Economic Burden and Current Managed Care Challenges Associated With Hepatitis C

A. Scott Mathis, PharmD

Abstract

Infection with hepatitis C virus (HCV) is associated with significant morbidity, mortality, and economic burden. However, HCV infection is challenging to treat, because it is underdiagnosed and undertreated. When patients receive standard therapies, sustained virological response is usually achieved in less than 50% of cases. Newer therapies improve the virological and liver-related outcomes associated with HCV, but at an increased cost of treatment. Because the economic burden of HCV extends beyond treatment costs, clinicians, patients, and managed care professionals must understand the cost-effectiveness of HCV treatment. Improvements in adherence and the delivery of effective care can promote cost-effective management due to reductions in long-term disease-related complications, such as hospitalization, liver transplantation, and death.

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For author information and disclosures, see end of text.

Infection with hepatitis C virus (HCV) is associated with significant morbidity, mortality, and costs related to treatment.[1,2] However, HCV infection is severely underdiagnosed and undertreated.[3] Newer therapies have the potential to improve the virological and liver-related outcomes associated with HCV, but at an increased cost of treatment.[4,5] Despite the barriers to treatment, the economic burden of HCV extends beyond treatment costs, and clinicians, patients, and managed care professionals must understand the full impact of cost-effective HCV treatment.[6] This article will review the economic burden associated with HCV and current challenges in the managed care setting, determine cost-effectiveness of HCV therapies, highlight issues surrounding adherence, and address challenges to managed care organizations.

Economic Burden of HCV

A study evaluated UnitedHealth Group–affiliated health plan claims from 1997 to 1999 for patients tested for HCV.[6] In that study, 0.7% of members were tested during the study period, and 6.7% of the population was diagnosed with chronic HCV. Treatment was given to 33.6% of male patients and 25.2% of female patients diagnosed with chronic HCV. Depending on the regimen used, 64.8% to 75.8% of patients completed the standard treatment course. Of the treated patients, 64.5% had a baseline HCV RNA test and 32.5% had a follow-up HCV RNA test within 6 months.[6] These findings highlight the barriers to treatment, including lack of diagnosis, undertreatment, poor adherence, and incomplete follow-up and monitoring.[3,6] Another study of inpatient data from the Healthcare Cost and Utilization Project, outpatient data from the National Ambulatory Medical Care Survey, and medication data from the Verispan Source Prescription Audit evaluated data from 1994 to 2001 in patients with chronic HCV.[7] In the 8 years of the study, there were 3- to 4-fold increases in the costs of care associated with an aging population and an increase in the number of patients with the disease. The increase in hospitalizations, charges, hospital days, and physician visits was 25% to 30% per year during the study, primarily in patients aged 40 to 60 years. From 1994 to 2001, patients aged 40 to 49 years had increased liver-related hospital days (from 32.3%

to 37.6%), and patients aged 50 to 59 years had increased liver-related hospital days (from 17% to 30.1%). For every $100,000 in nationwide charges for all hospitalizations, liver-related HCV hospitalizations increased from $145 in 1994 to $427 in 2001. For every $100,000 in new prescriptions, ribavirin-interferon costs rose from $78 in 1998 to $259 in 2001. Prior to 1998, spending was focused on interferon monotherapy. During the same period, patients coinfected with human immunodeficiency virus (HIV) and HCV had 7.5 times as many hospitalizations in 2001 as patients with HIV alone, and 2.9 times the charges in 1994.[7] Data from this resource utilization study demonstrated that direct expenditures for HCV-related morbidity increased significantly over time, largely due to an aging, undertreated population experiencing worsening of disease.[7] Estimates from 2010 to 2019 indicated that the direct costs of HCV-related disease in the United States would be $6.5 to $13.6 billion in 1999-adjusted dollars.[8]

The current estimate for HCV-related mortality in the United States is 8000 to 10,000 deaths per year.[9] US estimates predict 160,000 to 196,000 HCV-related deaths from 2005 to 2025, and from 2010 to 2019, the costs of premature mortality are expected to be $54.2 billion.[8,9] Lost productivity, due to disability from decompensated cirrhosis and hepatocellular carcinoma, is expected to contribute an additional $21.3 billion in costs. It is likely that these costs will increase, because the mortality rate for HCV is expected to peak in 2030 with an estimated death rate of 12,900 in the United States.[1] Recent evidence suggests that declining treatment rates will result in suboptimal prevention of liver-related deaths between 2002 and 2030, with only approximately 14.5% of deaths prevented.[10] These results highlight the costs associated with HCV and indicate that the direct costs are substantially less than the indirect costs, suggesting that therapy might be cost-effective if it could be delivered effectively, and that therapy could prevent HCV-related morbidity and mortality.

Strategies for Determining the Cost-effectiveness of Therapy

In 1998, the direct costs of HCV infection in the United States were estimated to be over $1 billion. Pharmacoeconomic analyses take into consideration both disease costs and treatment costs. Thus, cost-effectiveness studies must consider the treatment costs (direct costs) in the context of disease costs (direct and indirect costs) and societal costs, such as lost productivity (indirect costs).[11] A study published in 1999 suggested a $400 reduction in lifetime cost of care, and a 1.5-year increase in life expectancy with interferon therapy.[12] These data suggest that interferon was cost-effective because it was cost-saving, despite marginal efficacy. In an analysis of 9 studies of interferon taken from a societal perspective, nearly all studies identified an incremental cost-effectiveness ratio (ICER) of less than $5000 (1995 values) per quality-adjusted life-year (QALY) for 6 to 12 months of interferon monotherapy compared with no antiviral therapy.[11] For relapsed patients, 6 months of interferon and ribavirin combination therapy cost $280 more than interferon monotherapy retreatment, and had an ICER of $140 per QALY gained (1999 values).[11] For treatment-naïve patients, interferon plus ribavirin compared with interferon (with interferon plus ribavirin for patients experiencing relapse) had an ICER of $7500 per QALY gained. ICERs less than $50,000 to $100,000 per QALY gained are generally considered cost-effective.[11]

Because peginterferon with ribavirin surpassed interferon plus ribavirin as the standard of therapy for the management of chronic HCV, it is of potentially greater interest to compare the cost-effectiveness of regimens containing peginterferon. An early review suggested that 6 of 7 (85.7%) studies had ICERs per QALY gained less than US$25,000 for peginterferon plus ribavirin versus interferon plus ribavirin, while 1 of those studies demonstrated cost savings, and another study demonstrated an ICER of $12,000 to $90,000 per QALY gained.[11] The authors of the study that did not demonstrate robust cost-effectiveness[13] noted that the probability of chronic HCV patients developing cirrhosis over 30 years was 13% to 46% for men and 1% to 29% for women. The ICER of peginterferon with ribavirin was $26,000 to $64,000 per QALY gained for genotype 1, and $10,000 to $28,000 for other genotypes in men. For women, the ICER per QALY gained was $32,000 to $90,000 for genotype 1, and $12,000 to $42,000 for other genotypes. Improvements were found more in the form of health-related quality of life (HRQoL) gains than in prolonged survival. Thus, the cost per QALY was less than the cost per life-year.[13] Since $100,000 per QALY gained is generally considered cost-effective, these findings indicate that peginterferon plus ribavirin is cost-effective under a variety of clinical scenarios, but also highlights how patient and disease factors can change the success, and hence the cost-effectiveness, of therapy.

Another important factor in assessing the cost-effectiveness of peginterferon with ribavirin is the duration of therapy. Wong et al used a computer simulation to compare a 48-week course of peginterferon alfa-2b plus ribavirin with a potentially shorter course of peginterferon alfa-2b plus ribavirin, depending on the results of viral testing after 12 weeks of treatment.[14] The assessment of 12-week rapid viral response

(RVR) reduced the duration of antiviral treatment by 40% to 44% and antiviral costs by 44% to 45%, which corresponded to a savings of $15,116 to $16,268 for peginterferon plus ribavirin and $8300 for interferon plus ribavirin compared with 48-week dosing. The ICERs per discounted QALY gained were evaluated for a number of comparisons. Based on the 54% to 61% SVR rates from the study with peginterferon plus ribavirin, the expected extension of life expectancy was 3.6 years to 4 years, in general, and 5.9 years for patients with genotype 2 or 3. The 12-week evaluation demonstrated that peginterferon plus ribavirin had an ICER of $13,600 to $22,800 compared with interferon plus ribavirin. In the 24-week evaluation, peginterferon plus ribavirin had an ICER of $14,600 to $25,000 compared with interferon plus ribavirin. In patients with HCV genotype 1, the respective 12-week and 24-week ICERs were $13,500 to $19,300 and $15,100 to $20,600, relative to interferon plus ribavirin. In patients with genotype 2 or 3, the respective 12-week and 24-week ICERs were $15,400 to $47,100 and $15,100 to $46,700, due to the higher degree of efficacy of the interferon plus ribavirin regimen in that population. In these analyses, the lower range of the ICER was for weight-based ribavirin dosing, and the higher range was for ribavirin 800-mg fixed dosing, due to the greater efficacy of the weight-based regimen. These findings were mirrored in another study, which showed an increase in life expectancy of 4.3 years with peginterferon alfa-2b plus fixed-dose ribavirin, and 4.7 years with peginterferon alfa-2b plus weight-based ribavirin, as well as acceptable ICERs per QALY gained.[15] The results demonstrated that peginterferon plus ribavirin may reduce liver complications, increase life expectancy, improve quality-adjusted life expectancy, and be cost-effective. In addition, monitoring could reduce the morbidity associated with the adverse effects of medication due to a shortened duration of therapy.[14,15]

Management of adverse effects is an important consideration for cost-effectiveness of treatment. While it may be acceptable to reduce the duration of antiviral treatment when RVR is achieved, it is a less attractive option when viral response is not optimal. A common adverse effect of peginterferon plus ribavirin is anemia. Strategies for the management of anemia include reducing the dose of ribavirin or administering hematologic growth factors.[14,16] One study compared darbepoetin alpha, epoetin alpha, or ribavirin dose reduction for significant anemia (>3 g/dL reduction from baseline) in patients on standard doses of peginterferon alfa-2a or peginterferon alfa-2b with ribavirin 1200 mg per day for genotype 1, or standard doses of peginterferon alfa-2a or peginterferon alfa-2b with ribavirin 800 mg per day for genotypes 2 or 3. A Markov model was used to determine the cost-effectiveness of the hematologic growth factors. Dose reduction of ribavirin in patients with genotype 1 reduced SVR from 55.6% to 46.1%. Darbepoetin alpha increased costs by $14,100, and epoetin alpha by $24,600, compared with ribavirin dose reduction in the patients with genotype 1. The ICERs for darbepoetin alpha and epoetin alpha were $34,793 and $60,600 per QALY, respectively, relative to ribavirin dose reduction for genotype 1. Dose reduction of ribavirin in patients with genotype 2 or 3 reduced the SVR rate from 83.3% to 78.6%. The addition of darbepoetin alpha increased costs by $7000, and epoetin alpha increased costs by $13,200 compared with ribavirin dose reduction for patients with genotypes 2 and 3. For genotypes 2 and 3, the ICERs for darbepoetin alpha and epoetin alpha were $33,832 and $64,311 per QALY, respectively, relative to ribavirin dose reduction. These results suggest that administration of a hematologic growth factor, particularly darbepoetin alpha, rather than ribavirin dose reduction for anemia associated with HCV treatment, preserves efficacy and is cost-effective.[16]

Because direct-acting antivirals in combination with peginterferon and ribavirin (triple therapy) have proven superior efficacy to dual therapy with peginterferon and ribavirin, it is of interest to examine the cost-effectiveness of the triple-therapy regimens.[4,5] One study compared the cost-effectiveness of boceprevir and telaprevir in patients with HCV genotype 1 on peginterferon and ribavirin.[17] A Markov decision model was created for an untreated Caucasian patient aged 50 years, weighing 70 kg, with genotype 1 chronic HCV and a Metavir liver fibrosis score of F2 (mild to moderate), with a 20-year time horizon. Peginterferon alfa-2b at 1.5 mcg/kg subcutaneous weekly with ribavirin 600 mg to 1400 mg, or peginterferon alfa-2a at 180 mcg subcutaneous weekly with ribavirin 1000 mg to 1200 mg were the baseline regimens. Five protease inhibitor strategies were modeled according to interleukin 28B (IL28B) genotype and/or response to therapy as outlined in **Table 1**. The clinical and pharmacoeconomic responses to the various interventions were also provided. The study evaluated sustained virological response (SVR), life-years gained (LYG), and QALYs, and attributed ICER to each outcome. SVR occurred in 45.8% of the dual therapy group, and compared with other outcomes, it was more expensive to obtain an SVR outcome with triple therapy. SVR rates for boceprevir-based regimens ranged from 67.0% to 72.1%, with corresponding ICERs per SVR of 56,960 to 85,650 euros, relative to dual therapy (multiply euros by 1.25 to determine US dollars). Corresponding SVR rates for telaprevir-based regimens were 74.5% to 79%, with ICERs

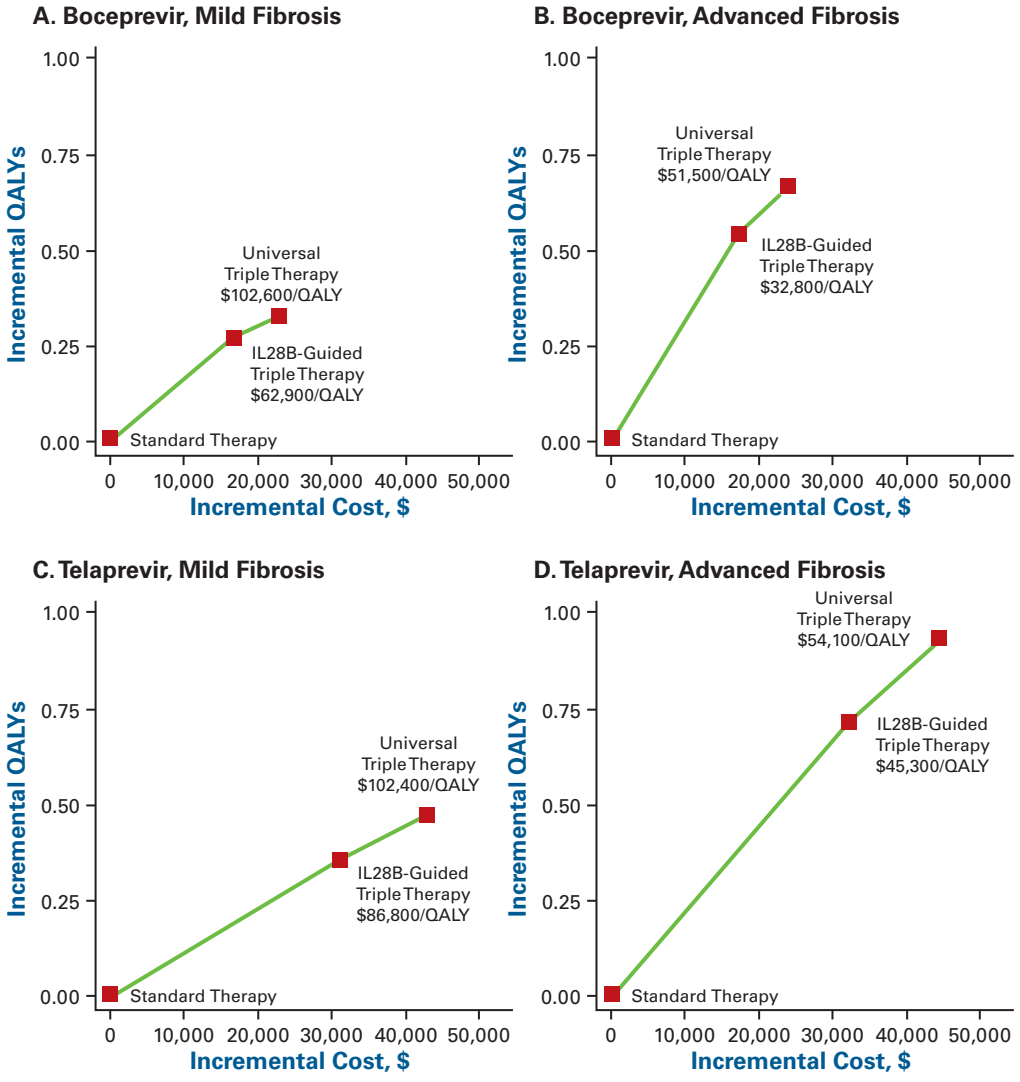
Table 1. Regimens Analyzed in a Pharmacoeconomic Comparison of Boceprevir and Telaprevir[17]

Regimen Name/Base Regimen	Response Characteristic	Duration
Dual Therapy		
Peginterferon alfa-2b 1.5 mcg/kg weekly with ribavirin 600 mg to 1400 mg daily (regimen 1)		
Peginterferon alfa-2a 180 mcg weekly with ribavirin 1000 mg to 1200 mg daily (regimen 2)		
Boceprevir Response–Guided Therapy		
Regimen 1 for 4 weeks, followed by regimen 1 with boceprevir 800 mg 3 times daily	Extended RVR (HCV negative weeks 8-24)	28 weeks total
Regimen 1 for 4 weeks, followed by regimen 1 with boceprevir 800 mg 3 times daily for 32 weeks, followed by 12 weeks of regimen 1	HCV detectable at week 4, but undetectable at week 24	48 weeks total
Regimen 1 for 4 weeks, followed by regimen 1 with boceprevir 800 mg 3 times daily for a total of 24 weeks	HCV detectable at week 24	24 weeks total
Boceprevir IL28B Genotype–Guided Therapy		
Regimen 1	IL28B C/C genotype	48 weeks total
Boceprevir response–guided therapy	IL28B C/T or T/T genotype	See *Boceprevir Response-Guided Therapy* above
Regimen 1, followed by retreatment with regimen 1 for 4 weeks, and 44 weeks of boceprevir with regimen 1	IL28B C/C genotype, no SVR	96 weeks total
Boceprevir RVR–Guided Therapy		
Regimen 1 for 4 weeks, followed by regimen 1	RVR achieved	48 weeks
Regimen 1 for 48 weeks, followed by regimen for 4 weeks and boceprevir response-guided therapy for 44 weeks	RVR achieved, but no SVR	96 weeks
Regimen 1 for 4 weeks followed by boceprevir response-guided therapy	No RVR	48 weeks
Telaprevir Response–Guided Therapy		
Regimen 2 for 24 weeks with telaprevir 750 mg 3 times daily for the first 12 weeks	Extended RVR (HCV negative weeks 4-12)	24 weeks
Regimen 2 for 48 weeks with telaprevir 750 mg 3 times daily for 12 weeks	Extended RVR not achieved	48 weeks
Regimen 2 for 12 weeks with telaprevir 750 mg 3 times daily for the first 12 weeks	HCV RNA >1000 IU/mL at week 12, or failure to decline 2 $\log_{10}$ at week 12	Discontinued for futility
Telaprevir IL28B Genotype–Guided Therapy		
Regimen 2	IL28B C/C genotype	48 weeks
Telaprevir response–guided therapy	IL28B C/T or T/T genotype	See *Telaprevir Response-Guided Therapy* above
Regimen 2 for 48 weeks, followed by retreatment with regimen 2 for 48 weeks, using telaprevir 750 mg 3 times daily for the first 12 weeks	IL28B C/C genotype, no SVR	96 weeks

HCV indicates hepatitis C virus; IL28B, interleukin 28B; RNA, ribonucleic acid; RVR, rapid virologic response; SVR, sustained virologic response.

per SVR of–74,600 to 118,000 euros. Assessment of LYG and QALY demonstrated similar patterns of results, with lower ICERs per outcome for boceprevir-based strategies, higher clinical responses for telaprevir-based strategies, and more acceptable cost-effectiveness per ICER for both boceprevir and telaprevir. The most cost-effective telaprevir-containing regimen was the IL28B genotype–guided strategy, and the most cost-effective boceprevir-containing regimen was the RVR-guided strategy.[17] Another cost-effectiveness analysis also created a hypothetical model and indirectly compared boceprevir and telaprevir, included assessment of IL28B genotype, and also evaluated severity of fibrosis.[18] As shown in **Figure 1**, triple-therapy regimens with both boceprevir and telaprevir were more cost-effective per QALY in patients with advanced fibrosis, relative to patients with mild fibrosis. Use of IL28B-guided therapy improved the ICER per QALY versus universal triple therapy. Boceprevir had slightly lower ICER per QALY than telaprevir, although telaprevir had slightly

Figure 1. Cost-Effectiveness Results: Incremental Costs Incurred and QALYs for Each Intervention[18]



IL28B indicates interleukin 28B; QALY, quality-adjusted life-year.
The graph plots the incremental discounted QALYs (y-axis) and incremental discounted total expected lifetime costs (x-axis) for each treatment strategy separately for cohorts of patients with mild and advanced fibrosis. The green lines represent the cost-effectiveness frontier, those strategies that are potentially cost-effective depending on one's willingness to pay per unit of health benefit gained, expressed as an incremental cost-effectiveness ratio (defined as the ratio of the additional costs of an intervention and its additional effects compared with the next-best alternative).
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higher efficacy (Table 2). A cost-effectiveness acceptability curve was presented in the publication (Figure 2). The model assumed a cost of $1100 per week for protease inhibitors, and demonstrated that standard therapy with peginterferon plus ribavirin was most cost-effective at low willingness-to-pay thresholds, but that advanced fibrosis shifted the curve to the left, especially for IL28 genotype–guided therapy. The curve demonstrated that triple therapy is cost-effective according to a willingness-to-pay threshold of $100,000.[18]

Two additional studies have examined the cost-effectiveness of telaprevir and/or boceprevir.[19,20] One of those studies compared empiric pegylated interferon and ribavirin, or pegylated interferon and ribavirin with telaprevir, guided by liver biopsy or FibroTest, a non-invasive biomarker assay for fibrosis. Liver biopsy is expensive and carries the risk of complications, but is considered the gold standard for assessing liver fibrosis for initiating treatment. It has been noted that the degree of fibrosis affects the degree of cost-effectiveness of triple-therapy regimens.[18] The study[19] assessed the cost-effectiveness of FibroTest and liver biopsy used alone or sequentially for 6 strategies, including: FibroTest only; FibroTest with liver biopsy for ambiguous results; FibroTest followed by biopsy to rule in;

Table 2. Lifetime Discounted Costs and Health Benefits of Treatment Strategies, by Severity of Fibrosis Stage[18,a]

Strategy	SVR, %	Lifetime Risk, %			Cost, $	QALYs	ICER, $/QALY	ICER Excluding IL28B, $/QALY[b]
		Decompensated Cirrhosis	HCC	Liver Transplant				
Base case (boceprevir scenario)								
Mild fibrosis[c]								
Standard therapy	38	8.4	4.7	1.5	160,456	10.97	—	—
IL28B–guided triple therapy	57	5.7	3.2	1.0	177,152	11.24	62,900	—
Universal triple therapy	61	5.1	2.9	0.9	183,257	11.30	102,600	70,100
Advanced fibrosis[d]								
Standard therapy	32	23.0	13.2	4.6	161,312	8.84	—	—
IL28B–guided triple therapy	48	17.6	10.1	3.6	179,090	9.38	32,800	—
Universal triple therapy	51	16.5	9.5	3.3	185,447	9.51	51,500	36,300
Telaprevir scenario								
Mild fibrosis[c]								
Standard therapy	38	8.4	4.7	1.5	160,456	10.97	—	—
IL28B–guided triple therapy	63	4.9	2.8	0.9	191,559	11.33	86,800	—
Universal triple therapy	70	3.9	2.2	0.7	203,285	11.44	102,400	91,000
Advanced fibrosis[d]								
Standard therapy	32	23.0	13.2	4.6	161,312	8.84	—	—
IL28B–guided triple therapy	54	15.9	9.1	3.2	193,805	9.56	45,300	—
Universal triple therapy	60	14.4	8.0	2.8	206,010	9.78	54,100	47,400

HCC indicates hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; IL28B, interleukin 28B; QALY, quality-adjusted life-year; SVR, sustained virologic response.
[a]Results are weighted averages over race and sex and are based on relative prevalence of these groups for patients with chronic hepatitis C virus from NHANES III (Third National Health and Nutrition Examination Survey) data (white male, 51%; white female, 23%; black male, 17%; and black female, 9%).
[b]If IL28B genotyping is unavailable, ICER compares universal triple therapy with standard therapy.
[c]F0, 30%; F1, 41%; and F2, 29%.
[d]F2, 29%; F3, 23%; and F4, 48%.
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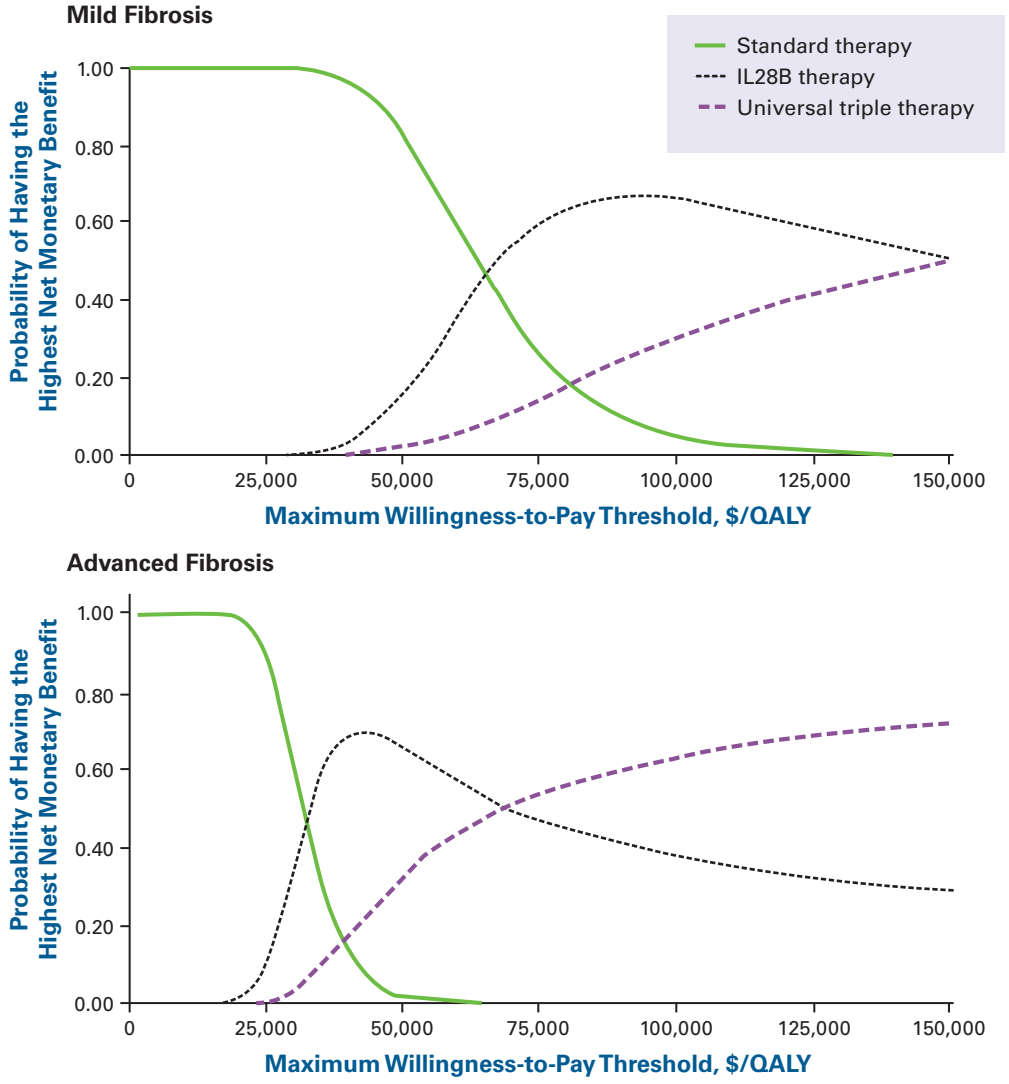
or to rule out significant fibrosis; biopsy only (recommended practice); and treatment without screening. The Markov model tracked fibrosis progression of chronic HCV and the outcomes; expected lifetime costs (2009 US dollars), QALYs, and ICER were assessed. The main results of the study were that treatment of chronic HCV without fibrosis screening was preferred for both men and women. For patients with genotype 1 treated with pegylated interferon and ribavirin, the ICERs were $5400/QALY (men) and $6300/QALY (women), compared with FibroTest only; the ICERs increased to $27,200/QALY (men) and $30,000/QALY (women) with the addition of telaprevir. For patients with genotypes 2 and 3, treatment was more effective and less costly than all alternatives. In clinical settings where testing is required prior to treatment, FibroTest only was more effective and less costly than liver biopsy.[19] The other study examined the adverse effects of the protease inhibitors with peginterferon and ribavirin therapy versus peginterferon and ribavarin.[20] The study noted that the adverse event impact of triple therapy is under-reported. The authors estimated the impact of adverse events on costs and treatment discontinuation. Triple therapy and dual therapy had comparable adverse event–related treatment discontinuation rates (~12%). Weighted adverse event-related treatment costs were US$2042, $1835, and $1076 for boceprevir-based triple therapy, dual therapy, and telaprevir-based triple therapy, respectively. Health-related quality of life (HRQoL) data were not reported in the triple-therapy studies; however, HRQoL data for common adverse events, including anemia, depression, fatigue, and/or influenza-like symptoms, were synthesized from 5 dual-therapy studies. These studies reported that adverse events negatively affected HRQoL. Decreased HRQoL predicted treatment discontinuation in 2 dual-therapy studies.[20] These data highlight that more adverse event–related economic and HRQoL outcomes are needed for triple-therapy regimens, but also highlight that adverse events may affect cost-effectiveness, an area which has not been extensively studied.

Figure 2. Cost-Effectiveness Acceptability Curve, Assuming Protease Inhibitor Costs of $1100 per Week[18]



IL 28B indicates interleukin-28B; QALY, quality-adjusted life-year.
The figure shows the probability of each strategy providing the maximum net monetary benefits at various willingness-to-pay thresholds.
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Challenges in Adherence

The biggest challenge in chronic HCV is making the diagnosis and referral for appropriate treatment.[21] Approximately 72% of primary care physicians will not refer patients with normal liver enzyme test results for treatment. Once patients see a specialist, less than one-third receive treatment, primarily due to contraindications of the medications, such as decompensated cirrhosis, severe depression, and severe cardiopulmonary disease. Specialists also tend to avoid treating patients with active substance abuse. Patients and clinicians also have concerns about actual or anticipated adverse effects, which may affect adherence or lead to treatment discontinuation.[21] Also, many patients who are prescribed antiviral therapy for HCV report difficulty paying for the antiviral medications, as well as other concomitant medications.[22] Both costs and mental state affect adherence.[22] Antidepressants are commonly used medications in patients with HCV; however, many physicians will not prescribe antivirals to patients with psychiatric disorders or substance abuse.[21-23] One study compared adherence, efficacy, and mental adverse effects of interferon alfa plus ribavirin in 81 patients with chronic HCV and psychiatric disorders (n = 16), methadone substitution (n = 21), or former drug addiction (n = 21) with controls without a history of psychiatric disorders or drug addiction (n = 23).

SVR did not differ significantly between subgroups. In the group of patients with psychiatric disorders, significantly more patients received antidepressants before and during treatment with IFN-alfa (P <.001) compared with the other groups, but no significant differences were observed between groups with respect to interferon-alfa–related development of depression during treatment. A greater percentage of patients in the former drug addiction group dropped out of the study (43%; P = .04) compared with the methadone group (14%), the control group (13%), and the group with psychiatric disorders (18%). No patient in the psychiatric disorders group had to discontinue treatment because of psychiatric deterioration. These data did not confirm the increased risk for mental adverse effects and dropouts in patients with psychiatric disorders on interferon-alfa.[23]

Adherence is critical because it affects the overall efficacy of treatment.[24] In a study that included patients on peginterferon alfa-2a or interferon alfa-2a, 10% of the total population discontinued treatment before 24 weeks. Treatment discontinuation was predicted by worsening fatigue scores (Fatigue Severity Score, FSS) and SF-36 Health Survey (SF-36) scores. The odds ratio (OR) of treatment discontinuation for higher FSS total score (difference of 25th and 75th percentiles) was significantly increased (OR, 1.48; 95% confidence interval [CI], 1.18-1.85; P <.001), as were the odds of treatment discontinuation for lower SF-36 scores, using the subscales SF-36 physical component score (OR, 1.35; 95% CI, 1.35-1.68; P <.01) and the SF-36 mental component score (OR, 1.28; 95% CI, 1.05-1.56; P <.05). Conversely, patients who achieved SVR had improvements in HRQoL and fatigue (P <.01) compared with patients who were non-responders. Results were similar across all HRQoL subgroups and liver histology subtypes.[24] These results are important because the diagnosis of HCV alone has been linked to reduced HRQoL, compared with population norms.[25]

In a real-world US managed care population, medication possession ratio (MPR), defined as total days supplied divided by the days in the observation period, and adherence, defined as MPR of 0.8 or greater, were assessed.[26] Peginterferon-ribavirin regimens had MPRs of 0.74 to 0.76 and adherence of 59.46% to 60.16% in the first 24 weeks of therapy, respectively. Among patients continuing beyond 24 weeks, MPRs were 0.73 for peginterferon-ribavirin regimens. Adherence was 64.58% in patients who obtained SVR and 52.49% in patients who did not, and adherence tended to decline as liver disease severity increased (mild 64.64%; moderate 62.44%; severe 50%). Adherence also had an impact on cost of care. All-cause inpatient costs were $10,920 for patients who were adherent to therapy and $17,377 for patients who were nonadherent (P <.0001). All-cause medication costs were $21,953 versus $12,645 ($P$ <.0001), respectively. All-cause nonpharmacy outpatient costs were $3693 for patients who were adherent to therapy and $6320 for patients who were nonadherent to therapy (P <.0001). HCV-related costs were $8733 for patients who were adherent to therapy and $13,612 for patients who were nonadherent to therapy for hospitalizations, $18,963 versus $10,233 ($P$ <.001), respectively, for medication costs, and $1370 versus $2463 ($P$ <.0001), respectively, for nonpharmacy outpatient costs. Hence, medication costs were higher for patients who were adherent to therapy on peginterferon-ribavirin, but other total costs were higher for patients who were nonadherent to therapy, owing to disease progression and the need for inpatient procedures.[26] These findings were confirmed in a follow-up publication by the same authors, in which HCV costs were compared with controls. Disease-related costs were found to account for one-third of the excess costs in the HCV group.[27]

The impact of triple drug regimens using protease inhibitors on adherence is relatively unknown outside of the clinical trial setting; however, based on prior studies, increasing the number of agents and the cost of the medication regimen is likely to adversely impact adherence.[21-26] In the clinical trials of telaprevir and boceprevir, discontinuation rates due to adverse events ranged from 8% to 53%.[28-34] Telaprevir or boceprevir, given in combination with peginterferon alfa and ribavirin, have quickly become the standard of care for treatment-naive and treatment-experienced patients with genotype 1 infection. These agents carry additional risks, and consequently barriers to adherence, relative to peginterferon alfa and ribavirin, such as additional anemia and rash, and drug-drug interactions owing to telaprevir and boceprevir metabolism through the cytochrome P450 3A4 pathway. In addition, viral resistance can develop during treatment, so patients will need to be educated on the importance of maintaining adherence to treatment to minimize the risk of resistance and improve their chances of cure of HCV infection.[35,36] More data are needed on the characterization of adherence issues in patients on triple-therapy regimens, strategies to improve adherence in those patients, and the impact of adherence on clinical and HRQoL outcomes.

Impact of New Treatment Options on Managed Care Organizations

Almost all published studies have found that HCV treatment was cost-effective.[11-20] Achievement of successful clinical outcomes is linked with adherence,[24] and adherence is

linked with reduced total cost of care in patients with HCV, due to delay in disease progression and consequent hospitalizations.[26] These associations set the stage for a positive scenario for patients, payers, and managed care organizations. It is incumbent on managed care organizations to find ways to deliver effective care to improve outcomes in their patients. While triple-therapy regimens will certainly increase the medication costs associated with HCV, they have been documented to improve SVR rates and QALY.[17] Increased risk of adverse effects and increased costs are potential barriers to adherence that should be addressed.[35,36]

Specialty pharmacy items are rapidly rising in cost, while traditional medications are remaining static in the market. The HCV market is expected to increase dramatically in the near future. A transition is occurring, wherein specialty medications are being transferred from the buy-and-bill medical benefit to the pharmacy benefit using specialty pharmacies.[37] By 2016, 6 of the top 10 pharmaceuticals are expected to be specialty pharmacy agents.[38] Specialty pharmacies are able to manage utilization of medication, monitor patients, and ensure adherence to reduce the potential for adverse effects or suboptimal treatment. Strategies employed by specialty pharmacies include obtaining prior authorization for patients, ensuring step-up therapy by providing documentation for patients in whom previous therapy has failed before requesting approval for more expensive agents, providing patient and provider training, determining quantity limits so that reauthorization is needed, determining dosing limits, establishing length of therapy limits, selecting alternative agents, and providing case-management services.[39] In an effort to control the selection and sequence of agents, pharmacy benefit managers (PBMs) have acquired or contracted with specialty pharmacies to manage the administration of high-cost pharmaceuticals. Through managing these medications as part of the pharmacy benefit, specialty pharmacies ensure safe handling and restricted drug distribution, and can provide better acquisition rates to payers by contracting with pharmaceutical companies.[39] The goal of these relationships between specialty pharmacies and payers is to improve quality of care while controlling costs.[41]

In the care of patients with HCV, it is important for managed care organizations to consider costs beyond the acquisition costs of the antiviral regimen.[41] If a specialty pharmacy offers a lower acquisition cost, it is not necessarily a better value for the managed care organization. Managed care organizations must consider the value-added service provided by the specialty pharmacy. If specialty pharmacies offer services such as monitoring of quantity limits for duration of therapy or assuring adherence, the specialty pharmacies may prove beneficial to the patient and the managed care organization. Thus, partnering with specialty pharmacies could improve clinical outcomes by ensuring rigorous monitoring and outcomes assessment.[41]

Summary

Both traditional dual-therapy regimens (peginterferon-ribavirin) and triple-therapy regimens (peginterferon-ribavirin plus boceprevir or telaprevir) are considered cost-effective in most clinical scenarios, according to standard definitions. Triple-therapy regimens are now preferred for the initial treatment or retreatment of patients due to improved SVR rates. Improvements in adherence will further improve efficacy rates. The current hesitancy observed in initiating this potentially life-saving therapy is unwarranted. Managed care personnel must be aware of these data since they can affect treatment decisions and contracting decisions.

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Address correspondence to: E-mail: smathis@barnabashealth.org.

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