressing HBV replication independent of pretreatment variables. However, as with interferons, increased pretreatment ALT values are strongly correlated with HBeAg seroconversion (51).

In the doses used for chronic HBV infection, lamivudine has an excellent safety profile (52). No mitochondrial toxicity or other toxicity has been noted during treatment. After lamivudine therapy is withdrawn, a twofold to threefold elevation in ALT level may occur (21% compared with 11% in controls). Jaundice or other signs of hepatic decompen-

sation have not been noted; however, patients should be closely monitored for several months after stopping treatment. Resumption of lamivudine therapy is usually effective in treating these "flares" in ALT level, and lamivudine can be used safely in patients with decompensated liver disease.

Lamivudine: YMDD Mutations

The YMDD motif is a highly conserved domain of all reverse transcriptases and is required for polymerase activation. In patients receiving long-term therapy with lamivudine, resistance has been noted in the form of mutations at the YMDD locus (53–57). The best described so far is the substitution of valine or isoleucine for methionine at residue 552 (53). The substitution of methionine for leucine at position 528 has been described (54), as have other, rarer mutations, including phenylalanine-leucine at position 501 and leucine-methionine at position 515. However, the clinical significance of these rarer mutations is less clear (55, 56).

In phase III clinical trials of lamivudine therapy in Asia (40), mutations in the YMDD motif of the polymerase gene were noted only after the first 6 months of treatment. The rate of detection increased progressively with additional therapy. In four international multicenter trials of lamivudine, 16% to 32% of patients developed the YMDD mutation after 1 year of lamivudine treatment. Patients with YMDD mutations of HBV continue to demonstrate partial suppression of HBV DNA, and many have improved ALT levels and histologic findings that are similar to those seen in patients without resistance. This suggests that continued therapy with lamivudine is prudent despite viral breakthrough. Two similar mutations have emerged (YVDD and YIDD), and it has been estimated that 99% of patients who are HBeAg-positive and have elevated ALT levels (>1.3 times the upper limit of normal) and detectable HBV DNA (>20 pg/mL by hybridization assay) after 24 weeks of lamivudine therapy have one of these two forms (56). Because lamivudine-resistant mutants do not replicate as well as wild-type virus (58), wild-type virus quickly replaces the mutated virus if treatment is discontinued (59). Thus, it is difficult to stop lamivudine treatment because of the risk for disease exacerbation.

A possible model for lamivudine resistance is as follows. The affinity of lamivudine for the reverse transcriptase enzyme of HBV correlates with the length of the amino acid side chain in position 552. Lamivudine binds at a pocket in the surface of the enzyme formed in part by residue 552. Substitution of methionine by isoleucine and then valine shortens the side chain progressively. As the side chain decreases, the binding pocket increases, making it

less capable of binding lamivudine and thereby inducing resistance (53).

Lobucavir

Lobucavir is a guanosine nucleoside analogue with broad-spectrum activity against many viruses. In 81 patients treated with lobucavir for 12 weeks at doses of 200 to 800 mg (60), the median suppression of HBV DNA was 3.5 log copies compared with 0.05 log copies in those who received placebo ($P < 0.001$). Hepatitis B virus DNA became undetectable in 68% of treated patients (compared with 9% of controls), and HBeAg loss occurred in 23% of patients in the 200-mg group. An inverse dose-response relation was observed: Loss of HBeAg was seen in 9% of patients in the 400-mg group and 5% of patients in the 800-mg group. Extended treatment with lobucavir was described as safe and efficacious (61). Side effects included mild anorexia, dizziness, and abdominal pain. Although lobucavir seemed promising, the manufacturer (Bristol-Myers Squibb, Wallingford, Connecticut) recently halted clinical testing because of concerns about a possible association between long-term administration and neoplasia in mice and rats. The future of lobucavir remains uncertain.

Famciclovir

Famciclovir is a well-absorbed oral form of penciclovir, an acyclic guanine derivative, that also inhibits HBV DNA polymerase (62–64). In a preliminary trial, famciclovir, 500 mg three times daily, suppressed HBV DNA in all patients and resulted in HBeAg seroconversion in a small minority of patients (64). Famciclovir suppresses HBV replication less rapidly and by a lower order of magnitude than lamivudine, resulting in less frequent HBeAg seroconversion (65). Famciclovir resistance (62) is associated with mutations at residue 528 (domain B) of the HBV DNA polymerase. Because of this, it fails to overcome resistance to lamivudine (66). For these reasons, famciclovir is less attractive than other nucleoside analogues.

Adefovir

Adefovir is an adenine nucleotide analogue with broad-spectrum activity (67) that is administered as the prodrug adefovir dipivoxil. Clinical trials (68–71) have suggested that adefovir may be effective as first-line monotherapy for the treatment of chronic HBV infection. In two phase II studies (72), 12 weeks of adefovir treatment at daily doses of 30 mg or greater resulted in a reduction of 4 log copies in levels of HBV DNA ($P < 0.001$ compared with controls). Loss or seroconversion of HBeAg occurred in 20% to 27% of patients and in 0% of controls. Levels of HBV DNA returned to baseline after

treatment in patients who did not seroconvert. Adefovir is well tolerated, but the development of renal injury in patients treated with doses of 30 mg and higher suggests that lower doses and renewed vigilance for adverse events are needed (73).

No resistant mutations have been reported to date with adefovir. In vitro, lamivudine-resistant strains are generally susceptible to adefovir (74, 75), although a higher concentration of the drug is required to suppress the M552V mutation. Mutated HBV strains that are resistant to famciclovir are also reported to be susceptible to adefovir (76). A recent clinical study supports the efficacy of adefovir in vivo (77).

Immunomodulator Therapy

Liver injury in chronic HBV infection occurs because of the host's immune response to HBV. The immune attack is mediated by the cellular immune response (78). Recognition of viral determinants on the liver cell surface leads to hepatocyte killing through this response, and viral replication is aborted when it is carried to completion. Patients who successfully clear the virus demonstrate effective viral antigen binding and recognition by cytotoxic lymphocytes, and those who lack this capability have persistent infection.

Immunomodulators that may be used in the treatment of chronic HBV infection are listed in **Table 1**. In general, nonspecific immunomodulation has been largely ineffective in clearing HBV infection. Although treatment with thymosin for 6 or 12 months has been associated with a greater HBV DNA and HBeAg response in some trials (79–81), these results have not been confirmed by other studies (82–84). Mutations of HBV have also been reported after thymosin treatment (85). In the past few years, several HBV-specific immunomodulator therapies have shown initial promise (86–92). Large-scale randomized, controlled studies in humans are awaited.

Combination Therapy

All of the treatments available for HBV infection are less than perfect. Interferon continues to have a place in the treatment of a select group of patients because it can bring about permanent seroconversion, a desirable goal, in a limited treatment period. Lamivudine yields a seroconversion response in nearly one third of patients after 1 year, but its efficacy is limited by the development of resistance. Monotherapy with nucleoside analogues is insufficient for viral eradication in most patients. Experi-

ence with HIV has taught us that combination therapy yields better responses. A possible future regimen for chronic HBV infection might involve one or more antiviral agents to decrease viral load, immunomodulator therapy to eliminate residual intracellular virus, and therapeutic immunization to induce loss of the carrier state.

To date, combination therapy has not been effective. A multicenter trial of lamivudine and interferon (42) conducted in the United States, Canada, and Europe did not show benefit of combination therapy in patients who had previously not responded to interferon alone. A similar trial (93) involving treatment-naïve patients reported slightly better HBeAg responses in the combination group. The limited success of these two studies does not necessarily preclude investigating other approaches to combination treatment. Several other regimens (94–97), including combination of two or more nucleoside analogues or a nucleoside analogue plus immunomodulator therapy, are being considered.

Cost-Effective Therapy

Antiviral therapy for chronic HBV infection is fairly expensive. In 1999, average wholesale prices were approximately \$5600 for a 16-week course of interferon and approximately \$1600 for lamivudine (100 mg/d for 1 year) (98, 99). However, it has been shown that therapy is more cost-effective than treatment of symptoms (100).

Conclusions

Treatment of chronic HBV infection is a rapidly evolving field. Interferons have been somewhat displaced by the more potent and easier-to-use nucleoside analogues. Interferons may be used in a selected group of patients who have a reasonable likelihood of responding (Figure 4), such as immunocompetent, noncirrhotic patients with elevated aminotransferase levels and HBeAg-positive wild-type virus who acquired the infection by horizontal rather than perinatal transmission. Interferon therapy is short-term and does not rule out later use of lamivudine if seroconversion does not occur. Furthermore, patients who receive interferon do not seem to develop YMDD mutations. A single daily dose of lamivudine (100 mg) has been found to be safe and efficacious in most patients with chronic HBV infection because it suppresses viral replication with limited associated seroconversion of HBeAg to anti-HBe and improves histologic characteristics in all patients. Unlike interferon, lamivudine can be used for all patients with HBV infection

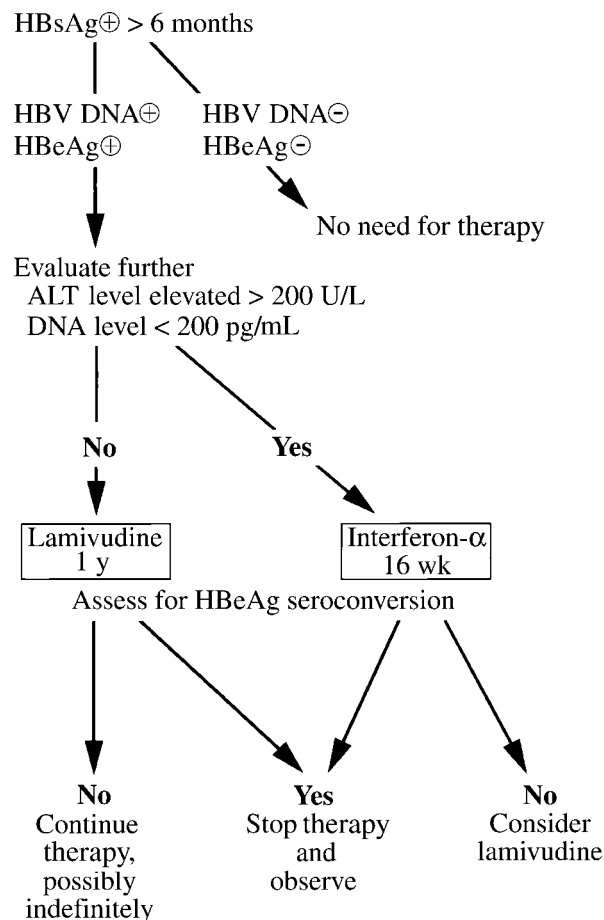


Figure 4. Proposed algorithm for treatment of chronic hepatitis B virus (HBV) infection. ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen.

who have active viral replication, although those with the highest ALT levels are most likely to seroconvert. Other nucleoside analogues are also being investigated for the treatment of chronic HBV infection. The drawback to nucleoside analogue monotherapy is the development of mutated HBV strains that are resistant to these drugs. Combinations of multiple nucleoside analogues or different types of agents may lead to better responses and delayed development of resistance.

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References

1. **Hoofnagle JH.** Chronic hepatitis B [Editorial]. *N Engl J Med.* 1990;323:337-9.
2. **Moyer LA, Mast EE.** Hepatitis B: virology, epidemiology, disease, and prevention, and an overview of viral hepatitis. *Am J Prev Med.* 1994;10(Suppl):45-55.
3. **Lee WM.** Hepatitis B virus infection. *N Engl J Med.* 1997;337:1733-45.
4. **Kane M.** Global programme for control of hepatitis B infection. *Vaccine* 1995;13(Suppl 1):47-9.
5. **Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, et al.** Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. *JAMA.* 1996;276:906-8.
6. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Morb Mortal Wkly Rep.* 1991;40:1-25.
7. **Hoofnagle JH, Dusheiko GM, Seeff LB, Jones EA, Waggoner JG, Bales ZB.** Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. *Ann Intern Med.* 1981;94:744-8.
8. **Carman WF, Jacyna MR, Hadziyannis S, Karayiannis P, McGarvey MJ, Makris A, et al.** Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet.* 1989;2:588-91.
9. **Hoofnagle JH, di Bisceglie AM.** The treatment of chronic viral hepatitis. *N Engl J Med.* 1997;336:347-56.
10. **Fried MW.** Therapy of chronic viral hepatitis. *Med Clin North Am.* 1996;80:957-72.
11. **Peters M.** Mechanism of action of interferons. *Semin Liver Dis.* 1989;9:235-9.
12. **Tompkins WA.** Immunomodulation and therapeutic effects of the oral use of interferon-alpha: mechanism of action. *J Interferon Cytokine Res.* 1999;19:817-28.
13. **Kuhen KL, Vessey JW, Samuel CE.** Mechanism of interferon action: identification of essential positions within the novel 15-base-pair KCS element required for transcriptional activation of the RNA-dependent protein kinase pkr gene. *J Virol.* 1998;72:9334-9.
14. **Kuhen KL, Samuel CE.** Mechanism of interferon action: functional characterization of positive and negative regulatory domains that modulate transcriptional activation of the human RNA-dependent protein kinase Pkr promoter. *Virology.* 1999;254:182-95.
15. **Taylor JL, Grossberg SE.** The effects of interferon-alpha on the production and action of other cytokines. *Semin Oncol.* 1998;25(Suppl 1):23-9.
16. **Dooley JS, Davis GL, Peters M, Waggoner JG, Goodman Z, Hoofnagle JH.** Pilot study of recombinant human alpha-interferon for chronic type B hepatitis. *Gastroenterology.* 1986;90:150-7.
17. **Hoofnagle JH, Peters M, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, et al.** Randomized, controlled trial of recombinant human α -interferon in patients with chronic hepatitis B. *Gastroenterology.* 1988;95:1318-25.
18. **Perrillo RP, Schiff ER, Davis GL, Bodenheimer HC Jr, Lindsay K, Payne J, et al.** A randomized, controlled trial of interferon alpha-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. *N Engl J Med.* 1990;323:295-301.
19. **Di Bisceglie AM, Fong TL, Fried MW, Swain MG, Baker B, Korenman J, et al.** A randomized, controlled trial of recombinant alpha-interferon therapy for chronic hepatitis B. *Am J Gastroenterol.* 1993;88:1887-92.
20. **Wong DK, 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. A meta-analysis. *Ann Intern Med.* 1993;119:312-23.
21. **Perrillo RP.** The use of corticosteroids in conjunction with antiviral therapy in chronic hepatitis B with ongoing viral replication. *J Hepatol.* 1986;3(Suppl 2):S57-S64.
22. **Perrillo RP, Regenstien FG, Peters MG, DeSchryver-Kecskemeti K, Bodicky CJ, Campbell CR, et al.** Prednisone withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis. A randomized, controlled trial. *Ann Intern Med.* 1988;109:95-100.
23. **Cohard M, Poynard T, Mathurin P, Zarski JP.** Prednisone-interferon combination in the treatment of chronic hepatitis B: direct and indirect metanalysis. *Hepatology.* 1994;20:1390-8.
24. **Niederer C, Heintges T, Lange S, Goldmann G, Niederer CM, Mohr L, et al.** Long-term follow-up of HBeAg-positive patients treated with interferon alpha for chronic hepatitis B. *N Engl J Med.* 1996;334:1422-7.
25. **Renault PF, Hoofnagle JH, Park Y, Mullen KD, Peters M, Jones DB, et al.** Psychiatric complications of long-term interferon alpha therapy. *Arch Intern Med.* 1987;147:1577-80.
26. **Perrillo R, Tamburro C, Regenstien F, Balart L, Bodenheimer H, Silva M, et al.** Low-dose, titratable interferon alpha in decompensated liver disease caused by chronic infection with hepatitis B virus. *Gastroenterology.* 1995;109:908-16.
27. **Brook MG, Karayiannis P, Thomas HC.** Which patients with chronic hepatitis B virus infection will respond to α -interferon therapy? A statistical analysis of predictive factors. *Hepatology.* 1989;10:761-3.
28. **Lok AS, Weller IV, Karayiannis P, Brown D, Fowler MJ, Monjardino J, et al.** Thrice weekly lymphoblastoid interferon is effective in inhibiting hepatitis B virus replication. *Liver.* 1984;4:45-9.
29. **Hoofnagle JH, Di Bisceglie AM, Waggoner JG, Park Y.** Interferon alpha for patients with clinically apparent cirrhosis due to chronic hepatitis B. *Gastroenterology.* 1993;104:1116-21.
30. **Paar DP, Hooton TM, Smiles KA, Di Bisceglie A, Havlir DV, Richman DD, et al.** The effect of FIAU on chronic hepatitis B virus (HBV) infection in HIV-infected subjects (ACTG 122b) [Abstract]. In: Programs and Abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, California, 10-14 October 1992. Washington, DC: American Soc for Microbiology; 1992:264.
31. **Fried MW, Di Bisceglie AM, Straus SE, Savarese B, Beames MP, Hoofnagle JH.** FIAU, a new oral anti-viral agent, profoundly inhibits HBV DNA in patients with chronic hepatitis B [Abstract]. *Hepatology.* 1992;16:127A.
32. **McKenzie R, Fried MW, Sallie R, Conjeevaram H, Di Bisceglie AM, Park Y, et al.** Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *N Engl J Med.* 1995;333:1099-105.
33. **Josefson D.** Oral treatment for hepatitis B gets approval in the United States. *BMJ.* 1998;317:1034.
34. **Schalm SW, de Man RA, Heijtkink RA, Niesters HG.** New nucleoside analogues for chronic hepatitis B. *J Hepatol.* 1995;22(Suppl 1):52-6.
35. **Cammack N, Rouse P, Marr CL, Reid PJ, Boehme RE, Coates JA, et al.** Cellular metabolism of (-) enantiomeric 2'-deoxy-3'-thiacytidine. *Biochem Pharmacol.* 1992;43:2059-64.
36. **Honkoop P, de Man RA, Niesters HG, Main J, Nevens F, Thomas HC, et al.** Quantitative hepatitis B virus DNA assessment by the limiting-dilution polymerase chain reaction in chronic hepatitis B patients: evidence of continuing viral suppression with longer duration and higher dose of lamivudine therapy. *J Viral Hepat.* 1998;5:307-12.
37. **Johnson MA, Moore KH, Yuen GJ, Bye A, Pakes GE.** Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinet.* 1999;36:41-66.
38. **Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M.** A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med.* 1995;333:1657-61.
39. **Nevens F, Main J, Honkoop P, Tyrrell DL, Barber J, Sullivan MT, et al.** Lamivudine therapy for chronic hepatitis B: a six-month randomized dose-ranging study. *Gastroenterology.* 1997;113:1258-63.
40. **Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al.** A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med.* 1998;339:61-8.
41. **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;341:1256-63.
42. **Schiff E, Karayalcin S, Grimm I, Perrillo R, Dienstag J, Husa P, et al.** A placebo controlled study of lamivudine and interferon alpha-2b in patients with chronic hepatitis B who previously failed interferon therapy [Abstract]. International Lamivudine Investigator Group. *Hepatology.* 1998;28:388A.
43. **Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al.** Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology.* 1981;1:431-5.
44. **Perrillo RP.** Factors influencing response to interferon in chronic hepatitis B: implications for Asian and western populations [Editorial]. *Hepatology.* 1990;12:1433-5.
45. **Leung N, Wu PC, Tsang S, Chan HL, Dent J, Roman L, et al.** Continued histological improvement in Chinese patients with chronic hepatitis B with 2 years lamivudine [Abstract]. *Hepatology.* 1998;28:489A.
46. **Liaw YF, Lai CL, Leung NW, Chang TT, Guan R, Tai DI, et al.** Two year lamivudine therapy in chronic hepatitis B infection: results of a placebo controlled multicenter study in Asia [Abstract]. *Gastroenterology.* 1998;114:A1289.
47. **Schiff E, Cianciara J, Kowdley K, Norkrans G, Perrillo R, Tong M, et al.** Durability of HBeAg seroconversion after lamivudine monotherapy in controlled phase II and III trials. International Lamivudine Investigator Group [Abstract]. *Hepatology.* 1998;28:163A.
48. **Brunetto MR, Giarin M, Saracco G, Oliveri F, Calvo P, Capra G, et al.** Hepatitis B virus unable to secrete e antigen and response to interferon in chronic hepatitis B. *Gastroenterology.* 1993;105:845-50.
49. **Brunetto MR, Oliveri F, Rocca G, Criscuolo D, Chiaberge E, Capalbo M, et al.** Natural course and response to interferon of chronic hepatitis B accompanied by antibody to hepatitis B e antigen. *Hepatology.* 1989;10:198-202.
50. **Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, et al.** Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Lamivudine Precore Mutant Study Group. *Hepatology.* 1999;29:889-96.
51. **Chien RN, Liaw YF, Atkins M.** Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Asian Hepatitis Lamivudine Trial Group. *Hepatology.* 1999;30:770-4.
52. **Leung N, Dienstag J, Schiff E, Sullivan M, Atkins M, Grice R, et al.** Clinical safety profile of lamivudine treatment in a large cohort of hepatitis B patients [Abstract]. *Hepatology.* 1998;28:587A.
53. **Allen MI, Deslauriers M, Andrews CW, Tipples GA, Walters KA, Tyrrell DL, et al.** Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Lamivudine Clinical Investigation Group. *Hepatology.* 1998;27:1670-7.
54. **Niesters HG, Honkoop P, Haagsma EB, de Man RA, Schalm SW, Osterhaus AD.** Identification of more than one mutation in the hepatitis B virus polymerase gene arising during prolonged lamivudine treatment. *J Infect Dis.* 1998;177:1382-5.
55. **Fu L, Cheng YC.** Role of additional mutations outside the YMDD motif of hepatitis B virus polymerase in L(-)SddC (3TC) resistance. *Biochem Pharmacol.* 1998;55:1567-72.

56. Atkins M, Hunt CM, Brown N, Gray F, Sanathanan L, Woessner M, et al. Clinical significance of YMDD mutant hepatitis B virus in a large cohort of lamivudine-treated hepatitis B patients [Abstract]. *Hepatology*. 1998;28:319A.
57. Honkoop P, Niesters HG, de Man RA, Osterhaus AD, Schalm SW. Lamivudine resistance in immunocompetent chronic hepatitis B. Incidence and patterns. *J Hepatol*. 1997;26:1393-5.
58. Melegari M, Scaglioni PP, Wands JR. Hepatitis B virus mutants associated with 3TC and famciclovir administration are replication defective. *Hepatology*. 1998;27:628-33.
59. Chayama K, Suzuki Y, Kobayashi M, Kobayashi M, Tsubota A, Hashimoto M, et al. Emergence and takeover of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy. *Hepatology*. 1998;27:1711-6.
60. Heathcote J, Chan R, McHutchinson J, Lee WM, Sherman M, Rutkiewicz V, et al. A phase 2 multi-center study of oral lobucavir for treatment of chronic hepatitis B. Lobucavir HBV Study Group [Abstract]. *Hepatology*. 1998;28:318A.
61. Bloomer J, Brennan-Rowe N, Denisky G, Bukenya T, Rutkiewicz V, Joshi S, et al. Extended treatment of chronic hepatitis B with oral lobucavir: safety and efficacy. Lobucavir Hepatitis Study Group [Abstract]. *Hepatology*. 1998;28:486A.
62. Bartholomeusz A, Groenen LC, Locarnini SA. Clinical experience with famciclovir against hepatitis B virus. *Intervirology*. 1997;40:337-42.
63. Trepo C, Jezek P, Atkinson GF, Boon RJ. Efficacy of famciclovir in chronic hepatitis B: results of a dose finding study [Abstract]. *Hepatology*. 1996;24:188A.
64. Main J, Brown JL, Howells C, Galassini R, Crossey M, Karayiannis P, et al. A double blind, placebo-controlled study to assess the effect of famciclovir on virus replication in patients with chronic hepatitis B virus infection. *J Viral Hepat*. 1996;3:211-5.
65. Lai CL, Yuen MF, Cheng CC, Wong WM, Cheng TK, Lai YP. An open comparative study of lamivudine and famciclovir for the treatment of chronic hepatitis B infection [Abstract]. *Hepatology*. 1998;28:490A.
66. Wolters LM, Honkoop P, Niesters HG, de Man RA. Efficacy of famciclovir treatment in chronic hepatitis B patients with different mutations at position 552 of the DNA polymerase gene. *J Hepatol*. 1998;28:909-10.
67. De Clerq E. Antiviral activity spectrum and target of action of different classes of nucleoside analogues. *Nucleosides Nucleotides*. 1994;13:1271-95.
68. Gilson RJ, Chopra K, Murray-Lyon IM, Newell AM, Nelson MR, Tedder RS, et al. A placebo-controlled phase III study of adefovir dipivoxil (bis-POM PMEA) in patients with chronic hepatitis B infection [Abstract]. *Hepatology*. 1996;24:281A.
69. Bloomer J, Chan R, Sherman M, Ingraham P, DeHertogh D. A preliminary study of lobucavir for chronic hepatitis B [Abstract]. *Hepatology*. 1997;26:428A.
70. Jeffers J, Heathcote E, Wright T, Carithers R, Di Bisceglie A, Perrillo R, et al. A phase II dose-ranging, placebo-controlled trial of adefovir dipivoxil for the treatment of chronic hepatitis B virus infection [Abstract]. *Antiviral Res*. 1998;37:A197.
71. Gilson RJ, Murray-Lyon IM, Nelson MR, Rice SJ, Tedder RS, Murray A, et al. Extended treatment with adefovir dipivoxil in patients with chronic hepatitis B virus infection [Abstract]. *Hepatology*. 1998;28:491A.
72. Heathcote EJ, Jeffers L, Wright T, Sherman M, Perrillo R, Sacks S, et al. Loss of serum HBV DNA and HBeAg and seroconversion following short term (12 weeks) adefovir dipivoxil therapy in chronic hepatitis B: two placebo-controlled phase II and III trials. Adefovir Dipivoxil HBV Study Team [Abstract]. *Hepatology*. 1998;28:317A.
73. Kahn J, Lagakos S, Wulfsohn M, Cherng D, Miller M, Cherrington J, et al. Efficacy and safety of adefovir dipivoxil with antiretroviral therapy: a randomized controlled trial. *JAMA*. 1999;282:2305-12.
74. Ono-Nita SK, Kato N, Shiratori Y, Lan KH, Yoshida H, Kato J, et al. Susceptibility of lamivudine resistant hepatitis B virus to other antivirals: adefovir and lobucavir [Abstract]. *Hepatology*. 1998;28:165A.
75. Xiong X, Flores C, Yang H, Toole JJ, Gibbs CS. Mutations in hepatitis B DNA polymerase associated with resistance to lamivudine do not confer resistance to adefovir in vitro. *Hepatology*. 1998;28:1669-73.
76. Xiong X, Yang H, Westland CE, Toole JJ, Gibbs CS. Human hepatitis B virus DNA polymerases which contain mutations arising during famciclovir treatment remain sensitive to adefovir [Abstract]. *Hepatology*. 1998;28:491A.
77. Perrillo R, Schiff E, Magill A, Murray A. In vivo demonstration of sensitivity of YMDD variants to adefovir [Abstract]. *Gastroenterology*. 1999;116:A1261.
78. Chisari FV, Ferrari C. Hepatitis B virus immunopathology. *Springer Semin Immunopathol*. 1995;17:261-81.
79. Mutchnick MG, Appelman HD, Chung HT, Aragona E, Gupta TP, Cummings GD, et al. Thymosin treatment of chronic hepatitis B: a placebo-controlled pilot trial. *Hepatology*. 1991;14:409-15.
80. Andreone P, Cursaro C, Gramenzi A, Zavaglic C, Rezakovic I, Altomare E, et al. A randomized controlled trial of thymosin-alpha1 versus interferon alfa treatment in patients with hepatitis B e antigen antibody—and hepatitis B virus DNA—positive chronic hepatitis B. *Hepatology*. 1996;24:774-7.
81. Chien RN, Liaw YF, Chen TC, Yeh CT, Sheen IS. Efficacy of thymosin alpha1 in patients with chronic hepatitis B: a randomized, controlled trial. *Hepatology*. 1998;27:1383-7.
82. Fattovich G, Giustina G, Alberti A, Guido M, Pontisso P, Favarato S, et al. A randomized controlled trial of thymopentin therapy in patients with chronic hepatitis B. *J Hepatol*. 1994;21:361-6.
83. Mutchnick MG, Lindsay KL, Schiff ER, Cummings GD, Appelman HD. Thymosin alpha 1 treatment of chronic hepatitis B: a multicenter, randomized, placebo-controlled double-blind study [Abstract]. *Gastroenterology*. 1995;108:A1127.
84. Andreone P, Cursaro C, Gramenzi A, Buzzi A, Covarelli MG, Di Giammarino L, et al. A double-blind, placebo-controlled, pilot trial of thymosin alpha 1 for the treatment of chronic hepatitis C. *Liver*. 1996;16:207-10.
85. Tang JH, Yeh CT, Chen TC, Hsieh SY, Chu CM, Liaw YF. Emergence of an S gene mutant during thymosin alpha1 therapy in a patient with chronic hepatitis B. *J Infect Dis*. 1998;178:866-9.
86. Pol S, Driss F, Carnot F, Michel ML, Berthelot P, Brechot C. Vaccination against hepatitis B virus: an efficient immunotherapy against hepatitis B multiplication. *Comptes Rendus de l'Académie des Sciences Paris*. 1993;316:688-91.
87. Mancini M, Hadchouel M, Davis HL, Whalen RG, Tiollais P, Michel ML. DNA-mediated immunization in a transgenic mouse model of the hepatitis B surface antigen chronic carrier state. *Proc Natl Acad Sci U S A*. 1996;93:12496-501.
88. Vitiello A, Ishioka G, Grey HM, Rose R, Farness P, LaFond R, et al. Development of a lipopeptide-based therapeutic vaccine to treat chronic HBV infection. I. Induction of a primary cytotoxic T lymphocyte response in humans. *J Clin Invest*. 1995;95:341-9.
89. Heathcote J, McHutchison J, Benner K, Wright T, Minuk J, Sacks S, et al. CY-1899: a therapeutic vaccine for chronic hepatitis B [Abstract]. *Hepatology*. 1996;24:283A.
90. Pol S, Driss F, Couillin I, Denis J, Tiollais P, Michel ML, et al. A controlled study of anti-HBV vaccine therapy in chronic hepatitis B infection [Abstract]. *Hepatology*. 1998;28:488A.
91. Senturk H, Tabak F, Akdogan M, Mert A, Erdem L, Turkoglu S, et al. Therapeutic vaccination with a pre-S2 containing vaccine in chronic hepatitis B: a promising approach [Abstract]. *Hepatology*. 1998;28:588A.
92. Putlitz J, Skerra A, Wands JR. An intracellular antibody fragment inhibits hepatitis B virus surface antigen secretion [Abstract]. *Hepatology*. 1998;28:590A.
93. Heathcote J, Schalm SW, Cinciara J, Farrell G, Feinmann V, Sherman M, et al. Lamivudine and Intron A combination treatment in patients with chronic hepatitis B infection [Abstract]. *J Hepatol*. 1998;28:43.
94. Marques AR, Lau DT, McKenzie R, Straus SE, Hoofnagle JH. Combination therapy with famciclovir and interferon-alpha for the treatment of chronic hepatitis B. *J Infect Dis*. 1998;178:1483-7.
95. Colledge D, Locarnini S, Shaw T. Synergistic inhibition of hepadnaviral replication by lamivudine in combination with penciclovir in vitro. *Hepatology*. 1997;26:216-25.
96. Leung YK, So T. Treatment of chronic hepatitis B using thymosin alpha 1 and a combination of two nucleoside analogs, lamivudine and famciclovir [Abstract]. *Hepatology*. 1998;28:216A.
97. Lau GK, Kwok A, Karlberg J, Lai ST, Lim W, Leung YK, et al. A twenty six weeks trial of thymosin alpha 1 plus famciclovir in the treatment of Chinese immune tolerant adult patients with chronic hepatitis B [Abstract]. *Hepatology*. 1998;28:216A.
98. Lacey LF, Cox FM, Payne SL. A drug budget perspective of lamivudine compared with interferon-alpha in the treatment of chronic hepatitis B in the United States [Abstract]. *Hepatology*. 1999;30:481A.
99. Drugs for non-HIV viral infections. *Med Lett*. 1999;41:113-20.
100. Haiderali AM, Villa K, Schrammel P. Cost effectiveness of lamivudine for the treatment of chronic hepatitis B in Canada [Abstract]. *Hepatology*. 1999;30:347A.