

## Economic Evaluation of Lamivudine Compared with Interferon- $\alpha$ in the Treatment of Chronic Hepatitis B in the United States

Elizabeth A. Brooks, PhD; Larry F. Lacey, PhD; Sarah L. Payne, MBA;  
and David W. Miller, PhD

**Objective:** To determine whether lamivudine or interferon- $\alpha$  (IFN- $\alpha$ ) is the more successful treatment for chronic hepatitis B given a fixed drug budget.

**Study Design:** A decision-tree model of 1 year.

**Patients and Methods:** Average wholesale prices were used to estimate drug costs. A fixed drug budget of \$558,910, sufficient to treat 100 patients with IFN- $\alpha$ , was assumed. Clinical data were taken from randomized controlled trials. The outcome measures used were hepatitis B "e" antigen (HBeAg) seroconversion rates and rates of progression to cirrhosis.

**Results:** The analysis showed that given the fixed drug budget, 353 patients could be treated with lamivudine, resulting in an expected 62 HBeAg seroconversions, with 6 patients progressing to cirrhosis. Given the same drug budget, 100 patients could be treated with IFN- $\alpha$ , leaving 253 patients untreated. This treatment scenario would result in an expected 32 HBeAg seroconversions, with 28 patients progressing to cirrhosis. Compared with no treatment, the costs per additional HBeAg seroconversion obtained were \$12,703 for lamivudine and \$39,922 for IFN- $\alpha$ . In addition, each case of cirrhosis avoided through lamivudine treatment resulted in significant annual cost savings. Lamivudine therapy also provided additional clinical benefits (eg, normalization of alanine transaminase levels, reduction in hepatitis B virus DNA levels, improvement in liver histology) to patients who do not seroconvert.

**Conclusion:** From the perspective of a third-party payer with a fixed drug budget, lamivudine is a more cost-effective therapy than IFN- $\alpha$  for the treatment of chronic hepatitis B.

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ed with HBV, HBcAg may be processed to form the "e" antigen [HBeAg], which is released into the host's bloodstream.) Hepatitis B virus can be transmitted through perinatal, parenteral, sexual, or horizontal modes and is one of the most common human pathogens. An estimated 2 billion people have been infected with HBV, and approximately 350 million people worldwide are chronic carriers of HBV.<sup>3</sup> After acute infection, most adolescents and adults clear the virus and develop immunity to HBV. Some people, however, remain persistently infected with HBV, as indicated by the presence of HBsAg in the bloodstream for more than 6 months; such individuals are classified as chronic HBV carriers. Currently, approximately 1.25 million people in the United States are chronic HBV carriers.<sup>4</sup> Among these chronic carriers, about one third will develop potentially progressive necroinflammatory changes in the liver, a condition known as chronic hepatitis B (CHB).

In the early stages of CHB, symptoms are generally mild and nonspecific. With progressive necroinflammatory liver damage, however, patients may develop end-stage cirrhosis with clinical signs of liver failure, and they may develop hepatocellular carcinoma.<sup>3</sup> Such long-term complications make chronic HBV infection an important cause of death and severe liver morbidity worldwide.<sup>5</sup>

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Address correspondence to: Larry F. Lacey, PhD, Global Health Outcomes, Glaxo Wellcome Research and Development, Greenford Road, Greenford, Middlesex UB6 0HE. E-mail: lfl3204@glaxowellcome.co.uk.

Hepatitis B is caused by the infectious hepatitis B virus (HBV).<sup>1,2</sup> (HBV is a DNA<sup>2</sup> virus consisting of an outer protein coat, or surface antigen [HBsAg], and an inner protein core [capsid], called the core antigen [HBcAg]. In liver cells infect-

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The costs associated with caring for and treating CHB and its sequelae are significant. (All subsequent cost estimates have been updated to 1999 US dollars using the consumer price index for US medical care services.) A US-based study of New England health-care databases found that over approximately 2 years, CHB patients incurred an average of US \$40,512 in costs for healthcare services and drugs.<sup>6</sup> Another US-based study found that the average cost per hospitalization for a CHB patient with active liver inflammation was US \$8464; the average cost per hospitalization for a CHB patient with cirrhosis was US \$14,063.<sup>7</sup> The cost of a liver transplant has been estimated at US \$89,076.<sup>8</sup>

HBeAg seroconversion is defined here as the loss of HBeAg from a patient's bloodstream combined with both the development of antibodies to HBeAg (gain of anti-HBe) and loss of detectable serum HBV DNA. HBeAg seroconversion is generally considered to be a predictor of long-term suppression of viral replication. The 2 drug treatments currently available for CHB are each intended to promote HBeAg seroconversion. The first treatment, interferon- $\alpha$  (IFN- $\alpha$ ) therapy for CHB patients, typically involves self-injections of 10 million units 3 times per week for a period of 16 weeks.<sup>9</sup> Therapy with IFN- $\alpha$  is effective (in terms of HBeAg loss) in 30% to 40% of patients with low initial levels of HBV DNA and elevated alanine transaminase (ALT) levels.<sup>10</sup> The second treatment, lamivudine 100 mg, an oral once-daily therapy for CHB patients with HBV DNA replication and liver disease, has recently become available on the US market. Evidence indicates that treatment with lamivudine for 1 year results in

rates of HBeAg loss and HBeAg seroconversion similar to those achieved with the typical IFN- $\alpha$  treatment regimen.<sup>11</sup>

To evaluate the cost effectiveness of a standard lamivudine regimen for the treatment of CHB compared with a typical IFN- $\alpha$  regimen, we calculated the number of patients expected to achieve HBeAg seroconversion given a fixed drug budget for each treatment. The economic evaluation was conducted from the perspective of a third-party payer/healthcare provider operating under budgetary constraints.

... METHODS ...

In this study, we use an HBeAg seroconversion rate of 17.5% for patients receiving lamivudine therapy and an HBeAg seroconversion rate of 18.8% for patients receiving IFN- $\alpha$  treatment. These rates were taken from the results of a 12-month randomized clinical trial comparing treatment with lamivudine once daily for 12 months with a single course of IFN- $\alpha$  10 million units 3 times weekly for 4 months and with lamivudine plus IFN- $\alpha$  as combination therapy.<sup>11</sup>

The HBeAg seroconversion rate of 5.0% for untreated patients was obtained from a pooled analysis of 2 placebo-controlled trials by combining the numbers of patients from the 2 studies who seroconverted while receiving placebo (7 of a total of 139 patients).<sup>12,13</sup> For lamivudine-treated patients, the rate of progression to cirrhosis for those who do not seroconvert (2.2%) was obtained from a pooled analysis of the 2 placebo-controlled trials and the

**Table 1.** Clinical Trial Results

Treatment Regimen	No Treatment	Lamivudine Therapy*	IFN- $\alpha$ Therapy <sup>†</sup>
Total drug costs	\$0.00	\$1580.80	\$5589.10
HBeAg seroconversion rate <sup>‡</sup>	5.0%	17.5%	18.8%
Rate of progression to cirrhosis <sup>§</sup>	8.7%	2.2%	8.7%

HBeAg = hepatitis B "e" antigen; IFN- $\alpha$  = interferon- $\alpha$ .

\*Therapy consisted of lamivudine 100 mg once daily for 1 year.

<sup>†</sup>Therapy consisted of IFN- $\alpha$  10 million units 3 times per week for 16 weeks.

<sup>‡</sup>Rates were obtained at the end of a 12-month period. HBeAg seroconversion rates for lamivudine-treated patients and for IFN- $\alpha$  treated patients were obtained from a 12-month randomized clinical trial.<sup>11</sup> The HBeAg seroconversion rate for untreated patients was obtained from a pooled analysis of 2 placebo-controlled trials.<sup>12,13</sup>

<sup>§</sup>The rate of progression to cirrhosis for lamivudine-treated patients and the weighted average rate of progression to cirrhosis for both IFN- $\alpha$  treated and untreated populations were obtained from a pooled analysis of the 2 placebo-controlled trials and the lamivudine/IFN- $\alpha$  comparator study.<sup>11-13</sup>

lamivudine/IFN- $\alpha$  comparator study by combining the numbers of patients from the 3 studies who progressed to cirrhosis while receiving lamivudine (4 of a total of 185 patients).<sup>11-13</sup> (Rates of progression to cirrhosis used in this study depend on patients' HBeAg seroconversion status. The abstract<sup>14</sup> cited reports a combined rate of progression to cirrhosis.) We conservatively assumed the same weighted average rate of progression to cirrhosis (8.7%) for both IFN- $\alpha$ -treated and untreated populations. The observed rates were 12.1% (4 of a total of 33 patients) for IFN- $\alpha$  and 7.4% (7 of a total of 94 patients) for placebo, respectively. A weighted average rate of 8.7% was used for both IFN- $\alpha$  and placebo treatments because of the lack of a statistically significant difference between the 2 treatments and because of the relatively small numbers of patients who received each treatment, particularly the IFN- $\alpha$  treatment.

The rates of progression to cirrhosis used in this analysis differ from those given in an exploratory integrated analysis.<sup>14</sup> This is because of the different populations under study (ie, this study was restricted to those patients who do not seroconvert after treatment) and use of weighted average progression rates for both IFN- $\alpha$ -treated and untreated placebo populations. The previously reported rates of progression to cirrhosis were 1.8% for lamivudine, 7.1% for placebo, and 9.5% for IFN- $\alpha$ .<sup>14</sup>

Medication costs are based on average 1999 wholesale prices of a 60-tablet pack of lamivudine and a 1-mL IFN- $\alpha$  vial containing 10 million units/mL. The total 1999 drug costs for the once-daily, 12-month lamivudine regimen were estimated to be \$1580.80; the cost of 4 months of treatment with IFN- $\alpha$  30 million units/week was estimated to be \$5589.10. The clinical and cost data are presented in **Table 1**.

It was assumed that the fixed drug budget contained funds sufficient for the treatment of 100 patients with a standard course of IFN- $\alpha$ . Within this fixed budget of \$558,910, it would be possible to treat 353 patients with a standard 12-month course of lamivudine therapy. The third-party payer/health-care provider would thus be faced with the option of treating 353 patients with lamivudine or 100 patients with IFN- $\alpha$  (leaving 253 patients untreated due to the budgetary constraint). The expected number of patients who would successfully seroconvert and the expected number of patients progressing to cirrhosis were calculated for each of these 2 treatment options. The decision tree model illustrating this analysis is presented in the **Figure**.

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## ... RESULTS ...

A summary of the modeled analysis is presented in **Table 2**. Based on the clinical trial results, of the 353 CHB patients who could receive lamivudine treatment within the fixed drug budget, 62 would be expected to achieve HBeAg seroconversion and only 6 would progress to cirrhosis. If the choice was made to treat 100 patients with IFN- $\alpha$  and leave the remaining 253 patients untreated, a total of 32 patients would be expected to seroconvert (19 treated, 13 untreated), with 28 patients progressing to cirrhosis (7 treated, 21 untreated). Within this fixed drug budget, assuming a spontaneous HBeAg seroconversion rate of 5.0% per year for untreated CHB patients, lamivudine therapy had a cost per additional HBeAg seroconversion obtained of \$12,703 compared with no treatment. The cost per additional HBeAg seroconversion for IFN- $\alpha$  was \$39,922. Furthermore, the treatment of 353 patients with lamivudine therapy resulted in 22 fewer patients progressing to cirrhosis than if the patients had received IFN- $\alpha$  therapy or had been left untreated. The average cost per hospitalization for a CHB patient with cirrhosis is estimated as US \$14,063<sup>7</sup>; hence, our modeled analysis showed that treatment with lamivudine resulted in hospital cost savings of US \$309,386. These cost savings offset the drug costs of lamivudine therapy by 55%.

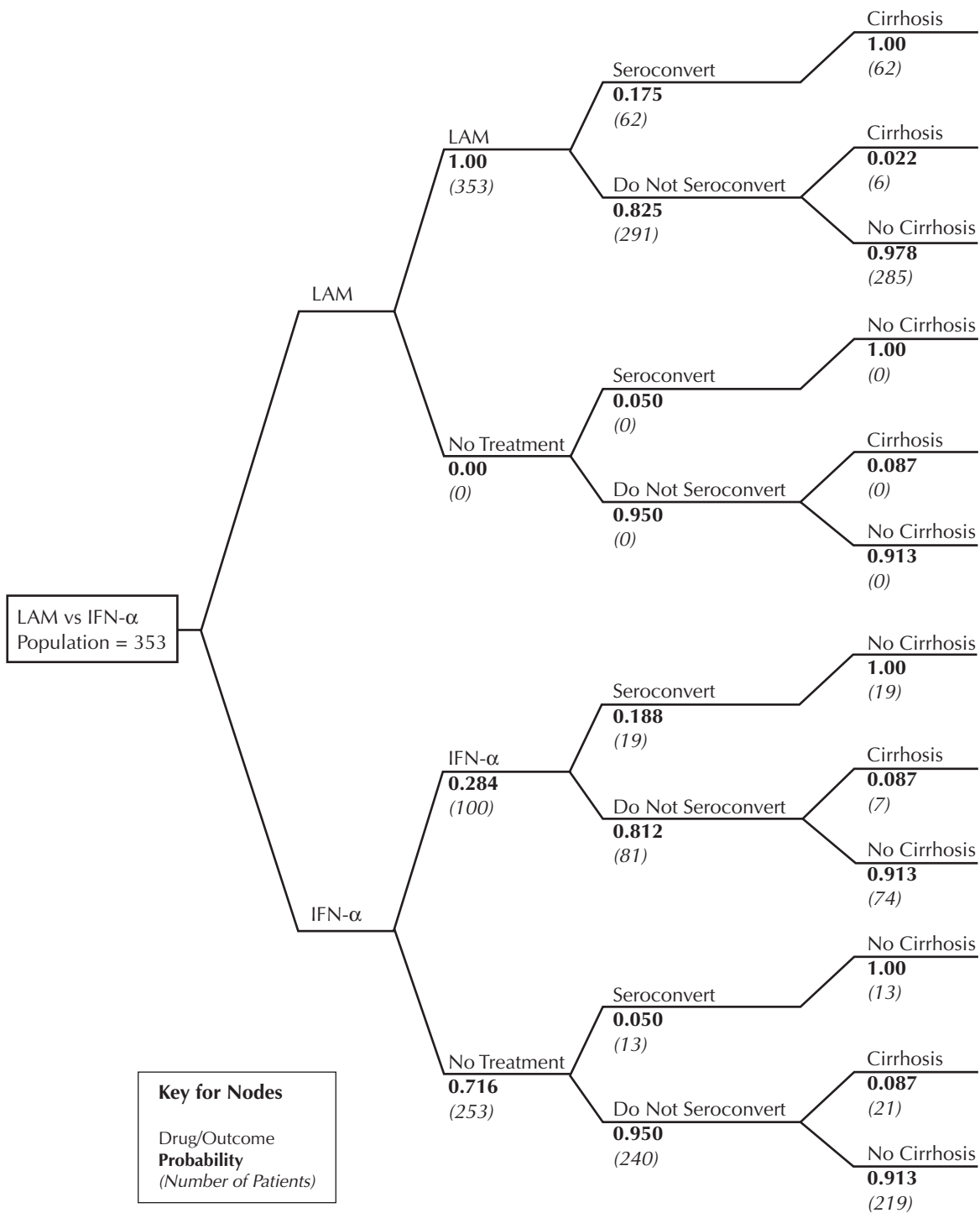
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## ... DISCUSSION ...

This economic evaluation establishes lamivudine as a more cost-effective therapy than IFN- $\alpha$ . Within a fixed drug budget, approximately 3.5 times as many CHB patients can be treated with lamivudine than with IFN- $\alpha$ , resulting in approximately 1.9 times as many HBeAg seroconversions. In addition, lamivudine therapy resulted in fewer patients progressing to cirrhosis. The cost per additional seroconversion achieved with lamivudine compared with no treatment was approximately \$12,703; for IFN- $\alpha$  that cost was \$39,922. Lamivudine therapy also is expected to offset significant direct medical costs of US \$14,063 for each case of cirrhosis avoided. (Margolis et al estimated the annual hospitalization costs associated with each case of cirrhosis as \$4652 in 1981 US dollars.<sup>7</sup> We used the consumer price index for US medical care services to update this cost estimate to 1999 US dollars.)

Therapy with IFN- $\alpha$  is effective in promoting seroconversion in patients who have low initial levels of

**Figure.** Decision Tree Model



IFN- $\alpha$  = interferon- $\alpha$ ; LAM = lamivudine.

actively replicating HBV and elevated ALT levels; however, it is less effective in patients with low ALT levels.<sup>10</sup> In particular, Asian patients usually have normal serum levels of transaminases and are less likely to respond to IFN- $\alpha$  therapy.<sup>10</sup> Lok et al found an HBeAg seroconversion rate of only 10% to 15% in a CHB population in Hong Kong receiving IFN- $\alpha$  treatment.<sup>15</sup> Furthermore, flu-like symptoms and depression are major side effects of IFN- $\alpha$ .<sup>16</sup> Thus, patients with a history of depression are ineligible for treatment with IFN- $\alpha$ , as are CHB patients with decompensated cirrhosis.<sup>10</sup>

By contrast, most CHB patients are eligible for lamivudine therapy. Clinical trials show that it is well tolerated, with a safety profile similar to that of placebo during treatment.<sup>17</sup> Furthermore, lamivudine is not contraindicated for any patient subset because of safety concerns. In addition, lamivudine has been shown to be effective for both IFN- $\alpha$ -naïve patients and patients who have previously failed IFN- $\alpha$  treatment.<sup>17</sup>

Although the rates of HBeAg seroconversion achieved with lamivudine also are associated with pretreatment ALT level,<sup>18</sup> other data show that lamivudine improves hepatic necroinflammation and fibrosis regardless of whether HBeAg seroconversion occurs.<sup>13,19</sup> This finding may account for the marked effect of lamivudine on progression to cirrhosis found in 1 preliminary study.<sup>14</sup>

This analysis has demonstrated the advantages of lamivudine therapy compared with IFN- $\alpha$  therapy at both the population and the patient levels; however, it is important to discuss the limitations of the study. First, the measurements of clinical trial outcomes in both treatment groups were taken 12 months after initiation of therapy. Because the treatment durations of the 2 therapies are different, at the end of 12 months lamivudine patients had just completed their course of treatment, while IFN- $\alpha$  patients had completed their treatment 8 months earlier. Schalm et al found that approximately 20% of patients regain HBeAg after seroconversion with lamivudine therapy, which is comparable to the regain rate seen with IFN- $\alpha$ .<sup>11</sup> However, even if a reduction in the seroconversion rate of

20% is assumed for the lamivudine treatment group only (which would allow for differences in the time posttreatment for the 2 therapies), lamivudine therapy would cost \$15,969 per additional seroconversion gained compared with no treatment, which is still approximately 60% less than the cost per seroconversion achieved with IFN- $\alpha$  treatment.

Second, this economic evaluation is based only on drug costs; it does not consider other costs associated with CHB and its treatment. For example, patients treated with IFN- $\alpha$  are likely to require more intensive monitoring than other patients, because of both the route of IFN- $\alpha$  administration and the nature of its side effects. Furthermore, the indirect costs associated with CHB and the potential differential benefits of the 2 therapies on quality of life were not assessed in this analysis. By not including other direct and indirect costs, this evaluation would be expected to underestimate the cost effectiveness of lamivudine compared with IFN- $\alpha$ .

Notwithstanding these limitations, sensitivity analyses demonstrate the robustness of the lamivudine cost-effectiveness result. For lamivudine not to be cost effective compared with IFN- $\alpha$  treatment, the price of a 1-year course of lamivudine would need to increase by approximately 250% (from \$1580.80 to the \$5589.10 per course of IFN- $\alpha$  treatment), or the 1-year seroconversion rate obtained with lamivudine would need to decrease by nearly 50% (from 15.5% to 9.1%).

Combination treatment options such as lamivudine plus IFN- $\alpha$  were not considered in this cost-effectiveness analysis.

**Table 2.** Results of Modeled Analysis

Outcomes	Lamivudine Therapy	IFN- $\alpha$ Therapy	Ratio Relative to IFN- $\alpha$
No. of patients treated	353	100 (with 253 who had no treatment)	3.53
No. of patients seroconverted	62	32	1.94
Cost per additional HBeAg seroconversion obtained	\$12,703	\$39,922	0.32
Number of patients progressing to cirrhosis	6	28	0.21

HBeAg = hepatitis B "e" antigen; IFN- $\alpha$  = interferon- $\alpha$ .

... CONCLUSION ...

This 12-month modeled analysis based on clinical trial data assessed the cost effectiveness of lamivudine compared with IFN- $\alpha$  for the treatment of CHB. From the perspective of a third-party payer/healthcare provider, lamivudine is the more cost-effective therapy. Given a fixed drug budget, lamivudine therapy allows a greater number of patients to achieve HBeAg seroconversion than IFN- $\alpha$  therapy. Furthermore, lamivudine reduces the rate of progression to cirrhosis and provides additional histological benefits to patients, regardless of whether seroconversion occurs.

... REFERENCES ...

1. **Dane DS, Cameron CH, Briggs NM.** Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. *Lancet* 1970;1:695-698.
2. **Kaplan PM, Greenman RL, Gerin JL, Purcell RH, Robinson WS.** DNA polymerase associated with human hepatitis B antigen. *J Virol* 1973;12:995-1005.
3. **Kane MA, Clements J, Hu D.** Hepatitis B. In: Jamison DT, Mosley WH, Measham AR, Bobadilla J, eds. *Disease Control Priorities in Developing Countries: A World Bank Book*. New York: Oxford University Press; 1993.
4. **Lee WM.** Hepatitis B virus infection. *N Engl J Med* 1997;337:1733-1745.
5. **Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, eds.** *Harrison's Principles of Internal Medicine*. New York, NY: McGraw-Hill, Inc; 1995.
6. **Rosenberg DM, Cook SF, Eaton S, Saunders WB, Lanza L.** The epidemiology, treatment patterns and resource utilization of hepatitis B patients in a large insured New England population. *Pharmacoepidemiol Drug Saf* 1998;7(suppl 2):S132.
7. **Margolis HS, Schatz GC, Kane MA.** Development of recommendations for control of hepatitis B virus infections: The role of cost analysis. *Vaccine* 1990;8(suppl):S81-S94.
8. **Shiell A, Briggs A, Farrell GC.** The cost effectiveness of alpha interferon in the treatment of chronic active hepatitis C. *Med J Aust* 1994;160(5):268-272.
9. **Janssen HLA, Schalm SW, Berk L, et al.** Repeated courses of alpha interferon for treatment of chronic hepatitis B. *J Hepatol* 1993;17(suppl 3):S47-S51.
10. **Hoofnagle JH.** Alpha interferon therapy of chronic hepatitis B: Current status and recommendations. *J Hepatol* 1990;11(suppl):S100-S107.
11. **Schalm SW, Heathcote J, Cianciara J, et al.** Lamivudine and interferon- $\alpha$  combination treatment of patients with chronic hepatitis B infection: A randomized trial. *Gut* 2000;46:562-568.
12. **Dienstag JL, Schiff ER, Wright TL, et al.** Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256-1263.
13. **Lai C-L, Chien R-N, Leung NWY, et al.** A 1-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998;339:61-68.
14. **Goodman Z, Dhillon AP, Wu PC, et al.** Lamivudine treatment reduces progression to cirrhosis in patients with chronic hepatitis B [abstract]. *J Hepatol* 1999;30(suppl 1):59. Abstract GS5/26.
15. **Lok ASF, Lai CL, Wu PC, et al.** Long-term follow-up in a randomized controlled trial of recombinant interferon- $\alpha$  in Chinese patients with chronic hepatitis B infection. *Lancet* 1988;2:298-302.
16. **Renault P, Hoofnagle J.** Side effects of alpha interferon. *Semin Liver Dis* 1989;9(4):273-277.
17. **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;333:1657-1661.
18. **Perrillo RP, Schalm SW, Schiff ER, et al.** Predictors of HBeAg seroconversion in chronic hepatitis B patients. *Hepatology* 1999;30(4):317A.
19. **Honkoop P, de Man RA, Zondervan PE, Schalm SW.** Histological improvement in patients with chronic hepatitis B virus infection treated with lamivudine. *Liver* 1997;17:103-106.