# Interferon Treatment for Chronic Hepatitis B or C Infection : Costs and Effectiveness

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## Abstract

***Introduction*** **: With recognition that resources are limited, health care payers and policy makers have increasingly turned toward economic analyses to determine whether particular therapies are an efficient use of economic resources. Both chronic hepatitis B and C infections can progress to cirrhosis or hepatocellular carcinoma over time. Interferon treatment has been shown to eradicate viremia, but only does so in a proportion of treated patients. It has potential side effects, has no proven long-term benefit on complications and is relatively expensive.**

***Objective*** **: To determine the cost-effectiveness of interferon treatment by estimating the lifelong economic and clinical outcomes associated with interferon therapy versus standard care for patients with either chronic hepatitis B or C infection.**

***Methods*** **: Computer cohort Markov model simulation to project the lifelong impact of the loss of hepatitis B or C viremia resulting from interferon on cirrhosis, life expectancy, and costs. The natural history of hepatitis B and C was based on published studies. Efficacy estimates for the loss of viremia were based on meta-analysis of published data. Using a societal perspective, economic estimates were based on cost of care data for patients with hepatitis and from estimates regarding the frequency of health resource utilization provided by expert panels.**

***Results*** **: For 20 year old patients with either hepatitis B e antigen positive chronic hepatitis or histologically mild chronic hepatitis C infection, interferon should be cost saving, extending life and reducing lifetime expenditures and morbidity. Life expectancy should increase by 4.8 to 3.1 years for patients with chronic hepatitis B or C, respectively. Lifetime costs should be reduced on average by $ 6,300 to $ 6,900 for each patient treated with interferon.**

***Conclusion*** **: Chronic infection with hepatitis B or C can result in liver failure and death. Although only effective in a proportion of treated patients, interferon for chronic hepatitis appears to be an efficient use of societal resources so that economic reasons should not limit its use.** (Acta gastroenterol. belg., **1998**, 61, **238-242**).

**Keywords** : hepatitis C, hepatitis B, interferon, cirrhosis, chronic hepatitis, cost-benefit.

## Introduction

Traditionally, evaluation of therapeutic interventions consists of determining the safety and then the benefit of treatment. Benefit is usually measured as efficacy, the benefit attainable in an ideal study setting, and later, as effectiveness, the benefit occurring with widespread use in general practice where compliance may be less. With recognition that resources are limited, however, health care payers and policy makers have increasingly turned toward economic analyses to determine whether particular therapies, in particular drugs, also provide an efficient use of economic resources, so called pharmacoeconomic analysis. There are principally four different types of economic analyses (1,2). Cost identification or minimization analysis examines only economic expenditures associated with the disease or treatment. Policy makers then support the strategy which yields the lowest cost without considering the health benefits associated with each strategy. Cost-benefit analysis examines both expenditures and health benefits in a single economic outcome measure. Thus, these types of analyses require translating the value of a human life into a monetary amount. Policy makers then support the treatments that yield a net positive economic benefit for society. Because of methodologic problems with assessing the value of a human life and societal principles of valuing all human life equally, these analyses have not been readily accepted in the medical literature.

Instead, cost-effectiveness analysis represents the most prevalent type of published medical economic analysis (3-5). Cost-effectiveness analysis estimates two outcome measures, usually lifetime costs and life expectancy. Policy makers then support treatments which 1) are cost-saving, i.e., those that increase life expectancy while lowering lifetime expenditures ; or 2) have marginal cost-effectiveness ratios falling within the range acceptable to society. The marginal cost-effectiveness ratio equals the incremental or additional cost (the cost associated with treatment minus that associated with no treatment) divided by the incremental or additional benefit (life expectancy with treatment minus that associated with no treatment). Thus, the cost-effectiveness ratio can be expressed as the additional cost to increase the life expectancy of the population by one year, thereby permitting the comparison of the economic efficiency of different treatments and different therapies for various diseases. Finally, because physicians and patients recognize that some health outcomes may be preferable to others, cost-utility analysis estimates the same two outcomes as cost-effectiveness analysis but adjusts life expectancy for the quality of life to reflect the morbidity of less desirable health conditions, such as being in a coma or having cancer.

Both chronic hepatitis B and C infections can progress to cirrhosis or hepatocellular carcinoma over time. Not all patients with infection progress, however,

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and complications usually occur only after infection has persisted for decades. Interferon treatment has been shown to eradicate viremia through the loss of hepatitis B virus e antigen (HBeAg) positivity or loss of hepatitis C virus antigen, but this occurs only in a proportion of treated patients. Interferon has potential side effects, has no proven benefit on long-term complications and costs several thousand U.S. dollars to administer. One approach to deciding whether to treat chronically infected patients with interferon would be to wait for the results of long-term studies on the effect of interferon on the development of cirrhosis, hepatocellular carcinoma or liver related death. Issues with such a study include the expense associated with the number of patients and the study duration required (6). In addition, with documented known complications associated with these infection, the ethics of withholding treatment in the control group might concern some physicians or patients. Lastly, patients with these chronic infections come to our offices now and would like to know now whether or not they should be treated. Decision analysis had gained increasing acceptance as an alternative to randomized controlled trials to assist policy makers, physicians and patients with these types of decisions by estimating the long-term morbidity and mortality of the disease along with the economic outcomes associated with interferon treatment and with standard care without interferon.

## Methods

A decision analysis requires seven steps : 1) framing the clinical question ; 2) specifying the alternative strategies to be considered ; 3) determining the events that may result from each strategy ; 4) estimating the likelihood of each event ; 5) assigning a value or utility for each outcome ; 6) calculating the lifetime costs and life expectancy associated with each strategy to estimate the marginal cost-effectiveness ratio ; and 7) exploring the effect of uncertainty surrounding the baseline assumptions by varying the value of each variable over a wide range in sensitivity analysis (7). To stimulate the natural history of either chronic hepatitis B or C infection, previously published computer cohort Markov models (8,9) were used to project the impact of treatment on cirrhosis, life expectancy, and lifetime disease associated costs. In a Markov model (10,11), hypothetical cohorts of identical patients begin the simulation in predefined states of health, for example imagine 10,000 patients with chronic viremia and histologically mild hepatitis. Over time, occurring as the ticks of a computer generated clock with each tick representing a year, some of those patients may progress histologically and develop moderate hepatitis but most would remain unchanged. A few might die from other causes as occurs within the general population matched for age, sex and race. By taking a snapshot of the population at the end of each year, the computer tracks the proportion of patients alive in each health state and their expenditures during that year. Following the cohort until all patients have died and summing these annual snapshots, the computer simulation yields an average lifetime cost and an average life expectancy for each cohort.

For these analyses, the clinical questions concerned the cost-effectiveness of interferon treatment of patients with either HBeAg-positive chronic hepatitis B infection or with histologically mild chronic hepatitis C infection. For patients with hepatitis B (8), the Markov model considered that some patients may lose HBeAg spontaneously or after treatment and then subsequently lose hepatitis B surface antigen. Histologically, patients with chronic hepatitis may progress to compensated cirrhosis and those who with compensated cirrhosis may develop decompensated cirrhosis. Patients with chronic hepatitis or cirrhosis may develop hepatocellular carcinoma. For patients with hepatitis C (9), the Markov model considered that viremia may resolve spontaneously or after treatment. Histologically, patients may progress from mild to moderate hepatitis and then to compensated cirrhosis. For this analysis, the mode of decompensation was separated into distinct states of health for patients presenting with variceal hemorrhage, hepatic encephalopathy, ascites, and diuretic refractory ascites. Additionally, some patients underwent liver transplantation after the development of decompensated cirrhosis. The annual likelihood of these events occurring were based on published natural history studies of hepatitis B and C infection. Using a societal perspective, economic estimates were based on cost of care data for patients with hepatitis and from utilization estimates provided by expert panels.

The data and assumptions used in these analyses are detailed in the original publications (8,9). Estimates for the efficacy of interferon-alfa2b were based on pooling either summary or primary data from published clinical trials. The analysis assumed that treatment for hepatitis B consisted of interferon alfa-2b at 10 million units administered subcutaneously three times weekly for 16 weeks and that for hepatitis C consisted of 3 million units administered subcutaneously three times weekly for six months. Treatment was discontinued in patients with hepatitis C who were unresponsive to 3 months of interferon. For patients with HBeAg-positive chronic hepatitis B, nine randomized controlled clinical trials involving 522 patients suggested that 9.1% and 45.6% of untreated and treated patients, respectively, became HBeAg negative after one year (8). For patients with chronic hepatitis C infection, five studies involving 287 patients suggested that 31% of patients with histologically mild disease have a sustained response (9). This is higher than the rate reported in many trials but reflects the exclusion of patients with fibrosis or cirrhosis, within whom sustained response occurred in only 9% to 11% of patients. This 31% sustained response rate was reduced to 27% to reflect patients who would have virologic relapse or persistent viremia despite normal hepatic transaminases (12).

## Results

Based on the data and assumptions within the previously published studies (8,9), Table I presents the predicted incidence of hepatic complications for 20 year old patients with HBeAg-positive chronic hepatitis B and those with histologically mild chronic hepatitis C infection. Patients with HBeAg-positive hepatitis B have more rapidly progressive disease both to cirrhosis and to decompensated cirrhosis than those with hepatitis C. For the later group, progression is delayed because patients must first progress to moderate hepatitis and only then may they progress to compensated cirrhosis, thus accounting for, in part, the lag in the development of complications. The lifetime likelihood of developing cirrhosis is lower for the hepatitis B patients only because more of them develop hepatocellular carcinoma prior to progressing to cirrhosis, thereby removing them from the pool at risk for developing cirrhosis.

Table II presents the projected effects of interferon-alfa2b on lifetime costs and life expectancy for 20 year old patients with chronic hepatitis B or C infection. For comparison the normal life expectancy of a 20 year old is 56.3 years. In the context of the results displayed in Table I, the effect of chronic hepatitis on life expectancy is, not surprisingly, greatest for patients with HBeAg-positive chronic hepatitis B infection. Interferon-alfa2b should extend life expectancy for patients with either chronic hepatitis B or C infection, with an absolute increase of 4.8 to 3.1 years, for patients with chronic hepatitis B or C infection, respectively. The gain in life expectancy is comparable to the 3.1 to 3.3 year increase afforded by hypothetically eliminating future coronary artery disease in 35 year olds (13). In addition, lifetime costs are also reduced by $ 6,900 to $ 6,300 for each hepatitis B or C patient treated with interferon. Because dollars spent in the future are less valuable than dollars spent now, the discounted results, as is standard economic practice, are also presented in Table II using the recently recommended 3% rate. Therefore, $ 1000 spent a year from now has a present value of only $ 971 and if spent 20 years from now, is equivalent to spending $ 554 now. Thus, despite the costs of interferon being incurred now and the expense of liver related complications being reduced by discounting (because they occur in the future), interferon remains cost saving. This is consistent with the previous results examining interferon treatment of hepatitis C using a 3% discount rate (8,9). In addition to the extension of life afforded by interferon, Table III summarizes the average future morbidity potentially avoided by treatment with interferon-alfa2b, among all treated patients and also among those who respond to treatment.

In sensitivity analysis, the above analyses were repeated for alternative assumptions regarding the efficacy of interferon-alfa2b. For example, assuming that only 32.6% of patients (instead of the baseline 45.6%) lose HBeAg-positivity with treatment, interferon-alfa2b remains cost-saving, increasing undiscounted life expectancy by 3.1 years (baseline 4.8 years) and decreasing discounted costs by $ 400. Similarly, if interferon-alfa2b has an efficacy of only 11% among

Table I. — **Predicted Incidence (%) of Complications Related to Duration of Follow-up for a 20 year old Patient with Chronic Hepatitis Infection Receiving Standard Care or Interferon-alfa2b**

| | HBeAg-positive Chronic Hepatitis B | | | | Histologically Mild Chronic Hepatitis C | | | |
|---|---|---|---|---|---|---|---|---|
| | Cirrhosis | | Decompensated cirrhosis | | Cirrhosis | | Decompensated cirrhosis | |
| Time Horizon | Standard Care | Interferon-alfa2b | Standard Care | Interferon-alfa2b | Standard Care | Interferon-alfa2b | Standard Care | Interferon-alfa2b |
| 10 years | 48 | 35 | 14 | 10 | 9 | 7 | 1 | 0.8 |
| 20 years | 58 | 44 | 28 | 21 | 28 | 21 | 7 | 5 |
| 30 years | 63 | 49 | 38 | 28 | 46 | 33 | 15 | 11 |
| 40 years | 65 | 51 | 41 | 32 | 59 | 43 | 25 | 18 |
| 50 years | 66 | 53 | 43 | 34 | 67 | 49 | 32 | 24 |
| Lifetime | 66 | 53 | 44 | 35 | 73 | 53 | 40 | 29 |

Table II. — **Projected Impact of Interferon-alfa2b Treatment of Chronic Hepatitis Infection in a 20 year old Patient on Lifetime Costs and Life Expectancy**

| | HBeAg-positive Chronic Hepatitis B | | | | Histologically Mild Chronic Hepatitis C | | | |
|---|---|---|---|---|---|---|---|---|
| | Lifetime Costs ($) | | Life Expectancy (Y) | | Lifetime Costs ($) | | Life Expectancy (Y) | |
| | Standard Care | Interferon-alfa2b | Standard Care | Interferon-alfa2b | Standard Care | Interferon-alfa2b | Standard Care | Interferon-alfa2b |
| No discounting | 66,800 | 59,900 | 29.6 | 34.4 | 30,400 | 24,100 | 44.3 | 47.4 |
| Discounting at 3% | 42,900 | 39,200 | 17.9 | 19.8 | 11,100 | 10,100 | 23.5 | 24.3 |

Table III. — **Years of Disease Morbidity Avoided by Interferon-alfa2b Treatment**

| | HBeAg-positive Chronic Hepatitis B | | Histologically Mild Chronic Hepatitis C | |
|---|---|---|---|---|
| | All Patients | Among Responders | All Patients | Among Responders |
| Chronic Cirrhosis | 1.3 | 3.2 | 8.1 | 29.7 |
| Hepatitis* | 1.8 | 4.4 | 3.3 | 12.2 |

*For HBV-infected patients, this represents the decreased number of years with HBeAg-positive chronic hepatitis.

patients with histologically mild chronic hepatitis C infection (14), interferon-alfa2b should still increase life expectancy by 1.2 years. When discounting at a 3% rate, however, interferon treatment would have a discounted lifetime cost exceeding that of standard care by $ 542 but would increase discounted life expectancy by 0.3 years, yielding a marginal cost-effectiveness ratio of $ 1600 per discounted life year gained ($ 542 ÷ 0.3 years). This compares favorably with the frequently cited marginal cost-effectiveness ratio threshold of $ 50,000 per discounted life year gained (15). Many commonly accepted medical interventions have cost-effectiveness ratios falling below this threshold, thus by comparison, even with only an 11% efficacy, interferon-alfa2b treatment should be an efficient use of resources.

## Conclusion

By providing an explicit context regarding strategies, data and assumptions, decision analysis affords a structure to engender discussions among physicians, researchers and patients regarding the components and contents of the analysis. In addition, it allows randomized clinical trial results that report the short-term benefits of treatment on viral markers to be extrapolated, thereby assisting policy makers by estimating the long-term clinical and economic implications. These estimates are based on the best available data, but further research regarding the natural history of hepatitis B and especially of C and the long-term effect of treatment would reduce uncertainties surrounding the data estimates used in the model. In addition, some studies suggest improved liver histology resulting from interferon treatment in hepatitis C in the absence of sustained transaminase normalization or loss of viremia (16), but the long-term benefits for developing subsequent complications among these patients with histologic improvement is unknown. If such benefits prove to exist, then by not incorporating these benefits in the current hepatitis C model, the above results underestimate the benefit of treatment. For hepatitis C, the results reported herein consider only at most 6 months of interferon treatment, but recently 12 months of treatment has been approved (17). A published economic analysis suggests that 12 months of treatment has a marginal cost-effectiveness ratio within the range of other well accepted therapies and is similar to that associated with 6 month treatment courses (14). Despite the clinical and economic benefits of interferon treatment, these results also support the need for further therapeutic innovation to improve the response rate, such as through combination therapy with ribavirin or induction therapy with higher doses. Lessons learned from monitoring HIV viral loads to adjust therapy may also eventually be applied to hepatitis B and C treatment. In the wake of litigation associated with human immunodeficiency virus (HIV) transmission associated with transfusion, an international interest has grown in estimating the long-term effects of transfusion associated hepatitis C. Decision analytic modeling may assist policy makers and the legal system in their deliberations. Finally, having demonstrated that therapy may be cost-saving or at least an efficient use of resources, should patients be screened for chronic hepatitis B or C and if so, how ?

In conclusion, chronic infection with hepatitis B or C can result in hepatic failure and premature death. In the absence of long-term clinical trials, these results support the routine use of interferon-alfa2b for chronic hepatitis B or C to prolong life expectancy and decrease morbidity. In general, the results are consistent with other published pharmacoeconomic analyses (14,18) but differ in time frame considered (lifetime versus 10 to 30 years), estimations of the likelihood of disease progression, types of costs included and methodologies for data estimation when compared to other studies (6, 19-21). Although only effective in a proportion of treated patients, interferon for chronic hepatitis B or C appears to be an efficient use of societal resources, so that economic reasons should not limit its use.

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