

The New England Journal of Medicine

©Copyright, 1995, by the Massachusetts Medical Society

Volume 333

DECEMBER 21, 1995

Number 25

A PRELIMINARY TRIAL OF LAMIVUDINE FOR CHRONIC HEPATITIS B INFECTION

JULES L. DIENSTAG, M.D., ROBERT P. PERRILLO, M.D., EUGENE R. SCHIFF, M.D.,
MARIA BARTHOLOMEW, M.D., CATHERINE VICARY, B.S., AND MARC RUBIN, M.D.

Abstract Background. Better treatments for chronic hepatitis B are needed. Lamivudine, the (–) enantiomer of 3'-thiacytidine, is a potent inhibitor of hepatitis B virus (HBV).

Methods. In a double-blind trial, we randomly assigned 32 patients with chronic hepatitis B (including 17 who had no response to earlier treatment with interferon) to receive 25, 100, or 300 mg of oral lamivudine daily for 12 weeks. The patients were then followed for 24 additional weeks. All the patients had hepatitis B e antigen in serum.

Results. Levels of HBV DNA became undetectable (≤ 1.5 pg per milliliter) in 70 percent of the patients who received the 25-mg dose of lamivudine and 100 percent of those treated with the 100-mg or 300-mg dose. In most patients, HBV DNA reappeared after therapy was completed; however, six patients (19 percent), including five who had not responded to interferon, had sustained suppression of HBV DNA accompanied by normalization

of alanine aminotransferase levels. Hepatitis B e antigen disappeared in four of these six patients (12 percent), three of whom had had no response to interferon. Levels of HBV DNA fell in all patients, including those who had had high levels at base line or normal alanine aminotransferase levels at base line, but sustained responses were more likely in patients with initially low HBV DNA levels and high alanine aminotransferase levels. During or after therapy, alanine aminotransferase levels at least doubled in five patients (50 percent) given the 25-mg dose and eight patients (36 percent) given the 100-mg or 300-mg dose. Minor adverse events occurred that were not related to the dose, as did transient, asymptomatic elevations of amylase, lipase, and creatine kinase levels.

Conclusions. In a preliminary trial, 12 weeks of lamivudine therapy was well tolerated, and daily doses of 100 mg and 300 mg reduced HBV DNA to undetectable levels. (N Engl J Med 1995;333:1657-61.)

ALTHOUGH interferon is an important advance in the treatment of chronic hepatitis B,^{1,2} it is effective in fewer than 40 percent of patients,³ must be given by injection, and has potentially dose-limiting side effects. Nucleoside analogues represent an alternative approach. Lamivudine, the (–) enantiomer of 3'-thiacytidine, is an oral 2',3'-dideoxynucleoside that inhibits DNA synthesis by terminating the nascent proviral DNA chain; it interferes with the reverse-transcriptase activity of the human immunodeficiency virus (HIV) and hepatitis B virus (HBV). Unlike other dideoxynucleosides, lamivudine does not inhibit mitochondrial DNA or marrow progenitor cells at concentrations that block the synthesis of HBV DNA, and it is not incorporated into mitochondrial

DNA.⁴ Lamivudine suppresses HBV DNA in cell lines, ducks, and chimpanzees.^{5,6} Among patients with HIV infection and chronic hepatitis B, lamivudine rapidly reduced HBV DNA to undetectable levels.⁷ In a preliminary, placebo-controlled, dose-ranging trial, 75 patients with chronic hepatitis B were treated with lamivudine for four weeks, in doses of 5 to 600 mg per day. No serious adverse events occurred, and all doses reduced serum levels of HBV DNA. Doses of 20 mg or less resulted in incomplete suppression of HBV DNA, whereas doses of 100 mg or more led to almost complete suppression. Rebound after therapy, however, occurred in all but three patients, in one of whom hepatitis B e antigen (HBeAg) disappeared.⁸

To assess further the potential efficacy and safety of this drug, we administered lamivudine for 12 weeks in a narrower dose range to 32 patients with chronic hepatitis B.

METHODS

We conducted a randomized, double-blind, dose-ranging trial of lamivudine in 32 patients with chronic, replicative hepatitis B. The patients were randomly assigned to receive oral doses of 25, 100, or 300 mg of lamivudine daily for 12 weeks, with monitoring at weeks 1, 2, 4, 6, 8, 10, and 12. Follow-up monitoring was done for 24 weeks after therapy, at weeks 14 and 16 and every 4 weeks thereafter to week 36. Liver biopsy was not done routinely before or after treatment.

Eligible participants included men and women 18 to 70 years of age

From the Gastrointestinal Unit and Liver–Biliary–Pancreas Center, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School, Boston (J.L.D.); the Division of Gastroenterology, Ochsner Clinic, New Orleans (R.P.P.); the Center for Liver Diseases, University of Miami School of Medicine and the Veterans Affairs Medical Center, Miami (E.R.S., M.B.); and Glaxo Research Institute, Research Triangle Park, N.C. (C.V., M.R.). Address reprint requests to Dr. Dienstag at the Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA 02114.

Supported by a grant from the Glaxo Research Institute, by the Hepatitis Research Fund of the Massachusetts General Hospital, and by a Clinical Research Center grant (MO1RR01066) from the National Institutes of Health to Massachusetts General Hospital.

Presented in part at the 45th Annual Meeting of the American Association for the Study of Liver Diseases, Chicago, November 14, 1994, and in abstract form (*Hepatology* 1994;20:199).

who had had hepatitis B surface antigen in serum for at least six months, HBeAg for at least three months, HBV DNA levels of at least 10 pg per milliliter (Genostics assay; Abbott Diagnostics, North Chicago, Ill.) for at least three months, and alanine aminotransferase levels ranging from normal to 300 U per liter. Randomization was stratified according to whether the patients had been treated previously with interferon and, if so, had had no response. Patients were excluded if they had received antiviral, immunomodulatory, or corticosteroid therapy within the preceding six months; had decompensated liver disease (bilirubin, >2.5 mg per deciliter [43 μ mol per liter]; prothrombin time prolonged by >2 seconds; albumin, <3 g per deciliter; or a history of ascites, variceal hemorrhage, or hepatic encephalopathy); were also infected with hepatitis C, hepatitis D, or HIV; had a creatinine concentration of more than 1.5 mg per deciliter (130 μ mol per liter); had a hemoglobin concentration below 10 mg per deciliter, a white-cell count below 3000 per cubic millimeter, or a platelet count below 100,000 per cubic millimeter; had a serious, confounding medical illness or another type of liver disease; or were pregnant or lactating.

Levels of HBV DNA were measured by a hybridization assay with iodine-125 labeling (Genostics assay, Abbott). Levels of 1.5 pg per milliliter or less were considered undetectable.

Statistical differences between means were calculated with Student's t-test or the Mann-Whitney test. Differences in proportions between groups were calculated by chi-square analysis with Yates' correction or Fisher's exact test (InStat Mac, version 2.0, GraphPad Software, San Diego, Calif.). The significance of the loss over time of HBV DNA during therapy was calculated by the log-rank test.⁹ All P values are two-tailed.

This study was approved by the institutional review board at each participating institution, and all patients gave written informed consent.

RESULTS

Of the 32 patients enrolled in the study, 15 had never been treated for HBV and 17 (53 percent) had been treated previously with interferon and had had no response. There were no significant differences between the three treatment groups — those given the 25-mg dose, those given the 100-mg dose, and those given the 300-mg dose — with respect to age, sex, known duration of infection, percentage who had not responded to previous treatment with interferon, percentage who were white, base-line alanine aminotransferase levels, or base-line HBV DNA levels (Table 1). There were also no significant differences in the mean (\pm SE) serum level of HBV DNA (205 \pm 48 vs. 288 \pm 150 pg per milliliter) or alanine aminotransferase (110 \pm 14 vs. 114 \pm 16 U per liter) at base line between patients who had been treated previously with interferon and those who had never been treated.

Figure 1 shows the percentage of patients in each dose group with suppression of HBV DNA during lamivudine therapy. By week 12, 70 percent of the patients in the 25-mg group had undetectable levels of HBV DNA, as compared with 100 percent of patients in the 100-mg and 300-mg groups (global P=0.003 by the log-rank test). The kinetics of HBV DNA suppression were dose-dependent: levels were suppressed in 50 percent of the patients by week 2 in the 300-mg group, by week 4 in the 100-mg group, and by week 8 in the 25-mg group. Similarly, levels were suppressed in 100 percent of patients by week 6 in the 300-mg group and by week 10 in the 100-mg group.

The changes in the mean serum levels of HBV DNA during and after lamivudine therapy are shown in Figure 2. Levels of HBV DNA fell precipitously during the 12 weeks of therapy in all patients (including those with

Table 1. Characteristics of the 32 Patients at Base Line, According to the Treatment Assignment.*

CHARACTERISTIC	LAMIVUDINE DOSE		
	25 mg (N = 10)	100 mg (N = 11)	300 mg (N = 11)
Received interferon and had no response — no. (%)	6 (60)	6 (55)	5 (45)
Age — yr	42.6 \pm 4.3	37.5 \pm 3.8	42.6 \pm 4.3
Male sex — no. (%)	9 (90)	9 (82)	11 (100)
Duration of infection — yr	5.6 \pm 1.0	4.3 \pm 0.8	5.0 \pm 1.2
White race — no. (%)	9 (90)	7 (64) [†]	9 (82)
Weight — kg	82 \pm 4	81 \pm 3	82 \pm 4
Alanine aminotransferase — U/liter	95 \pm 15	127 \pm 18	104 \pm 13
HBV DNA — pg/ml	261 \pm 92	136 \pm 27	185 \pm 48

*Plus-minus values are means \pm SE.

[†]The only Asian patient was in this group.

HBV DNA levels exceeding 200 pg per milliliter at base line or with normal alanine aminotransferase levels at base line) and rebounded after week 12, but the decline during therapy was less complete and the rebound more prominent in the 25-mg group.

As shown in Figure 2, the mean levels of alanine aminotransferase became elevated during therapy. In addition, we noted a dose-related trend in the timing of the peak mean alanine aminotransferase level during therapy: it occurred at 4 weeks in the 25-mg group, 6 weeks in the 100-mg group, and 10 weeks in the 300-mg group. After therapy was discontinued, a second peak occurred at week 24 in all three groups.

The alanine aminotransferase level more than doubled in 50 percent of the patients in the 25-mg group (five patients) and 36 percent of those in the high-dose groups (eight patients) (Table 2); this change was not related to the dose. Elevations in alanine aminotransferase occurred in three patients during therapy, four after therapy, and six both during and after therapy. The alanine aminotransferase level more than tripled in one patient in the 25-mg group at week 24 and in two patients each in the 100-mg group (at 28 and 32 weeks) and the 300-mg group (at 8 and 10 weeks) (Table 2).

The time needed to suppress HBV DNA in 50 percent of patients was shorter in the 100-mg and 300-mg groups than in the 25-mg group, and at the end of 12 weeks of therapy, mean levels of HBV DNA were lower in those groups (Table 2). After therapy was stopped, all patients in the 25-mg group relapsed, whereas in four patients in the 100-mg group and two in the 300-mg group suppression of HBV DNA was sustained through the 36 weeks of the trial. In four of these patients in the high-dose groups HBeAg also disappeared between 12 (three patients) and 24 (one patient) weeks after therapy was completed. Thus, suppression of HBV DNA was sustained in 19 percent of the study group (27 percent of the high-dose groups), and the disappearance of HBeAg was sustained in 12 percent of the group (18 percent of the high-dose groups).

Although levels of HBV DNA became undetectable during the 12 weeks of therapy in every patient treated with 100 or 300 mg of lamivudine, two patients in the 100-mg group and three in the 300-mg group had low-

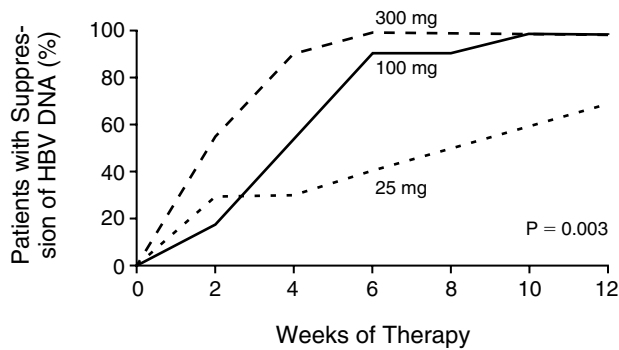


Figure 1. Percentage of Patients with Suppression of HBV DNA during 12 Weeks of Therapy with 25, 100, or 300 mg of Lamivudine.

Lamivudine therapy suppressed HBV DNA in a significant percentage of patients in all three groups (global $P=0.003$ by the log-rank test).

level fluctuations near the cut-off value for the detection of HBV DNA (1.5 pg per milliliter), which account for the respective 12-week mean levels of 1 and 3 pg per milliliter in these two groups (Table 2). These five patients relapsed when therapy was stopped, but all responded again when treatment was resumed (data not shown).

Sustained suppression of HBV DNA was invariably associated with sustained normalization in the levels of alanine aminotransferase. Five of the six patients with sustained suppression of HBV DNA had had no response to interferon therapy, as was true for three of the four patients in whom the disappearance of HBeAg was sustained. Alanine aminotransferase levels became elevated during therapy in three of the six but were limited in amplitude (less than twofold increases). One patient, described below, had a substantial elevation in alanine aminotransferase five months after therapy was stopped.

The mean HBV DNA levels (in picograms per milliliter) were significantly lower at base line in the 4 patients in whom the disappearance of HBeAg was sustained (28 ± 5 pg per milliliter, $P < 0.001$ by the Mann-Whitney test) and the 6 with sustained suppression of HBV DNA (who included the 4 in whom the disappearance of HBeAg was sustained) (60 ± 25 pg per milliliter, $P = 0.009$) than in the 26 patients with only transient suppression of HBV DNA (286 ± 89 pg per milliliter). Conversely, the mean alanine aminotransferase levels were significantly higher at base line in the 4 patients in whom the disappearance of HBeAg was sustained (210 ± 32 U per liter) and the 6 with sustained suppression of HBV DNA (181 ± 28 U per liter) than in the 26 patients with transient suppression of HBV DNA (96 ± 9 U per liter, $P < 0.001$ by the unpaired t-test).

An elevation in alanine aminotransferase was associated with a late acute exacerbation of disease followed by sustained suppression of HBV DNA in one patient who had had no response to interferon therapy. Four months after completing therapy with 100 mg of lamivudine daily, which was associated with a transient suppression of HBV DNA, he had an abrupt increase in

HBV DNA, which peaked a month later at 627 pg per milliliter — more than 10 times the base-line level. Thereafter, HBV DNA levels started to fall spontaneously, accompanied by an acute, symptomatic, hepatitis-like elevation of alanine aminotransferase, to a peak of 940 U per liter (>10 times base line), followed by the disappearance of detectable HBV DNA (by week 42) and a return of alanine aminotransferase levels to normal (by week 45). Because the patient's response was sustained through the end of observation in the trial, he was categorized as having a sustained response; however, HBeAg remained detectable, and he relapsed 3 months after week 45 of observation.

Minor, nonspecific adverse events occurred that were not related to the dose (Table 3). During therapy, four patients had transient elevations in lipase, and two of the four also had transient elevations in amylase after therapy (the levels of both enzymes became elevated in another patient after therapy). Transient elevations in creatine kinase occurred in seven participants, four during therapy and three after. All were asymptomatic, and most of the elevations that occurred during therapy resolved despite the continuation of therapy. There were no instances of acidosis or anion gap and no serious adverse events, such as lactic acidosis, clinical pan-

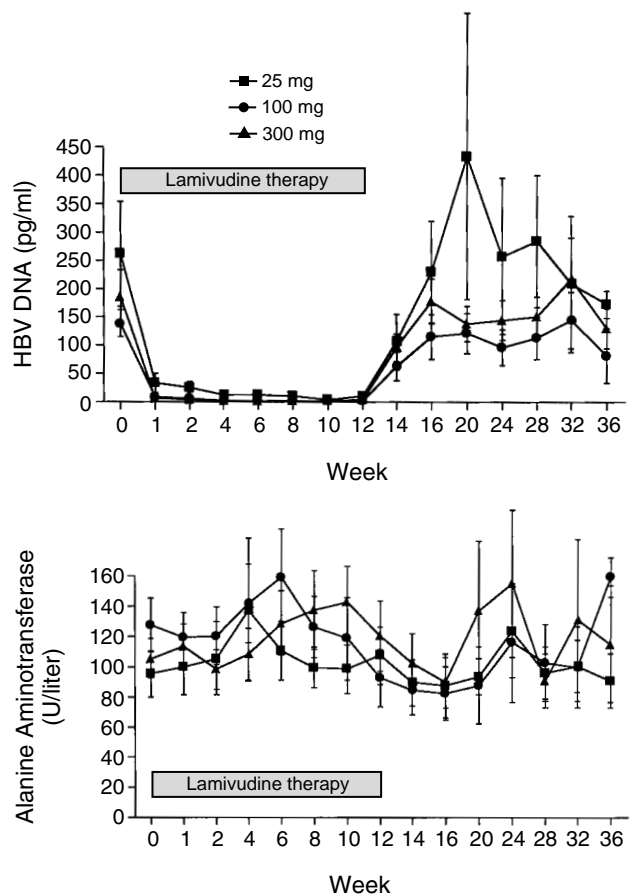


Figure 2. Changes in Mean (\pm SE) Serum Levels of HBV DNA (Upper Panel) and Alanine Aminotransferase (Lower Panel) during and after 12 Weeks of Therapy with 25, 100, or 300 mg of Lamivudine.

Table 2. Outcomes in the Three Treatment Groups.*

VARIABLE	LAMIVUDINE DOSE			ALL PATIENTS (N = 32)
	25 mg (N = 10)	100 mg (N = 11)	300 mg (N = 11)	
HBV DNA at week 12 — pg/ml	9±4	1±0	3±2	—
Suppression of HBV DNA during therapy — no. (%)	7 (70)	11 (100)	11 (100)	29 (91)
Time to suppression of HBV DNA in 50% of patients — wk	8	4	2	—
Sustained suppression of HBV DNA — no. (%)	0	4 (36)	2 (18)	6 (19)
Disappearance of HBeAg — no. (%)	0	2 (18)	2 (18)	4 (12)
Elevation in alanine aminotransferase — no. (%)†				
>2-fold	5 (50)	4 (36)	4 (36)	13 (41)
>3-fold	1 (10)	2 (18)	2 (18)	5 (16)

*Plus-minus values are means ±SE.

†During treatment, follow-up, or both.

creatitis, myopathy, hepatic decompensation, or renal impairment.

Treatment was stopped prematurely in only one patient. At week 4, one patient in the 25-mg group had an increase in alanine aminotransferase levels from 198 to 548 U per liter. Therapy was stopped at week 6, and a liver biopsy showed moderate chronic hepatitis with mild steatosis indistinguishable from that in a pretreatment biopsy specimen. There was no lactic acidosis or

Table 3. Adverse Effects Reported during Lamivudine Therapy.

ADVERSE EFFECT	LAMIVUDINE DOSE			ALL PATIENTS (N = 32)
	25 mg (N = 10)	100 mg (N = 11)	300 mg (N = 11)	
	no. of patients (%)			
Symptom				
Fatigue	3	3	3	9 (28)
Headache	2	2	3	7 (22)
Abdominal discomfort	1	3	2	6 (19)
Head cold	2	3	1	6 (19)
Nausea	4	2	0	6 (19)
Muscle or joint ache	3	1	1	5 (16)
Feeling of warmth	2	2	0	4 (12)
Influenza	0	2	2	4 (12)
Diarrhea	2	1	0	3 (9)
Dry mouth	2	0	1	3 (9)
Numbness	2	0	0	2 (6)
Dizziness	0	1	1	2 (6)
Rash	0	1	0	1 (3)
Laboratory abnormality				
Elevation in creatine kinase*	1	1	2	4 (12)
Elevation in lipase†	1	0	3	4 (12)
Elevation in amylase‡	0	0	2	2 (6)

*Elevations in creatine kinase occurred during therapy in four patients (peak level, 212 to 1118 U per liter [normal, 22 to 198 U per liter]) and after therapy in another three (one in each dose group; peak level, 204 to 2830 U per liter), for a total of seven patients (22 percent) during the entire 36-week study period.

†Elevations in lipase occurred during therapy in four patients (peak level, 168 to 378 U per liter [normal, 10 to 140 U per liter]); lipase levels returned to normal during continued therapy in three of the four. In addition, an increase in lipase to 843 U per liter occurred in one additional patient in the 25-mg group four weeks after therapy was prematurely discontinued at week 6 because of elevated alanine aminotransferase activity. Thus, a total of five patients (16 percent) had lipase elevations during the entire 36-week study period.

‡Elevations in amylase occurred during therapy in two of the four patients with lipase elevations (one of whom had an elevated amylase level before therapy, which continued throughout the 36-week study period; peak levels, 105 to 154 U per liter [normal, 1 to 88 U per liter]). In addition, the patient whose lipase levels increased after therapy also had an increase in amylase after therapy (peak level, 198 U per liter). Therefore, a total of three patients (9 percent) had amylase elevations during the 36-week study period.

anion gap. Levels of HBV DNA remained undetectable for another six weeks after therapy was stopped.

DISCUSSION

In this study, 12 weeks of lamivudine therapy was well tolerated and doses of 100 and 300 mg suppressed HBV DNA to undetectable levels. This suppression was sustained in 6 of 32 patients (19 percent; 1 relapsed three months after week 45 of observation), and HBeAg disappeared in 4 of 32 patients (12 percent). The only advantage of the 300-mg dose over the 100-mg dose was earlier suppression of HBV DNA.

Lamivudine was active in patients who had had no response to interferon therapy and in subgroups that rarely respond to interferon (patients with very high levels of HBV DNA and patients with normal or near-normal alanine aminotransferase levels).^{1,10} Although the 12 percent rate of disappearance of HBeAg did not exceed the spontaneous annual seroconversion rate,¹¹ the seroconversion rate among patients receiving the higher doses of lamivudine during the 36 weeks of the study was 18 percent.

In two patients HBV DNA was suppressed but HBeAg was not; in interferon-treated patients, this has been categorized as an indeterminate response,¹ whose ultimate outcome has not been characterized. One of these two patients relapsed three months after week 45 of observation.

As they lose markers of HBV replication, the majority of patients who respond to interferon have elevations in aminotransferase activity similar to those seen in acute hepatitis.^{1,12} This effect has been attributed to an immunomodulatory action of interferon on the interaction between cytolytic T cells and HBV-infected hepatocytes. Despite the fact that lamivudine, like other nucleoside analogues,^{13,14} has no recognized, direct effect on the immune system, 41 percent of our patients had elevations in alanine aminotransferase similar to those reported in interferon-treated patients. In addition, some patients had self-limited elevations of alanine aminotransferase — resembling those seen in acute hepatitis — several months after therapy was completed, which were followed by suppression of HBV DNA, as has been reported in patients with chronic hepatitis B who were treated with cytarabine¹³ and flialuridine.¹⁵

Treatment was stopped at week 6 in one patient in the 25-mg group after an abrupt increase in his alanine aminotransferase levels. A liver biopsy at that time showed no changes from the histologic findings at base line. Because elevations in alanine aminotransferase in lamivudine-treated patients were inversely, rather than directly, related to the dose, we considered drug hepatotoxicity unlikely. Lamivudine caused none of the adverse effects — refractory lactic acidosis, hepatic and renal failure, pancreatitis, or myopathy —

associated recently with fialuridine therapy, nor does it have the mitochondrial toxicity characteristic of fialuridine.^{4,5,16-22} The mild, nonspecific side effects observed with lamivudine therapy were not dose-dependent, and the laboratory abnormalities reported were transient, asymptomatic, and not related temporally to therapy.

Because five of the six patients with sustained suppression of HBV DNA had not responded to previous treatment with interferon, it is possible that that treatment contributed to the subsequent success of lamivudine therapy. In a placebo-controlled trial, we are now studying lamivudine alone or combined with interferon in patients with no response to previous treatment with interferon.

All patients who relapsed in this trial are now being retreated with 100 mg of lamivudine per day. Thus far, HBeAg has disappeared in three additional patients, at 12, 16, and 28 weeks of treatment. The results of the current study and the preliminary results of a follow-up trial suggest that larger, controlled trials of lamivudine are warranted.

We are indebted to Eloise Watkins, R.N., M.P.H., study coordinator, and the nursing staff of the Mallinckrodt General Clinical Research Center (Massachusetts General Hospital); to Carol J. Bodicky, R.N., study coordinator (St. Louis Veterans Affairs Medical Center); to Kathy Roach, study coordinator (University of Miami School of Medicine); and to Lynn M. Crowther and JoAnne Bixler, M.S., study monitors, and Andrew Hill and James Esinhart, Ph.D., statisticians (Glaxo).

REFERENCES

- Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. *N Engl J Med* 1990;323:295-301.
- Di Bisceglie AM, Fong T-L, Fried MW, et al. A randomized, controlled trial of recombinant α -interferon therapy for chronic hepatitis B. *Am J Gastroenterol* 1993;88:1887-92.
- 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: a meta-analysis. *Ann Intern Med* 1993;119:312-23.
- Lau D, Mostowski H, Hoofnagle JH, Sallie R. Nucleoside analogue toxicity and mitochondria. *Hepatology* 1994;20:189A. abstract.
- Doong SL, Tsai CH, Schinazi RF, Liotta DC, Cheng YC. Inhibition of the replication of hepatitis B virus in vitro by 2',3'-dideoxy-3'-thiacytidine and related analogues. *Proc Natl Acad Sci U S A* 1991;88:8495-9.
- Tyrrell DLJ, Fischer K, Savani K, Ian W, Jewell L. Treatment of chimpanzees and ducks with lamivudine, 2',3'-dideoxy 3' thiacytidine results in a rapid suppression of hepadnaviral DNA in sera. *Clin Invest Med* 1993;16: Suppl 4:B77. abstract.
- Benhamou Y, Dohin E, Lunel-Fabiani F, et al. Efficacy of lamivudine on replication of hepatitis B virus in HIV-infected patients. *Lancet* 1995;345:396-7.
- Tyrrell DLJ, Mitchell MC, De Man RA, et al. Phase II trial of lamivudine for chronic hepatitis B. *Hepatology* 1993;18:112A. abstract.
- Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley, 1980.
- Perrillo RP. Factors influencing response to interferon in chronic hepatitis B: implications for Asian and western populations. *Hepatology* 1990;12:1433-5.
- 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.
- Hoofnagle JH, Peters M, Mullen KD, et al. Randomized, controlled trial of recombinant human α -interferon in patients with chronic hepatitis B. *Gastroenterology* 1988;95:1318-25.
- Hoofnagle JH, Hanson RG, Minuk GY, et al. Randomized controlled trial of adenine arabinoside monophosphate for chronic type B hepatitis. *Gastroenterology* 1984;86:150-7.
- Zoulim F, Trepo C. Nucleoside analogs in the treatment of chronic viral hepatitis: efficiency and complications. *J Hepatol* 1994;21:142-4.
- 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. *Hepatology* 1992;16:127A. abstract.
- Levine ES, Colacino JM, Bowsher RR, Sallie R, Lewis W. FIAU incorporates into DNA from human liver and from human hepatoblastoma cells. *Hepatology* 1994;20:189A. abstract.
- Sallie R, Kleiner D, Richardson F, et al. Mechanisms of FIAU induced hepatotoxicity. *Hepatology* 1994;20:209A. abstract.
- Richardson FC, Engelhardt JA, Bowsher RR. Fialuridine accumulates in DNA of dogs, monkeys, and rats following long-term oral administration. *Proc Natl Acad Sci U S A* 1994;91:12003-7.
- Lewis W, Meyer RR, Simpson JF, Colacino JM, Perrino FW. Mammalian DNA polymerases α , β , γ , δ , and ϵ incorporate fialuridine (FIAU) monophosphate into DNA and are inhibited competitively by FIAU triphosphate. *Biochemistry* 1994;33:14620-4.
- Cui L, Yoon S, Schinazi RF, Sommadossi J-P. Cellular and molecular events leading to mitochondrial toxicity of 1-(2-deoxy-2-fluoro-1- β -D-arabino-furanosyl)-5-iodouracil in human liver cells. *J Clin Invest* 1995;95:555-63.
- Colacino JM, Malcolm SK, Jaskunas SR. Effect of fialuridine on replication of mitochondrial DNA in CEM cells and in human hepatoblastoma cells in culture. *Antimicrob Agents Chemother* 1994;38:1997-2002.
- McKenzie R, Fried MW, Sallie R, 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.

Massachusetts Medical Society
Registry on Continuing Medical Education

To obtain information on continuing medical education courses in the New England area, call between 9:00 a.m. and 12:00 noon, Monday through Friday, (617) 893-4610 or in Massachusetts 1-800-322-2303, ext. 1342.