

# Watchful Waiting with Periodic Liver Biopsy versus Immediate Empirical Therapy for Histologically Mild Chronic Hepatitis C

## A Cost-Effectiveness Analysis

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**Background:** Not all patients with histologically mild chronic hepatitis C progress to cirrhosis.

**Objective:** To compare no antiviral treatment, periodic liver biopsy with subsequent antiviral treatment for moderate hepatitis or cirrhosis, and immediate antiviral therapy.

**Design:** Cost-effectiveness analysis.

**Data Sources:** Clinical trial data and published studies.

**Target Population:** Hepatitis C virus–infected patients with histologically mild hepatitis.

**Time Horizon:** Lifetime.

**Perspective:** Societal.

**Intervention:** Immediate combination antiviral treatment or biopsy every 3 years plus combination antiviral therapy for moderate hepatitis or cirrhosis.

**Outcome Measures:** Life expectancy, quality-adjusted life expectancy, and costs.

**Results of Base-Case Analysis:** Over 20 years, biopsy every 3 years with treatment of moderate hepatitis would avoid treatment

in 50% of the cohort and would result in an 18% likelihood of cirrhosis compared with 16% for immediate treatment and 27% for no antiviral therapy. Immediate antiviral treatment should increase life expectancy by 1.0 quality-adjusted life-year compared with biopsy management. Over an average lifetime, biopsy management would lead to six liver biopsies costing \$6200; immediate antiviral treatment would cost \$5100 less than biopsy management because of savings related to biopsy and prevention of future hepatitis C–related morbidity. Immediate therapy was cost-effective compared with biopsy management and had a cost-effectiveness ratio of \$7000 compared with no antiviral therapy.

**Results of Sensitivity Analysis:** When age, sex, genotype, and estimates of histologic progression or compliance with follow-up are varied, immediate therapy should result in an increase of at least 0.8 quality-adjusted life-year compared with biopsy management.

**Conclusion:** For histologically mild chronic hepatitis C, initial combination treatment compared with periodic liver biopsy should reduce the future risk for cirrhosis, prolong life, and be cost-effective.

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Chronic hepatitis C, which affects an estimated 170 million persons worldwide and 2.7 million persons in the United States, is the leading cause of chronic liver disease and liver transplantation (1, 2). Recent international and U.S. randomized clinical trials (3, 4) have shown that combination therapy with interferon- $\alpha$ 2b and ribavirin (Rebetron, Schering-Plough, Kenilworth, New Jersey) results in greater sustained loss of detectable virus compared with interferon therapy alone. Most hepatologists agree that patients with moderate hepatitis, bridging fibrosis, or cirrhosis should be treated and that most persons with normal histologic findings should not be treated.

Management of patients with mild histologic findings, however, remains controversial because not all patients with chronic hepatitis C progress to cirrhosis and some may wish to avoid treatment and its potential side effects (5). When interferon monotherapy was the standard of care, Foster and colleagues (6) advocated watchful waiting

with periodic biopsy to detect patients who develop progressive liver disease. Biopsy avoids treatment of patients in whom disease is less likely to progress, but it entails repeated procedures and the associated risk for morbidity and death. Now that combination therapy has more than doubled response rates, we sought to compare the projected effect of biopsy management of mild hepatitis with that of immediate antiviral therapy. With delayed treatment, all patients become older and some might also progress to cirrhosis in the interval between biopsies; these two factors decrease the likelihood of a viral-negative response. In addition, patients with impaired quality of life from hepatitis C virus (HCV) would not receive the benefit of treatment-induced viral eradication

## METHODS

We considered patients with chronic hepatitis C who met the entry criteria of two large clinical trials (3, 4).

Patients had elevated levels of serum aminotransferase, known genotype, and liver biopsy revealing histologically mild liver inflammation (defined as Knodell periportal inflammation scores of 0 to 1) (3, 4). The studies were randomized, placebo-controlled trials comparing interferon and placebo to combination therapy with ribavirin and interferon. We compared the risks and benefits of periodic biopsy with antiviral treatment alone in patients who progressed histologically with the risks and benefits of immediate antiviral treatment by considering four strategies: 1) natural history with no antiviral treatment, 2) watchful waiting with liver biopsy every 3 years and combination therapy in patients found to have cirrhosis on liver biopsy, 3) watchful waiting with liver biopsy every 3 years and combination therapy in patients found to have moderate hepatitis on liver biopsy, and 4) immediate empirical combination therapy. Treatment consisted of combination therapy for 24 weeks in patients with genotype 2 or 3 and liver biopsy showing no cirrhosis. All other patients received combination therapy for 48 weeks, but as is recommended, treatment was discontinued in patients who had not responded at 24 weeks (3, 4, 7, 8).

### Decision Analytic Model

With cohorts of hypothetically identical patients for each strategy, we used a previously described and validated Markov simulation model to estimate the long-term prognosis of each cohort with chronic hepatitis C (9, 10). The Markov model tracked cohort members as they moved through alternative states of health determined by clinical and histologic descriptors. Time was represented by annual cycles during which patients may 1) remain in the same histological or clinical state; 2) progress to another histological or clinical state; 3) die of liver disease; 4) die of other causes based on sex, ethnicity, and attained age; or 5) undergo liver biopsy. The simulations continued until all patients died.

Although our model was based on those in previously published articles, it differs in the following regards. First, one previous analysis considered only optimizing pretreatment evaluation (10); in contrast, ours considers serial liver biopsy with potential subsequent treatment. Second, two previous analyses considered interferon therapy alone (9, 10), whereas ours includes combination therapy. Finally, our analysis uses a logistic regression model of actual clinical trial data with combination therapy and applies differ-

ential durations of therapy depending on genotype and histologic findings (7, 9, 10).

### Survival, Data, and Costs

The natural history of hepatitis C was based on a previously published and validated decision model (9). Progression rates from mild to moderate hepatitis and then to cirrhosis (Knodell fibrosis score of 4) were based on limited data from 126 patients (11–13) but are supported by recent data suggesting a relationship between histologic inflammation and progression (14, 15). Estimates for progression from compensated to decompensated cirrhosis were based on the only published natural history study of patients with hepatitis C and cirrhosis at that time (16); these estimates were conservative compared with more recent data (17, 18). Prognosis for patients who developed decompensated liver disease was based on the presenting mode of decompensation (19–21). Rates of death from hepatocellular carcinoma were based on a large series (22), and survival after liver transplantation was based on pooled results of three large studies (23–25).

The probability of sustained viral-negative response was based on a multivariate logistic regression model involving the 1010 patients in the combined U.S. and international trials who received combination therapy (3, 4). **Table 1** lists the estimates included in the model (26). This calculation was performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Pairwise agreement in interpretation of liver biopsy findings have shown high concordance among observers (27). As a bias against antiviral therapy, we assumed that biopsies yielded sufficient samples so that biopsy had perfect sensitivity (28) and biopsies repeated because of inadequate sampling would be unnecessary (29, 30). If biopsy were less sensitive, patients might not receive antiviral treatment for undetected progressive disease and would be at risk for hepatic complications. Paradoxically, if liver biopsy were less specific (misleadingly suggesting progressive disease and thereby leading to antiviral treatment), liver biopsy management strategies would avoid antiviral treatment less often, would have higher antiviral treatment costs, and should prolong life in patients who respond to treatment.

To reflect the morbidity associated with some states of health, we adjusted life expectancy for quality of life on a scale from 0 (dead) to 1 (perfect health) on the basis of assessments by an expert panel of senior hepatologists (10) familiar with treatment and liver disease. Using a modified

Table 1. Baseline Data

Variable	Value*	Reference	Variable	Value*	Reference
Mean age, y†	40.1 ± 8.9	3, 4	Health-related quality-of-life weight		
Probability			Long-term health state		
Female sex, %‡	34.6 ± 0.1	3, 4	Mild chronic hepatitis‡	0.98 ± 0.03	10
Genotype 2 or 3, %‡	31.7 ± 0.1	3, 4	Moderate chronic hepatitis‡	0.92 ± 0.10	10
Sustained negativity for virus in a patient 40 years of age‡§		3, 4	Compensated cirrhosis‡	0.82 ± 0.18	10
Women, %			Ascites‡		10
Genotype 2 or 3			Diuretic-sensitive	0.75 ± 0.21	10
No cirrhosis	71.6		Diuretic-refractory	0.52 ± 0.14	10
Cirrhosis	49.8		Variceal hemorrhage‡	0.55 ± 0.16	10
Not genotype 2 or 3			Hepatic encephalopathy‡	0.53 ± 0.17	10
No cirrhosis	36.7		Hepatocellular carcinoma‡	0.55 ± 0.20	10
Cirrhosis	18.7		Liver transplantation‡	0.86 ± 0.10	
Men, %			Viral positive‡	0.95 ± 0.7	10
Genotype 2 or 3			Short-term health state		
No cirrhosis	62.5		Combination therapy, days deducted‡	-7 ± 7	10
Cirrhosis	39.6		Liver biopsy, days deducted‡		10
Not genotype 2 or 3			Without complication	-5 ± 0.3	
No cirrhosis	27.7		With complication	-11 ± 0.3	
Cirrhosis	13.1		Cost, U.S. \$		
Annual risk, %			Combination therapy		
Initial health state			24 weeks for genotype 2 or 3 and no cirrhosis‡	9011 ± 742	7
Mild hepatitis			48 weeks for all others		
Remission‡	0.2 ± 0.1	26	24-week viral negative‡	16 098 ± 3276	7
Moderate hepatitis‡	4.1 ± 1.0	11-13	24-week viral positive‡	7921 ± 2446	7
Moderate hepatitis			Liver biopsy		
Cirrhosis‡	7.3 ± 1.1	11-13	Without complication‡	1032 ± 310	10
Cirrhosis			With complication‡	2745 ± 600	10
Ascites‡			Annual care		
Refractory ascites‡	6.7 ± 1.4	19	Mild hepatitis‡	107 ± 32	9
Death‡	11 ± 1.7	19	Moderate hepatitis‡	111 ± 33	9
Refractory ascites			Compensated cirrhosis‡	794 ± 238	9
Death‡	33 ± 2.6	19	Decompensated cirrhosis‡		
Variceal hemorrhage			Ascites		
Death, first year‡	40 ± 3.4	20	Diuretic sensitive‡	1792 ± 538	9
Death, subsequent years‡	13 ± 2.3	20	Diuretic refractory‡	18 094 ± 5428	9
Hepatic encephalopathy			Hepatic encephalopathy		
Death, first year‡	68 ± 1.1	21	First year‡	11 861 ± 3558	9
Death, subsequent years‡	40 ± 1.1	21	Subsequent years‡	2748 ± 824	9
Hepatocellular carcinoma			Variceal hemorrhage		
Death‡	86 ± 1.2	22	First year‡	18 479 ± 5544	9
Decompensated cirrhosis			Subsequent years‡	3616 ± 1085	9
Liver transplantation					
Liver transplantation					
Death, first year‡	21 ± 0.9	23-25			
Death, subsequent years‡	5.7 ± 0.5	23-25			

\* Values with the plus/minus sign are the mean ± SD.

† Normal distribution based on the standard deviation observed in clinical trials or standard errors around β-coefficient estimates.

‡ Logit normal distribution; standard deviation based on that observed in clinical trials for mean age or binomial estimate using sample size for remaining variables.

§ Based on logistic regression analysis of the combination therapy groups of international and U.S. trials that considered age, sex, cirrhosis, genotype and 24-week duration of treatment for all patients except 24-week responders without genotype 2 or 3 or cirrhosis who receive an additional 24 weeks of treatment. The odds ratio was 0.979 for each year of age (P = 0.006), 1.514 for women (P = 0.007), 9.118 for genotype 2 or 3 (P < 0.001), 2.098 for not genotype 2 or 3 and treatment for 48 weeks (P = 0.001), and 0.393 for cirrhosis and treatment for 48 weeks (P = 0.08). Except for age (a continuous variable), the reference value for each variable was 1 for its presence and 0 for its absence. The natural logarithm of each odds ratio converts it to a β-coefficient. The probability of a sustained response then equals 1/(1 + exp(α + β<sub>1</sub>X<sub>1</sub> + β<sub>2</sub>X<sub>2</sub> + ... + β<sub>n</sub>X<sub>n</sub>)), where α is the constant (-0.8656), β is the β-coefficient, and X is the particular variable.

|| As a bias against combination therapy, these factors were assumed to have a quality-of-life value of 1.0 for the base-case analysis. This assumption was relaxed in sensitivity analysis, so that for patients who are viremic for hepatitis C virus infection and have mild or moderate chronic hepatitis or compensated cirrhosis, quality-of-life estimates would be 0.95 × 0.98 = 0.93, 0.95 × 0.92 = 0.87, or 0.95 × 0.82 = 0.78, respectively.

¶ Log-normal distribution; range for treatment costs based on standard deviation for actual patients, with other ranges based on ± 30% of base-case estimates.

Table 2. Results of Base-Case Analysis\*

Screening Strategy	20-Year Likelihood of Cirrhosis	20-Year Likelihood of Antiviral Treatment	Life Expectancy	Quality-Adjusted Life Expectancy	Lifetime Additional Liver Biopsies†
	%		y	QALY	n
Natural history (no antiviral treatment)	27.5	0	32.7	30.7	0
Liver biopsy every 3 years, treat if moderate hepatitis is found	18.4	50.3	33.9	32.1	6.0
Immediate combination therapy	16.0	100	34.3	33.1	0
Liver biopsy every 3 years, treat if cirrhosis is found	27.5	22.6	33.0	30.9	8.2

\* QALY = quality-adjusted life-year.

† Assuming that patients have a known initial liver biopsy.

‡ Compared with natural history. Combination therapy dominates liver biopsy with treatment if cirrhosis is found by reducing costs and providing a higher life expectancy. It is a more efficient use of resources because it has a lower cost-effectiveness ratio than liver biopsy with treatment if moderate hepatitis is found (so-called extended or weak dominance). Specifically, compared with no antiviral therapy, liver biopsy every 3 years, and treatment if moderate hepatitis is found had a marginal cost-effectiveness ratio of \$12 700 per discounted QALY gained. Compared with liver biopsy every 3 years and treatment if moderate hepatitis is found, combination therapy had a marginal cost-effectiveness ratio of \$600 per discounted QALY gained. Thus, spending an extra \$100 000 on liver biopsy management with treatment if moderate hepatitis is found would buy 7.8 discounted QALYs. Spending it on combination therapy instead would buy 167 QALYs. Therefore, liver biopsy management with treatment if moderate hepatitis is found should not be considered because investing that money in combination therapy instead would yield more benefit for a given expenditure.

Delphi technique, members of our expert panel received a description of the Markov model and assessed their own utilities for each of the health states by using the standard reference gamble (which balances near-term risk for death against living with improved quality of life) and the time-tradeoff technique (which balances longer survival with poorer quality of life against shorter survival with higher quality of life). In these analyses, patients who were alive but in less desirable states of health were not given full credit for each year lived but instead received only partial credit (for example, 0.7 year for 1 year of life with cirrhosis). Although the side-effect profile of combination therapy is similar to that of interferon therapy alone (3, 4) and although oral medications are generally preferred to those delivered by injection (31), we assumed that combination therapy had twice the negative impact on quality of life as interferon therapy alone to bias against combination therapy; in sensitivity analysis, we allowed combination therapy to have four times the negative impact of interferon therapy. As a further bias toward watchful waiting, despite the panel opinions, we assumed that mild hepatitis and viremia did not affect quality of life in our baseline analysis.

To estimate health resource consumption, we used antiviral treatment-associated clinic visits, laboratory testing (electrolytes, blood counts, and liver and thyroid tests), adverse events, pregnancy tests, and contraception and abortion costs associated with ribavirin because of its teratogenicity in animal studies (32). Antiviral drug costs were based on average wholesale costs of \$6.20 for 200 mg of ribavirin and \$11.64 per million U of interferon (33)

but were adjusted for the actual drug dose received in the trial, which reflected patient weight, dose reduction due to side effects, and drug discontinuation in patients who tested positive for HCV after 24 weeks of therapy. Therapy was discontinued in the latter patients because further therapy is unlikely to produce a sustained response (8).

Post-treatment costs were based on previously published actual variable treatment costs, wholesale drug costs, and charges adjusted with cost to charge ratios for patients with hepatitis C (9, 10). Resource estimates used a bottom-up accounting practice that combined unit cost estimates for hospitalization, outpatient visits, laboratory tests, and medications and therapeutic interventions (such as endoscopy) with health resource utilization frequencies estimated by an expert panel. All costs were inflated from 1995 to 1998 U.S. dollars by using the Medical Care component of the Consumer Price Index (Table 1). The analysis took the societal perspective, assuming that quality-of-life adjustments considered time or indirect costs (34). As is recommended, survival and costs were discounted at an annual rate of 3%, but a discount rate of 5% was used in sensitivity analyses to permit comparison with previously published studies (34). Strategies that prolong life at a lower cost are cost-saving and dominate the alternatives. Likewise, a strategy that prolongs life and has a lower marginal cost-effectiveness ratio than a less costly strategy has extended dominance over the less expensive strategy and the latter strategy can be eliminated (35). By tracking annual costs and survival, computer simulations performed by using DecisionMaker 7.0 software (Pratt Medical Group,

Table 2—Continued

Lifetime Cost of Additional Liver Biopsies†	Lifetime Cost of Antiviral Treatment	Lifetime Cost	Lifetime Discounted Cost	Discounted Life Expectancy	Discounted Marginal Cost-Effectiveness Ratio‡
←—————\$—————→				QALY	\$/discounted QALY gained
0	0	17 714	8237	19.0	
6198	7370	26 249	14 954	19.6	Inferior
0	10 728	21 073	15 238	20.1	7000
8544	5719	33 288	17 167	19.1	Inferior

Boston, Massachusetts) yielded the expected average lifetime costs, life expectancy, and quality-adjusted life expectancy associated with each strategy.

**Sensitivity Analysis**

To examine the extent to which our results varied with alternative assumptions, we performed additional analyses for different estimates of disease progression and for clinical subgroups. In addition, we performed a Monte Carlo analysis, in which all parameters are varied simultaneously over probability distributions defined by the 95% CIs or reasonable ranges (Table 1) (36, 37). A unique set of random values was sampled for each variable (including patient characteristics, liver disease progression rates, treatment response rates, and costs). For each unique set of values, the simulation projected the discounted quality-adjusted life expectancy and lifetime cost results for each strategy using four identical cohorts of 10 000 patients. These analyses were repeated 1000 times.

**Role of the Funding Source**

The study was funded in part by an unrestricted grant from Schering-Plough Corp. to the investigators' institutions. The grant recipients had complete independence regarding study design, data analysis, manuscript preparation, and the decision to submit the paper for publication. The Schering-Plough Research Institute provided raw data from their clinical trial database, but the authors performed all analyses. One of the authors (RSK) has grant support from the Schering-Plough Research Institute for clinical research studies and has served as a consultant.

**RESULTS**

**Model Validation**

The model was validated previously by comparing model mortality predictions (9) with data from published studies of transfusion recipients and patients with cirrhosis (16, 38). In addition, we compared model predictions with data from five other prospective studies of transfusion-associated acute non-A, non-B hepatitis (39). Assuming a linear rate of progression to cirrhosis to adjust for differences in follow-up, the 20-year cumulative incidence of cirrhosis ranged from 14% to 45%, with a weighted pooled estimate of 24%. After adjustment for the 15% of cases of acute hepatitis C that resolve spontaneously, the 24% incidence increases to 28%, which is nearly identical to the 27.5% incidence predicted by the model.

**Base-Case Analysis**

*Incidence of Cirrhosis, Life Expectancy, and Quality of Life*

Table 2 shows results of the base-case analysis. Results of biopsy management and treatment if cirrhosis is found is shown in all tables; however, because this strategy was always inferior (higher costs and lower life expectancy), for simplicity the remaining text on biopsy management refers only to biopsy management plus treatment if moderate hepatitis is found. After 20 years, model projections suggested that watchful waiting avoided antiviral treatment in 50% of the cohort and decreased the absolute risk for cirrhosis by 9.1% through selective treatment of patients who progressed and inducement of sustained viral-negative

**Table 3. One-Way Sensitivity Analysis\***

Factor	Immediate Treatment versus Watchful Waiting for Cirrhosis		Immediate Treatment versus Watchful Waiting for Moderate Hepatitis	
	Gain in Years of Life	Gain in QALYs	Gain in Years of Life	Gain in QALYs
Age 30 years	2.5	4.4	0.6	1.9
Age 50 years	0.5	1.4	0.1	0.8
Male	1.1	2.2	0.3	1.1
Female	1.8	3.5	0.4	1.6
Not genotype 2 or 3	1.0	2.0	0.3	1.0
Genotype 2 or 3	1.9	4.0	0.4	1.9

\* QALY = quality-adjusted life-year.

responses in some. Immediate treatment reduced the absolute risk by an additional 2.4% because it induced more sustained responders. The simulation predicted that among treated patients, the overall rates of sustained viral-negative response decreased from 42% with immediate antiviral treatment to 33% with biopsy management and treatment of moderate hepatitis (17% with biopsy plus treatment for cirrhosis) because of advancing patient age and development of cirrhosis.

In the long term, the reduced risk for cirrhosis associated with immediate therapy translated into a 0.4-year gain compared with biopsy management and a 1.6-year gain compared with no antiviral therapy. When quality of life was considered, the benefit of immediate therapy increased to 1.0 quality-adjusted life-year (QALY) compared with biopsy management and to 2.4 QALYs compared with no antiviral therapy. The benefit of immediate antiviral treatment increased with quality adjustment because such therapy resulted in a higher proportion of sustained responders sooner, decreasing the likelihood and proportion of life spent in less desirable states of health, such as decompensated cirrhosis or hepatocellular carcinoma.

### Costs

Table 2 shows the effect of each strategy on costs. Although watchful waiting reduced costs of antiviral therapy by \$3400, costs of biopsy reached \$6200. After including the cost of potential future HCV-related complications, the lifetime cost of biopsy management exceeded the lifetime cost associated with immediate therapy by at least \$5100. Because immediate therapy also prolonged life while reducing costs, it dominated biopsy management and was cost-saving.

### Discounting

In discounting, money spent now is considered to have a higher value than money spent in the future. Because immediate combination therapy has higher current costs and its benefits occur in the future, discounting reduced the benefit of immediate therapy and increased its relative costs compared with future biopsy or no antiviral treatment. Immediate therapy increased lifetime discounted costs by \$7000 and life expectancy by 1.0 discounted QALY, yielding a marginal cost-effectiveness ratio of \$7000 per discounted QALY gained compared with no antiviral therapy (Table 2). When discounted at 5%, this ratio increased to \$13 500 per discounted QALY gained. Compared with biopsy management, immediate therapy had extended dominance over biopsy management by providing more efficient use of economic resources (Table 2) (35). If immediate antiviral treatment was not an option, biopsy management with treatment for moderate hepatitis dominated biopsy management with treatment for cirrhosis and had a marginal cost-effectiveness ratio of \$10 700 compared with no antiviral treatment.

The above analyses assumed that mild hepatitis and viremia were not associated with any deficit in quality of life. The following results are based on the values shown in Table 1.

### Frequency of Biopsy

When alternative frequencies of liver biopsy were considered, the results remained stable for biopsy every 4 or 5 years as well as for increasing the interval between biopsies by 1 year (for example, first biopsy after 3 years, second biopsy 4 years after the first, and so on). More patients developed cirrhosis during the higher interval between biopsies, which offset the reduced lifetime cost of liver biopsies.

We also considered performance of only one, two, or three liver biopsies over the lifetime of the patient. Assuming that such biopsies occurred every 3, 4, or 5 years for the first 3 to 15 years did not change the results.

### Compliance

The above analyses assume that patients comply perfectly with follow-up and with future biopsy. If noncompliance with liver biopsy was 25% at each follow-up, the benefit of immediate therapy improved slightly. If, however, noncompliance increased progressively (25% noncompliance after 3 years, 50% after 6 years, and 75% after

9 years), the benefit of immediate therapy over biopsy management increased to 1.0 year. With decreasing compliance, immediate therapy had extended dominance over biopsy management for annual discount rates of 3% or 5%.

**Sensitivity Analysis**

Using the model, our base-case estimates predicted a 27.5% incidence of cirrhosis after 20 years. In sensitivity analysis, we reduced the annual likelihood of histologic progression by half (even lower than the SDs in Table 1) so that the cumulative 20-year incidence of cirrhosis without antiviral treatment decreased to 9.5%. Even in such a scenario, combination therapy had extended dominance over biopsy management and had a marginal cost-effectiveness ratio of \$10 700 per discounted QALY gained compared with no antiviral treatment. A faster progression rate strengthened the benefit and cost-effectiveness of combination therapy.

The natural history of patients with persistently mild histologic findings for 10 to 20 years is unknown. Assuming that disease in such patients would not progress in the future and that liver biopsies would be performed for only 10 or 20 years, combination therapy still had extended dominance over biopsy management and had a marginal cost-effectiveness ratio less than \$7500 per discounted QALY gained compared with no antiviral treatment.

Table 3 shows the life expectancy benefits in various clinical subgroups of immediate antiviral treatment compared with biopsy management. Adjustment for quality of life enhanced the benefit of antiviral treatment, and the largest gains occurred in subgroups with favorable response characteristics: younger age, women, and persons with geno-

type 2 or 3. In these groups, a higher proportion of patients became negative for HCV and avoided the impairment of quality of life associated with viremia over a longer period of time. Conversely, for these subgroups, the non-quality-adjusted gains in life expectancy associated with immediate antiviral treatment were lower because delayed therapy still had a high likelihood of response and no quality-of-life benefits accrued from earlier response.

Immediate antiviral therapy always had extended dominance over biopsy management. Even at 60 years of age, immediate antiviral therapy dominated biopsy management and had a marginal cost-effectiveness ratio of \$18 900 per discounted QALY gained compared with no antiviral therapy. Combination therapy was favored unless the quality of life associated with antiviral therapy was less than 0.22; this represents a 9-month reduction in length of life for 1 year of treatment, more than 11 times the baseline morbidity value, and more than twice the negative impact on quality of life associated with the advanced liver disease states.

In probabilistic sensitivity analysis for patients 40.1 ± 8.9 years of age with histologically mild hepatitis, the 25th, 50th, and 75th percentiles of the marginal cost-effectiveness of immediate antiviral therapy compared with no antiviral therapy were \$4300, \$7300, and \$11 700 per discounted QALY gained, respectively. Immediate antiviral therapy dominated watchful waiting in 99.6% of the iterations, so that biopsy managed care would be superior to immediate therapy in only 4 of 1000 patients (Table 4). In three cases, the marginal cost-effectiveness of immediate antiviral therapy exceeded \$50 000 per discounted QALY gained, but it never exceeded \$100 000 per discounted

**Table 4. Monte Carlo Sensitivity Analysis\***

Incremental Cost of Immediate Antiviral Therapy	Incremental Benefit of Immediate Antiviral Therapy							
	<0 DQALY	0 to ≤0.5 DQALY	0.5 to ≤1.0 DQALY	1.0 to ≤1.5 DQALY	1.5 to ≤2.0 DQALY	2.0 to ≤2.5 DQALY	2.5 to ≤3.0 DQALY	3.0 to ≤3.5 DQALY
Less than -\$7500	0	0	1	0	0	0	0	0
-\$7500 to -\$5000	0	1	0	1	0	1	0	1
-\$5000 to -\$2500	0	23	19	3	3	1	4	0
-\$2500 to \$0	2	113	137	48	14	2	1	1
\$0 to \$2500	2	253	173	49	17	8	1	2
\$2500 to \$5000	0	76	31	7	2	0	0	0
\$5000 to \$7500	0	3	0	0	0	0	0	0

\* Results of Monte Carlo simulation showing the relative frequencies of the mean incremental costs in discounted (3%) U.S. dollars and mean effectiveness gained in discounted quality-adjusted life-years (DQALY) gained with immediate antiviral treatment compared with biopsy management plus antiviral treatment if moderate hepatitis is found. Positive incremental benefits imply a gain in life expectancy with immediate antiviral therapy. Negative incremental costs imply cost savings associated with immediate antiviral therapy. The most frequent outcome was an increase of 0 to 0.5 DQALY at \$0 to \$2500 additional cost associated with antiviral treatment. The four cases in the first column were ones for which biopsy management was superior. For the first four rows, immediate antiviral therapy reduced costs and prolonged life.

QALY gained. Thus, biopsy management had a marginal cost-effectiveness ratio less than \$50 000 per discounted QALY in 0.7% of the simulations. In contrast, immediate combination therapy was cost-saving in 37.5% of cases, both prolonging life and reducing lifetime costs.

## DISCUSSION

Consensus among hepatologists is that HCV-infected patients with cirrhosis or bridging fibrosis should be treated. These patients have a high likelihood of progressing to liver decompensation, and the shortage of donor organs limits the availability of liver transplantation once decompensation has occurred. Similarly, most hepatologists agree that patients with moderate hepatitis should be treated, especially those who are young and healthy and whose future length of life make it likely that they may eventually develop liver complications. Most physicians would not treat patients with normal results on liver biopsy unless hepatitis C viremia appeared to be severely affecting their quality of life and treatment was undertaken to relieve symptoms. The most controversial group is patients with mild histologic findings; only some will progress to cirrhosis after many years, and treatment has potential side effects, is relatively expensive, and is not effective in all patients (5). Consequently, management with periodic biopsy has been proposed for patients with histologically mild hepatitis C who do not wish to be treated and in whom disease may not progress (6).

Our analysis suggests that biopsy management would avoid treatment in many patients, especially over the next 20 years. Compared with immediate antiviral treatment, however, biopsy management permitted an increased cumulative incidence of cirrhosis and decreased survival. Among the biopsy strategies, treatment of patients in whom disease progressed to moderate hepatitis is superior to waiting until cirrhosis develops because treatment response is higher in patients without cirrhosis. Among patients unwilling to undergo immediate antiviral treatment, biopsy plus treatment of moderate hepatitis was cost-effective. However, to achieve those benefits, patients must be willing to comply with follow-up biopsy. Data on compliance with follow-up liver biopsy are currently unavailable, but Foster and colleagues (6) reported that among 104 patients, 34 did not return for follow-up after discovery of their HCV infection and another 24 declined liver biopsy.

After years of persistent infection, HCV appears to insidiously result in progressive fibrosis, ultimately leading

to cirrhosis (40). A recent natural history study suggests a lower likelihood of cirrhosis (41); however, that study consisted of young women, and female sex and young age favor slower progression rates (42). Future monitoring for further progression among the 51% of patients with hepatic fibrosis will further clarify the natural history of hepatitis C. Despite this uncertainty about the natural history of hepatitis C, our computer model (9) has been validated in comparison with other mortality studies (16, 38) and five prospective studies of transfusion-associated non-A, non-B hepatitis (39). Moreover, our conclusions remained stable even if only 9.5% of patients progressed to cirrhosis after 20 years.

The quality-of-life benefits of treatment exceed the life expectancy benefits by decreasing the likelihood of and the proportion of life spent in less desirable health states, such as advanced liver disease. These results occurred despite the following quality-of-life assumptions, which all biased against antiviral therapy. Because nearly all of the quality-of-life estimates used in this analysis are higher than those in other published studies (9, 43, 44), our results underestimate the quality-of-life deficits associated with chronic hepatitis C. Other studies have considered viral eradication to restore the quality-of-life value to 1 (43, 44). In our analysis, viral eradication was associated with improved quality of life from loss of viral positivity, but patients continued to have the quality-of-life deficit associated with their last underlying liver histology. Thus, our model did not consider the benefits associated with the improved liver histology that have been found in treatment studies (45, 46). Lastly, in our base case, we did not consider any quality-of-life deficit for having mild chronic hepatitis or being viremic with HCV infection. Quality-of-life studies suggest deficits equivalent to the deficit in patients with diabetes mellitus (47), and a study of patients with noncirrhotic hepatitis C suggests that values cluster mostly between 0.7 and 0.8 (48). For mild hepatitis, we used 1.0 in the base-case analysis and 0.93 ( $0.98 \times 0.95$ ) in sensitivity analysis.

From an economic standpoint, our analysis also suggests that long-term biopsy management might actually increase overall costs because future biopsy costs nearly equalled current treatment costs. Discounting decreased these future biopsy costs, but biopsy management would still be economically less efficient than immediate treatment. Similarly, declining compliance would also decrease the costs of liver biopsy, but costs related to future com-

plications from advanced liver disease would increase because more patients would progress to cirrhosis.

Our analysis linked sustained loss of viremia to improved survival and decreased liver complications, but long-term randomized treatment trials demonstrating these benefits are lacking. Despite some controversy (49–53), an increasing number of studies suggest that viral eradication improves liver histologic findings, decreases the risk for hepatocellular carcinoma or cirrhosis and decompensation, and perhaps improves survival (17, 18, 45, 46, 53–68). Treatment-induced viral eradication also restores impaired quality-of-life measures in those with chronic hepatitis C (47, 69, 70).

Some 5% of patients with mild histologic findings may be among the group of rapid progressors, but distinguishing rapid progressors from other patients with chronic hepatitis C is not currently possible (42). However, factors that are known to accelerate progression include alcohol intake exceeding 50 g/d, male sex, and advanced age (42). Thus, for these patients, physicians should consider substance abuse counseling and antiviral treatment. On the other hand, patients who decline antiviral treatment should be aware that they will probably need repeated liver biopsy every 3 to 5 years to minimize their risk for clinically inapparent advanced fibrosis. Our analysis emphasizes the need to find an inexpensive noninvasive method to assess the extent of liver fibrosis and to identify patients who are likely to experience progressive liver disease. In the interim, our analysis suggests that immediate antiviral therapy should increase survival and reduce costs for the group with histologically mild hepatitis.

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To believe in medicine would be the height of folly, if not to believe in it were not a greater folly still. For from this mass of errors a few truths have in the long run emerged.

Marcel Proust  
*Remembrance of Things Past*  
 Volume II, *The Guermantes Way*  
 New York: Random House; 1992:308-309

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