

Erythropoietic Growth Factors for Treatment-Induced Anemia in Hepatitis C: A Cost-Effectiveness Analysis

BRENNAN M. R. SPIEGEL,^{*,†,§} KRISTINA CHEN,[¶] CHIUN-FANG CHIOU,^{||} SEAN ROBBINS,^{||} and ZOB AIR M. YOUNOSSI[#]

*Division of Gastroenterology, VA Greater Los Angeles Healthcare System, Los Angeles; †Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles; §UCLA/VA Center for Outcomes Research and Education (CORE), Los Angeles; ¶Cerner Health Insights, Beverly Hills; ||Amgen Inc. Global Health Economics, Thousand Oaks, California; and the #Inova Fairfax Hospital, Annandale, Virginia

Background & Aims: Treatment-induced anemia undermines the efficacy of antiviral therapy in hepatitis C by mandating ribavirin dose reduction and diminishing adherence to therapy. Erythropoietic growth factors (EGFs) may correct treatment-induced anemia, facilitate maintenance of full-dose therapy, and improve rates of sustained virologic response (SVR). We sought to determine the cost effectiveness of adjunctive treatment with an EGF vs standard care in the treatment of hepatitis C. **Methods:** We used a decision analysis to calculate the cost effectiveness of 2 treatment strategies for a patient cohort with chronic hepatitis C, increased transaminase levels, and no cirrhosis who were receiving pegylated-interferon and ribavirin (RBV): (1) RBV dose-reduction for anemia, followed by discontinuation of therapy if anemia persisted (standard care strategy), (2) adjunctive treatment with EGF therapy for anemia, with RBV dose reduction reserved for persistent anemia despite EGF therapy (EGF strategy). We conducted cost-effectiveness and cost-utility analyses to compare short- and long-term outcomes between the strategies. **Results:** The percentage achieving SVR was 52.3% in the standard care strategy and 59.5% in the EGF strategy. Compared with standard care, the EGF strategy cost an incremental \$36,568 per unadjusted life-year gained and \$16,443 per quality-adjusted life-year gained. In a sensitivity analysis, if a third-party payer was willing to pay \$50,000 per quality-adjusted life-year gained for the use of an EGF, then 86.1% of patients would be within the budget. **Conclusions:** Compared with standard care, adjunctive therapy with an EGF for the management of treatment-induced anemia may increase the probability of achieving SVR, increase unadjusted lifespan, and increase quality-adjusted lifespan at an acceptable cost.

effectiveness^{2,3} and cost effectiveness.⁴⁻⁶ Although this regimen achieves a high rate of sustained virologic response (SVR) when therapeutic adherence is optimal, the SVR rate decreases dramatically when adherence is low.⁷ In 1 study of PEG-IFN and RBV, the impact of nonadherence was most pronounced in patients with genotype 1 HCV, in which SVR decreased from 52% in adherent patients (defined as those receiving at least 80% of both drugs for at least 80% of the treatment duration) to only 33% in nonadherent patients.⁷ Because the primary goal of treatment in HCV is to achieve SVR and ultimately minimize long-term complications of chronic liver disease, it is imperative to maximize therapeutic compliance to preserve the well-established efficacy of PEG-IFN and RBV.

However, compliance with combination therapy is undermined significantly by the development of anemia resulting from RBV-induced hemolysis⁸ and, to a lesser extent, by IFN-related bone marrow suppression.⁹ Data indicate that up to one third of patients receiving combination therapy develop anemia (hemoglobin [Hgb] level <12 g/dL or a 3 g/dL decrease from baseline Hgb level)² and 13% progress to a Hgb level less than 10 g/dL.¹⁰ Moreover, the fatigue and health-related quality of life (HRQOL) decrement associated with treatment-induced anemia¹¹ leads to dose reduction or discontinuation in nearly one fourth of all patients receiving combination therapy.^{12,13} These data present a marked disconnect between the goal of achieving SVR through optimal adherence and the clinical reality of prevalent noncompliance.

Chronic hepatitis C virus (HCV) infection is a prevalent and expensive condition affecting 4 million people in the United States at a cost of over \$700 million annually.¹ Combination therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) is adopted widely as the standard of care for HCV on the basis of its

Abbreviations used in this paper: EGF, erythropoietic growth factor; EVR, early virologic response; HCV, hepatitis C virus; Hgb, hemoglobin; HRQOL, health-related quality of life; ICER, incremental cost-effectiveness ratio; PEG-IFN, pegylated interferon; QALY, quality-adjusted life-year; RBV, ribavirin; SVR, sustained virologic response.

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1542-3565/05/\$30.00

PII: 10.1053/S1542-3565(05)00695-6

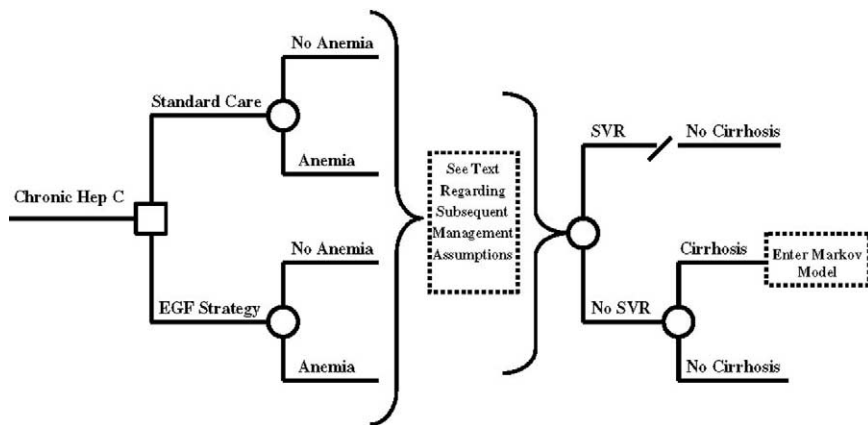


Figure 1. Truncated decision model. The base-case patient has chronic hepatitis C infection, increased transaminase levels, and no clinical or histologic evidence of cirrhosis. The clinician either may treat with IFN and RBV alone without EGF therapy in case of anemia (standard care), or use EGF therapy in case of anemia (EGF strategy). Within each strategy patients either develop treatment-induced anemia or do not. Similarly, in each strategy patients may achieve SVR 6 months after cessation of therapy. Finally, patients failing to achieve SVR are eligible to develop cirrhosis and resulting complications over the course of their lifetime. See text for details regarding specific assumptions governing patient management and probability estimates for individual branch points.

Evolving data indicate that the use of adjuvant erythropoietic growth factors (EGFs) in the treatment of HCV may increase and maintain hemoglobin levels in many patients without requiring RBV dose reduction or outright discontinuation.¹⁴⁻¹⁹ In particular, treating RBV-induced anemia with either epoetin alfa¹⁴⁻¹⁸ or darbepoetin alfa¹⁹ allows maintenance of full-dose therapy in greater than 80% of anemic patients while improving HRQOL.^{19,20} In contrast, a recent study showed that only 60% of anemic patients receiving standard care (ie, PEG-IFN and RBV without EGF therapy) were able to maintain full-dose therapy.¹⁶ Taken together, these data suggest that the efficacy of EGF therapy may optimize adherence to full-dose combination therapy by treating anemia, increasing SVR, and, ultimately, minimizing long-term complications of HCV vs the standard approach of relying on RBV dose-reduction alone for treatment-induced anemia. We performed a lifetime cost-effectiveness analysis to determine the degree to which up-front costs of EGF therapy are offset by downstream savings engendered by its improved effectiveness compared with standard care.

Methods

Decision Model Framework

Decision analysis is a quantitative method for estimating the financial costs and clinical outcomes of alternative strategies under conditions of uncertainty.²¹ By using decision analysis software (DATA 4.0; TreeAge Software, Inc., Williamstown, MA), we evaluated a hypothetical cohort of 45-year-old patients with chronic HCV infection, increased transaminase levels, and no clinical or histologic evidence of cirrhosis. Patients entered the hypothetical model without

previous treatment for HCV and were treated with PEG-IFN and RBV. Patients subsequently received 1 of 2 competing strategies for the management of treatment-induced anemia: (1) RBV dose-reduction if the hemoglobin level decreased to less than 10 g/dL, followed by discontinuation of treatment if the hemoglobin level decreased to less than 8.5 g/dL (standard care strategy), or (2) adjunctive treatment with an EGF for anemia (defined as a Hgb level <12 g/dL or a ≥ 3-g/dL decrease) with RBV dose reduction reserved for continued Hgb level decrease despite EGF therapy (EGF strategy).

Figure 1 shows a truncated version of the decision tree. Patients entering the model either developed treatment-induced anemia or maintained an acceptable hemoglobin level. Patients without anemia continued RBV and PEG-IFN treatment at full dose, whereas those with anemia required additional evaluation, as described in the Model Assumptions section later. Patients were followed-up for a lifetime horizon after the initial treatment course. Patients achieving SVR after treatment did not develop cirrhosis and were subjected to a normal life expectancy, as supported by evolving natural history data.²² In contrast, patients failing to develop SVR were eligible to develop cirrhosis. The subset developing cirrhosis then entered a Markov model governing patient transitions between relevant health states (Figure 2).

Model Assumptions

Base-case patients. To reflect the cohorts described in primary treatment trials, we assumed the base-case patients were 45 years of age and had chronic HCV seropositivity, persistently increased transaminase levels, no symptoms or signs of chronic liver disease, no evidence of anemia, and no other contraindications to treatment. Liver biopsy examination showed no evidence of cirrhosis, although early fibrosis (ie, grades 1-2) was not an exclusion criterion. In accordance with

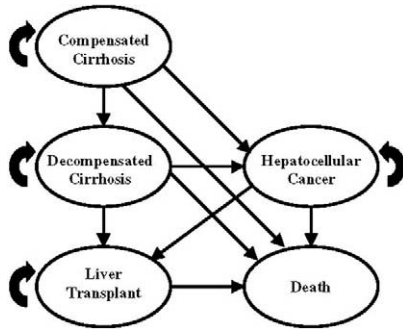


Figure 2. Markov state diagram for a subset of patients developing cirrhosis. Patients enter the model with compensated cirrhosis. During each 1-year cycle individual patients either remain in their assigned health state (recursive arrow), or progress to a new health state (straight arrow). Patients with compensated cirrhosis may develop decompensated cirrhosis (including variceal hemorrhage, ascites, or encephalopathy). Hepatocellular cancer may develop at any stage of cirrhosis. Transition rates between health states (including liver transplant and mortality rates) were derived from the literature (Table 1).

primary treatment trials, 70% of the cohort had genotype 1 HCV.^{2,3,23–26}

Standard care strategy. Patients receiving standard care therapy began with appropriate doses of PEG-IFN and RBV, and subsequently either developed anemia (Hgb level <12 g/dL or ≥3-g/dL decrease) or maintained a normal hemoglobin level. Patients without anemia continued therapy and either remained compliant with full-dose therapy or were

inadequately compliant (defined as <80% IFN dose, <80% RBV dose, <80% of the time).⁷ Patients with anemia also continued full-dose therapy and were monitored for progression of anemia. These patients either progressed to a Hgb level of less than 10 g/dL or maintained their Hgb level greater than 10 g/dL. Patients with a Hgb level of less than 10 g/dL required RBV dose reduction. After this maneuver, patients either maintained or improved their hemoglobin level or developed further progression to a Hgb level of less than 8.5 g/dL. Patients with a Hgb level of less than 8.5 g/dL required discontinuation of all therapies and were assumed to not achieve SVR. Table 1 shows the individual probability estimates governing this strategy.

Erythropoietic growth factor strategy. Patients in the EGF strategy began therapy with combination PEG-IFN and RBV and were monitored for anemia as described in the standard care strategy. Unlike the standard care strategy, patients developing anemia (Hgb level <12 g/dL or ≥3-g/dL decrease) began adjunctive EGF therapy in lieu of RBV dose reduction. After this therapeutic addition, the patients either maintained or improved their Hgb level or developed progressive anemia. Patients with progressive anemia despite EGF therapy then were required to reduce their RBV dose. Patients maintaining their Hgb level greater than 8.5 g/dL after these maneuvers were allowed to continue therapy whereas those with Hgb levels of less than 8.5 g/dL required discontinuation of all therapies and did not achieve SVR. Table 1 shows the individual probability estimates governing this strategy.

Table 1. Base-Case Clinical Probability Estimates

Variable	Base-case estimate	Range in sensitivity analysis	References
Probability of genotype-1 HCV	70%	0%–100%	2,3,23–26
Probability of SVR assuming adequate compliance in genotype-1 HCV (adequate compliance = >80, >80, >80 dosing)	52%	25%–75%	7
Probability of SVR assuming adequate compliance in genotype non-1	90%	70%–100%	7
Probability of SVR assuming inadequate compliance in genotype-1 HCV	33%	20%–50%	7
Probability of SVR assuming inadequate compliance in genotype non-1	89%	70%–100%	7
Probability of SVR assuming dose reduction of RBV in genotype 1 HCV	39%	20%–60%	2
Probability of SVR assuming dose reduction of RBV in genotype non-1	75%	50%–90%	2
Probability of adequate compliance assuming no anemia (accounting for other potential adverse events)	75%	50%–90%	12
Probability of adequate compliance assuming development of anemia	60%	40%–80%	12
Probability of developing Hgb level <10 from PEG-IFN and RBV	16%	0%–50%	2,3,7,12,35
Probability of RBV dose reduction reversing anemia once Hgb level <10	45%	10%–50%	2
Probability of EGF therapy reversing anemia (Hgb <10)	85%	40%–90%	14–19
Probability of developing cirrhosis assuming no SVR	20%	5%–30%	36,37
Mean number of years until development of cirrhosis	20	5%–25%	36,37
Annual rate of progression from uncomplicated to complicated cirrhosis	4%	2%–6%	5
Annual rate of progression from cirrhosis to hepatocellular cancer	2.1%	1%–3%	5
Annual rate of mortality in hepatocellular cancer	43.3%	20%–60%	5
Annual rate of mortality in complicated cirrhosis	30.6%	10%–50%	5
Probability of developing variceal bleed in cirrhosis	28%	10%–50%	38–42
Probability of developing ascites in cirrhosis	22%	50%–90%	38–42
Probability of developing overt encephalopathy in cirrhosis	15%	5%–30%	38–42
Annual rate of mortality after successful transplant (adjusted to account for decreasing mortality over time from transplant)	6.9%	2%–12%	5
Probability of receiving a transplant in complicated cirrhosis	3%	0%–20%	43

Relationship between sustained virologic response and subsequent health. We assumed that patients developing SVR after treatment were cured of HCV. These patients were subjected to a normal lifespan and lived an additional 34 years in accordance with US population life tables for persons aged 45 years.²⁷ Patients without SVR were eligible to develop cirrhosis. We assumed that 20% of patients without SVR developed cirrhosis over a mean of 20 years.

Clinical Probability Estimates

Our base-case model incorporated a wide range of estimates governing relevant clinical probabilities in the management and natural history of chronic HCV infection (Table 1). To derive these estimates we performed a structured search of published reports from the MEDLINE bibliographic database to identify English-language publications pertaining to our clinical inputs from January 1990 to January 2005. Because our base-case estimates are unlikely to be reproduced precisely in varying populations, we varied each estimate over a wide range in sensitivity analysis as described later.

Outcomes

The clinical outcome of greatest importance to patients with chronic HCV is uncertain. Although The National Panel on Cost-Effectiveness in Health and Medicine suggests that quality-adjusted life-years (QALYs) are the most appropriate unit for cost-effectiveness analysis,²⁸ previous economic models for HCV therapy also have relied on unadjusted life-years as the main outcome measure.^{4,6} Because chronic HCV infection is known to impact both the quality and quantity of life negatively, we performed 2 primary analyses: (1) a cost-effectiveness analysis measuring the incremental cost per unadjusted life-year gained between strategies, and (2) a cost-utility analysis measuring the incremental cost per QALY gained between strategies.

Although the ultimate goal of treating HCV is to minimize long-term complications of chronic liver disease, there are several interim outcomes with relevance to treatment choices in HCV. We therefore performed secondary analyses to measure the following short-term outcomes: (1) proportion of patients in each strategy completing a full-dose therapeutic course, (2) proportion of patients achieving SVR at 6 months after cessation of therapy.

Utilities

To calculate QALYs, we adopted utilities over a wide-range of HCV-related health states. Based on published standard gamble utility elicitation in patients with chronic HCV, we assumed a utility of .79 for mild/moderate chronic HCV, .60 for decompensated cirrhosis, .73 after successful liver transplant, .72 for hepatocellular cancer, and .86 for SVR after successful treatment.²⁹ There are no established utilities for treatment-induced anemia in HCV, although studies have measured utilities for anemia in other disorders. For example, Peeters et al³⁰ found a 3.1% decrease in utility scores (as measured by the visual analog scale) for every 1-g/dL Hgb

decrease in rheumatoid arthritis patients with anemia of chronic disease. By using this relationship, a patient with a typical³¹ 4- to 5-g/dL decrease in Hgb level from HCV treatment (eg, from 15 g/dL at baseline to 10 g/dL) would have a utility of .85 (assuming a baseline utility of 1.0). Moreover, data in HCV indicate that patients with treatment-induced anemia score up to 30% lower on the Short Form 36 (SF-36) Health Survey (a generic measure of HRQOL) compared with their pretreatment HRQOL measurements.¹⁶ By using a published regression equation designed to convert SF-36 scores into utility scores,³² we estimated utilities of .85 and .7 for Hgb levels of less than 12 g/dL and Hgb levels of less than 10 g/dL, respectively. Because these utilities are not derived from a traditional standard gamble technique and do not strictly comply with econometric theory, we varied the estimates over a wide range in sensitivity analysis. All utilities were discounted at a rate of 3% as recommended by the National Panel on Cost-Effectiveness in Health and Medicine.²⁸

Cost Estimates

We conducted our analysis from the perspective of a third-party payer and incorporated the direct health care costs for a range of therapies, physician visits, diagnostic tests, and complications of chronic liver disease (Table 2). We obtained costs for physician services and procedures from the 2004 American Medical Association Current Procedural Terminology codebook and the 2004 Medicare Fee Schedule, and derived our base-case pharmaceutical costs from the average wholesale prices listed in the 2004 Red Book. We obtained cost estimates for cirrhosis and related health states from a published study of detailed itemized inpatient and outpatient direct costs incurred by patients with cirrhosis.⁵ We updated all cost estimates to 2004 dollars using the medical care component of the consumer price index.³³ We discounted all future costs at a rate of 3% per year as recommended by the National Panel for Cost-Effectiveness in Health and Medicine.²⁷

Sensitivity Analyses

Table 1 shows our base-case probability estimates with the plausible range of values for each estimate. To test the influence of all variables on the model results we performed a multivariable sensitivity analysis (tornado analysis³⁴) and rank-ordered the most influential variables. We then performed 1-way sensitivity analyses on the most influential variables.

Although 1-way sensitivity analyses provide information regarding the robustness of a model, they are inadequate to simulate real-world conditions. To acknowledge the reality that each individual carries a unique composition of clinical probabilities we conducted a probabilistic (Monte Carlo) simulation under the assumption that all variables were triangular in distribution.³⁴ The triangular distribution assumes that a parameter's base-case value is most likely to occur and that the minimum and maximum values are least likely to occur. The probability of observing a value between the base-case and

Table 2. Base-Case Cost Estimates

Variable	Base-case estimate	Range in sensitivity analysis	References
Drug costs			
Cost per week of EGF therapy (cost modeled after darbepoetin alfa, 3 µg/kg once every 2 wk)	515	200–700	44
Cost per week of PEG IFN	200	100–300	44
Cost per week of RBV	235	100–300	44
Nondrug costs of treatment period			
Cost per physician visit	52	25–10	45
Cost per complete blood count	10	1–75	45
Costs of developing cirrhosis^a			
Cost per year of uncomplicated cirrhosis	964	500–5000	5
Cost of first year after variceal hemorrhage (assuming survival)	22,444	10,000–30,000	5
Cost per subsequent year after variceal hemorrhage	4393	2000–10,000	5
Cost per year of ascites	4058	1000–10,000	5
Cost of first year of encephalopathy	14,406	5000–25,000	5
Cost per subsequent year after encephalopathy	3337	1000–10000	5
Cost of liver transplantation	127,499	50,000–150,000	5
Cost per year of follow-up care after liver transplantation	22,266	10,000–50,000	5
Discount rate for costs	3%	1%–5%	28

^aAll cirrhosis cost estimates were updated to 2004 dollars using the medical care component of the consumer price index.³³

extreme value is interpolated linearly. We evaluated 1000 trials through this simulation and report the median, 2.5, and 97.5 percentile values of the incremental cost-effectiveness ratio (ICER) between the competing strategies. Because different third-party payers have different willingness-to-pay thresholds we also report the percentage of trials decreasing to less than 3 ICER thresholds: \$100,000, \$50,000, and \$20,000 per QALY gained.

Results

Base-Case Results

We estimated the potential clinical and economic impact of implementing the 2 alternative strategies in separate cost-effectiveness and cost-utility analyses (Table 3). The standard care strategy cost \$16,597 per average patient treated and yielded a mean of 11.385 QALYs and 12.298 unadjusted life years, and was less expensive yet less effective than the EGF strategy. Compared with usual care, the use of EGF therapy for treat-

ment-induced anemia cost an incremental \$16,443 to gain 1 additional QALY and \$36,568 to gain 1 additional unadjusted life year. The model projected that 61% of patients in the standard care strategy completed their intended course of full-dose combination therapy and 52.3% achieved SVR. In contrast, the EGF strategy increased adherence to therapy by 9% and SVR by 7.2% over and above standard care.

Sensitivity Analyses

Tornado analysis revealed that the model was sensitive to the following variables, in descending order of influence: annual discount rate, use of HCV seropositivity, cost of EGF, cost of RBV, cost of PEG IFN, and probability of SVR given adequate compliance. Table 4 shows the results of 1-way sensitivity analysis for each of these parameters and lists the thresholds for the \$10,000, \$20,000, and \$30,000 cost per QALY ICER willingness-to-pay lines.

Table 3. Base-Case Results From Cost-Effectiveness and Cost-Utility Analyses

Analysis	Strategy	Cost ^a	Effectiveness ^b	Incremental cost/effectiveness ^c
Cost effectiveness analysis (cost per LY)	Standard therapy strategy	\$16,597	12.298	–
	EGF strategy	\$20,339	12.400	\$36,568
Cost-utility analysis (cost per QALY)	Standard therapy strategy	\$16,597	11.385	–
	EGF strategy	\$20,339	11.612	\$16,443

LY, life year.

^aAverage discounted lifetime cost per patient.

^bDiscounted life-years gained (cost-effectiveness analysis) or discounted QALYs gained (cost-utility analysis).

^cIncremental cost per additional life-year gained compared with standard therapy (cost-effectiveness analysis), or incremental cost per additional QALY gained compared with standard therapy (cost-utility analysis).

Table 4. Results of 1-Way Sensitivity Analyses Comparing Standard Therapy Versus EGF Therapy for Anemia

Variable	Base-case estimate	\$10,000 ICER threshold	\$20,000 ICER threshold	\$30,000 ICER threshold
Annual discount rate	3.0%	2.1%	3.3%	4.0%
Utility of HCV seropositivity	.79	.73	.81	.84
Cost per week of EGF therapy	\$515	\$300	\$620	\$1000
Cost per week of ribavirin	\$225	None	\$680	\$1850
Cost per week of interferon	\$200	None	\$750	\$2200
Probability of SVR assuming adequate compliance with therapy (>80/80/80)	52%	20%	75%	95%

NOTE. The thresholds are listed according to 3 incremental cost-effectiveness values: \$10,000, \$20,000, and \$30,000 per QALY gained. For example, the incremental cost of using EGF therapy for anemia decreases from \$16,443 per QALY gained (base-case result) to \$10,000 per QALY gained vs standard therapy when the weekly cost of EGF therapy decreases from its base-case cost of \$515 to \$300. Similarly, the incremental cost of using EGF therapy increases from \$16,443 per QALY gained to \$30,000 per QALY gained vs standard therapy when the utility of seropositivity increases from .79 (base-case estimate) to .84.

Figure 3 shows the results of 1000 trials through a probabilistic Monte Carlo simulation comparing standard therapy with EGF therapy for anemia. The median ICER of these trials was \$16,974 per additional symptomatic improvement (2.5 and 97.5 percentiles, \$12,547 and \$21,096). The percentage of trials resulting in less than the \$20,000, \$50,000, and \$100,000 willingness-to-pay thresholds were 62.3%, 86.1%, and 97.5%, respectively. For example, if a third-party payer were willing to pay \$50,000 per QALY for the use of EGF

therapy, then 86.1% of the patients in this simulation would be within the budget.

Discussion

This analysis indicates that adjunctive therapy with an EGF (such as epoetin alfa or darbepoetin alfa) for treatment-induced anemia may be cost effective vs standard care in the management of patients with chronic HCV infection. Specifically, in a hypothetical cohort that closely resembles patients in community practice, our analysis shows that the use of EGF therapy in lieu of RBV dose reduction for early anemia (Hgb <12 g/dL or a ≥3-g/dL decrease) cost an additional \$16,443 to provide 1 additional year of quality-adjusted life—an incremental cost that compares favorably with commonly accepted medical interventions (Table 5). For example, PEG-IFN–based regimens cost between \$15,000 and \$55,000 more per additional QALY gained compared with traditional nonpegylated IFN-based regimens.⁵ The widespread adoption of PEG-IFN and RBV in clinical practice suggests that this range of incremental costs is acceptable in the treatment of HCV. Our analysis indicates that EGF therapy may extend the effectiveness of PEG-IFN–based regimens at an incremental cost that complies with currently accepted standards. Moreover, the use of EGF therapy is likely to be cost effective across a wide range of health care budgets from the most conservative to the most liberal (Figure 3).

It is well established that patients with persistent seropositivity have a lower HRQOL compared with patients achieving SVR after treatment of HCV.^{11,49,50} Because the use of EGF therapy to treat anemia may increase SVR over and above standard care, it may provide not only more years of life, but also more quality-adjusted years of life. Our results are highly sensitive to assumptions regarding the impact of persistent seropos-

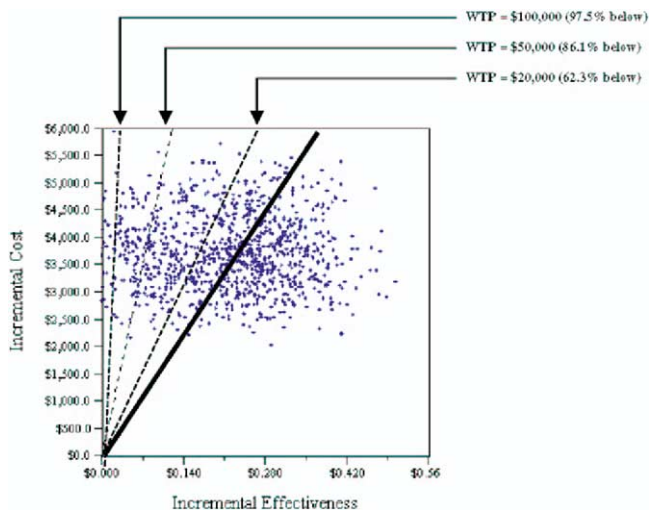


Figure 3. Probabilistic sensitivity analysis using 1000 trials comparing standard therapy vs EGF therapy for anemia. This analysis simultaneously varies all parameters over the full range of plausible values. Each point represents the ICER generated by 1 trial through the simulation. The bold line delineates the median ICER of \$16,974 per QALY gained, and, by definition, 50% of the trials will be on either side of the line. The remaining 3 diagonal lines represent willingness-to-pay (WTP) thresholds. Points below and to the right of each line represent trials that generated an ICER of less than the specified threshold. For example, if a third-party payer were willing to pay \$50,000 per QALY gained for the use of EGF therapy then 86.1% of the patients in this simulation would be within the budget.

Table 5. League Table of Incremental Cost per QALY of Common Medical Therapies

Medical intervention	Incremental cost/QALY	Reference
Primary angioplasty vs thrombolysis in patients with acute myocardial infarction	\$ 13,100	46
EGF therapy vs standard care in HCV patients with treatment-induced anemia	\$ 16,443	Present analysis
PEG IFN plus RBV vs non-PEG IFN plus RBV in the treatment of hepatitis C	\$15,000–\$55,000	5
Initiating prophylactic gancyclovir for cytomegalovirus retinitis vs no prophylaxis in human immunodeficiency virus–infected patients with a CD4 lymphocyte count <100 cell/mm ³	\$ 80,000	47
Using a cox-2 selective inhibitor vs naproxen in patients with chronic arthritis	\$275,809	48

itivity on HRQOL. Specifically, if the decrement in HRQOL engendered by seropositivity decreases by only 5% in our model, then the incremental cost of using EGF therapy decreases to only \$10,000 per QALY gained (Table 4). These results are consistent with a recent decision analysis in HCV that found the incremental cost of PEG-IFN and RBV to be highly dependent on HRQOL assumptions regarding treatment outcomes.⁵ The convergent validity of our analyses reinforces the importance of measuring not only the HRQOL decrement from complications of chronic liver disease, but also the decrement associated with persistent seropositivity in the absence of advanced disease.

The cost effectiveness of EGF therapy is achieved not only by improving posttreatment HRQOL compared with standard care but also by improving HRQOL during treatment compared with standard care. In particular, recent data indicate that the reduction in anemia and attendant fatigue achieved by EGF therapy translates into a significant improvement in treatment-related HRQOL.¹⁶ In contrast to liver transplant, variceal hemorrhage, or encephalopathy—events that diminish HRQOL but are relatively rare and economically discounted in light of the 10- to 20-year latent period before they develop—treatment-induced anemia is a common up-front event that is not subjected to economic discounting. Because health economic theory dictates that common and early events are weighted more heavily than late and rare events, the initial treatment-related HRQOL benefits of reversing anemia contribute significantly toward the cost effectiveness of EGF therapy.

There are several limitations to this analysis. As with any decision analysis, the results depend on the validity of the base-case estimates. Because our base-case point estimates are unlikely to reflect all populations, our results are unlikely to be reproduced precisely in all populations. Moreover, several of our estimates are based on studies of varying design, patient population, follow-up evaluation, and quality. However, we have attempted to guard against inaccurate base-case results by systematically reviewing the literature and by performing a probabilistic sensitivity analysis to ac-

knowledge that each estimate is likely to vary in clinical practice. Despite this conservative approach, our model indicates that EGF therapy is likely to be cost effective under most combinations of probability and cost estimates (Figure 3).

Our model is limited further by the state of existing data regarding EGF therapy in the treatment of HCV. Although there are several studies supporting the role of EGF therapy in RBV-induced anemia,^{14–20} many of these studies are uncontrolled case series.^{14,15,19} Of the 2 currently available EGF agents, only epoetin alfa has randomized controlled data to support its efficacy in HCV.^{16,17,20} In contrast, darbepoetin alfa, a hyperglycosylated protein with a 3-fold longer half-life than epoetin alfa, has not yet been subjected to a randomized controlled trial in HCV. Future research should aim to measure the effectiveness, cost effectiveness, and cost utility of both agents in prospective randomized trials. In the meantime, our data provide an evidence-based estimate of how EGF therapy might behave as a class if subjected to a prospective health economic analysis.

We assumed the perspective of a third-party payer and used Medicare reimbursement costs. This approach is limited because it does not account for indirect or societal costs including transportation costs for physician visits and opportunity costs from missed work and diminished work productivity. Although indirect costs may impact the cost effectiveness of competing therapeutic strategies in HCV, there are limited data regarding these costs in patient cohorts with HCV. In light of this shortcoming, we could not use a societal perspective without relying on conjectural cost estimates. Moreover, because patients with treatment-induced anemia and posttreatment seropositivity have diminished HRQOL compared with nonanemic patients or those achieving SVR,^{11,13,49} there is reason to expect that their indirect costs might be higher and their work productivity might be lower. If we included these potential indirect costs then it likely would bias the model in favor of the EGF strategy by further penalizing patients with anemia or posttreatment seropositivity (which are more common in the standard care strategy).

Our model is limited further by assuming that clinicians only measure 6-month postcessation SVR as the short-term treatment outcome rather than also measuring the early virologic response (EVR). Because evolving data indicate that the 12-week EVR is a highly accurate predictor of treatment success,⁵¹ the use of EVR is a relevant comparator for purposes of cost-effectiveness modeling in HCV treatment. However, our assumption that clinicians rely solely on SVR tends to bias the model against the EGF strategy by requiring many patients with genotype 1 HCV to continue EGF therapy unnecessarily in an unsuccessful treatment course when they might have otherwise discontinued therapy after failing to achieve 12-week EVR. It is reasonable to hypothesize that the EVR-based use of EGF therapy might be significantly more cost effective than the current model projects on the basis of reserving EGF therapy only for patients most likely to achieve SVR in the first place. Despite our explicit assumption that EVR was not considered, our model nonetheless found that the use of EGF therapy was more cost effective than standard care.

In conclusion, this analysis shows that the use of EGF therapy for treatment-induced anemia is likely to be cost effective in the management of HCV on the basis of increasing adherence to therapy, improving HRQOL, and minimizing complications of chronic liver disease vs standard care. Future research should aim to measure the cost effectiveness of epoetin alfa and darbepoetin alfa prospectively in representative samples of community-based patients with HCV.

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Address requests for reprints to: Brennan M. R. Spiegel, MD, MSHS, Assistant Professor of Medicine, VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA, UCLA/VA Center for Outcomes Research and Education (CORE), 11301 Wilshire Boulevard, Building 115, Room 215E, Los Angeles, California 90073. e-mail: bspiegel@mednet.ucla.edu; fax: (310) 268-4510.

Supported by a VA HSR&D Research Career Development Award and a Center for Ulcer Research and Education Named New Investigator Award (B.M.R.S.). Also supported by a research grant from Amgen Inc. Global Health Outcomes. B.M.R.S. and Z.M.Y. have received research funding and served as consultants for Amgen Inc. C.-F.C. and S.R. are employees of and own stock in Amgen Inc.