Managed Care Considerations in the Management of Hepatitis C Virus Infection

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Abstract
Chronic hepatitis C virus (HCV) infection has been dubbed the “silent epidemic” because the infection remains quiescent for years, even decades, before clinically significant symptoms appear. The majority of Americans currently living with chronic HCV infection were infected before testing for the virus in blood products began in the early 1990s; therefore, an “age wave” of HCV infection complications is expected to occur as these individuals enter their 50s and 60s. Treating HCV infection and liver diseases in an elderly population will bring challenges specific to this population. Also, the current gold standard therapy for HCV infection, combination pegylated interferon and ribavirin, results in lower rates of sustained virologic response (SVR) in elderly populations, with higher risks of cytopenia and anemia. The age-related increase in HCV-related morbidity and mortality is expected to result in dramatically higher medical costs. Several comorbidities are associated with HCV infection, including human immunodeficiency virus infection, which can impact the efficacy of treatment, outcomes, and medical costs. Although cost-effective and moderately efficacious therapies exist to manage chronic HCV infection, none are ideal in terms of efficacy and safety, and all have significant barriers to use. The introduction of newer therapies, including the protease inhibitors, has the potential to shift the natural history of chronic HCV infection by triggering much higher SVR rates in treatment-naïve patients, nonresponders to previous therapies, and those who have relapsed following therapy.

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Introduction
It has only been 22 years since the identification of the hepatitis C virus (HCV). Today, however, HCV infection is the most common blood-borne disease, with 2.7 to 3.9 million Americans and 130 to 170 million people worldwide chronically infected. Chronic HCV infection has been dubbed the “silent epidemic” because the infection remains quiescent for years, even decades, before clinically significant symptoms appear. Given that the majority of Americans currently living with chronic HCV infection were infected before testing for the virus in blood products began in the early 1990s, an “age wave” of HCV infection complications is expected to occur as these individuals enter their 50s and 60s.

Currently, an estimated 66% of patients with HCV infection in the United States are baby boomers (those born between 1944 and 1964), with a prevalence up to 3-fold higher in those 40 years and older. Unfortunately, many of these individuals are not aware that they are infected. By 2015, over 3 million people may have HCV infection which has been present for more than 20 years, resulting in a significant increase in the incidence of hepatic disease associated with the virus. A multiple cohort model of HCV infection prevalence and disease progression estimated that 25% of patients with HCV infection would experience cirrhosis in 2010, and 45% by 2030. The prevalence of hepatic decompensation and liver cancer was expected to increase for at least another decade.

In parallel with these estimates, significant growth in inpatient and outpatient visits for HCV infection were observed during the 1990s, along with a significant increase in the rate of hepatocellular carcinoma (HCC). HCV infection is responsible for at least half of the cases of HCC in the United States. The number of HCC cases in the United States is predicted to nearly double by 2030, and then the rate is expected to plateau.

Canadian hospitalizations for HCV-related liver complications increased 4-fold between 1994 and 2004, or 15% to 18% annually (P < .0005), with the largest annual increase in patients aged 40 to 59 years. Grant et al reported similar temporal trends in HCV-related hospitalizations in the United States.

Treating HCV infection and liver diseases in an elderly population will bring challenges specific to this population. For instance, antiviral therapy is limited by existing comorbidities such as hypertension, heart failure, chronic obstructive lung disease, diabetes,
and coronary heart disease, all of which are more prevalent in older patients.16 Also, the current gold standard therapy for HCV infection, combination pegylated interferon and ribavirin, results in lower rates of sustained virologic response (SVR) in elderly populations, with higher risks of cytopenia and anemia.17-19

**Healthcare Resource Use**

Chronic HCV infection exerts a significant toll on patient quality of life and results in significantly increased healthcare costs, with annual healthcare-related costs exceeding those for cardiovascular disease and type 2 diabetes.20 An analysis of medical and pharmacy claims from 325,000 managed care organization members diagnosed with HCV infection described median annual medical costs that were $4600 (1999 US dollars) higher for the HCV infection cohort than for those without the disease (HCV-related costs were $2470 higher).21 Another analysis in a similar population determined that costs were 26% higher in patients with HCV infection than in those without. Compared with patients with genotype 1 HCV infection, costs were generally higher in patients with genotypes 2 and 3 ($9877 vs $12,433, respectively [2007 US dollars]), even though patients with genotypes 2 and 3 are typically less likely to develop cirrhosis because they are more likely to receive antiviral treatment (62%) than patients with genotype 1 (35%).20

Hepatitis C infection accounts for approximately 53,200 annual hospitalizations in the United States, with the cost of liver-related hospitalizations estimated at $742.8 million (1995 US dollars). Patients with concomitant alcoholism experience far higher hospitalization rates and costs.22

An analysis of data from the 2009 US National Health and Wellness Survey that compared health-related quality of life (HRQoL) and healthcare resource use between infected and noninfected patients found significantly lower levels of HRQoL in the HCV infection cohort, particularly in the physical component score and health utilities (both $P < .0001$). Those with HCV infection also had more emergency department and physician visits in the past 6 months (0.59 vs 0.55 and 7.7 vs 5.9, respectively, both $P < .05$).23

Because the long-term clinical consequences of HCV infection tend to occur during middle age, when individuals are still employed in the workforce, indirect costs related to productivity must also be considered. Su et al compared employee records from several large employers in the United States. Patients with HCV infection were absent an average of 4.15 more days than those without HCV infection. Annual healthcare costs were $8352 higher in those with HCV infection compared with those without.24

The age-related increase in HCV-related morbidity and mortality is expected to result in dramatically higher medical costs. One estimate predicted that during 2010 to 2019, direct medical expenditures for HCV-related conditions would reach $10.7 billion, societal costs $21.3 billion, and indirect costs related to deaths in those younger than 65 years $54.2 billion (all cost are in 1999 US dollars).25

**Comorbidities Associated With HCV Infection**

Several comorbidities are associated with HCV, each of which can impact the efficacy of treatment, outcomes, and medical costs.26-28 Human immunodeficiency virus (HIV) coinfection is particularly prevalent, given that both viruses are transmitted through blood. A prospective evaluation of 4364 HCV-infected veterans at 24 medical centers found that 8.4% of those tested positive for HIV.29 Sherman et al identified an HCV infection prevalence of 16.1% in an HIV-infected representative sample from the US Adult Acquired Immunodeficiency Syndrome (AIDS) Clinical Trials Group, similar to the 19% identified in an analysis of 10,481 HIV-infected individuals in community medical clinics.30-32 The risk of coinfection, as expected, is much higher in high-risk groups, with 37% of HIV-infected veterans who engaged in high-risk behavior also coinfected with HCV.32

Patients infected with both viruses demonstrate significant barriers to effective management of either condition, including a greater likelihood of substance abuse and a mental health diagnosis.32 They are also significantly more likely to progress to cirrhosis and have decompensated liver disease (relative risk, 2.92, 95% confidence interval [CI], 1.70-5.01).31-35

Coinfection with HCV affects the progression of HIV infection, and it is independently associated with a 70% increased risk of progression to a new AIDS-defining clinical event or death (hazard ratio, 1.7; 95% CI, 1.26-2.30).36 Because individuals with HIV infection now live longer due to highly active antiretroviral therapy, HCV infection has become the leading non-AIDS-related cause of death in coinfected patients.37,38

Other common comorbidities include diabetes, obesity, and end-stage renal disease (ESRD). A cross-sectional retrospective review of the medical history of 800 patients with HCV infection found a 44% increased risk of diabetes and a 25% increased risk of obesity ($P = .001$ and $P = .041$, respectively), while the incidence of ESRD was 13 times higher than that of the general population.26 Patients with HCV were also more likely to be diagnosed with depression ($P < .001$).
Economic Implications of Treatment

The clinical issues related to treatment decisions in chronic HCV infection were discussed in the article by Schiff in this supplement. This paper focuses on the economic implications of HCV infection. While it is clear that treatment improves overall outcomes, just one-third of patients with HCV infection currently have their disease medically managed, and currently available therapies are effective in just half of those infected.

However, long-term data are emerging in support of the theory that early treatment of chronic HCV infection may reduce the risk of cirrhosis, liver failure, and HCC, and may increase life expectancy. If treatment can reduce the risk of these conditions, it has the potential to significantly affect overall costs. For example, the cost of HCC in the United States is $454.9 million; almost all cases of HCC are associated with HCV infection.

Such cost benefits, however, only accrue in patients who have cleared the virus. Davis et al estimated that if 30% of patients with HCV were diagnosed, and 25% of those received treatment, the incidence of cirrhosis in 2020 would decline by just 1%. Treating half of those diagnosed would lead to a reduction of 8.8%, and treating all would result in a reduction of 15.8%.

The cost benefit of treatment versus no treatment depends, to a certain extent, on the population studied and HCV genotype. Yeh et al assessed the cost utility of pegylated interferon alfa-2a or alfa-2b combined with ribavirin compared with no therapy in treatment-naive male patients aged 45 or 55 years with liver fibrosis but no cirrhosis. Treatment regimens were more cost-effective than no treatment, producing significantly lower lifetime HCV-related medical costs in patients with genotypes 2 and 3, but not in those with genotype 1.

In a multinational trial, treatment with pegylated interferon alfa-2a was cost-effective in patients with persistently normal aminotransferase levels; it was estimated to reduce the risk of cirrhosis at 30 years from 32% with no treatment to 19% with combination therapy, and increased quality-adjusted life-years (QALYs) by 0.74 at an incremental cost of €16,831 (2004 euros) in patients with genotype 1 HCV infection. For patients with genotype 2 or 3, the 30-year risk of cirrhosis would fall to 9%, and QALYs would increase 1.34 years at an incremental cost per QALY gained of €3000.

Treatment may also be cost-effective in prison populations, with a comprehensive therapy program using consensus interferon with weight-based ribavirin in the North Dakota prison system demonstrating a 45% cost savings and an SVR of 54.2% in those with genotype 1 HCV infection (SVR of 75% in those with genotypes 2 and 3 infection).

Several analyses suggest that treatment is also cost-effective in individuals with HIV coinfection. Kuehne et al estimated the cost utility and effect on quality of life of several HCV infection therapies (no treatment, monotherapy for 48 weeks with interferon or pegylated interferon; combination therapy with interferon/ribavirin for 24 and 48 weeks, or pegylated interferon and ribavirin for 48 weeks). Combination therapy for 48 weeks provided the greatest quality-adjusted life expectancy gains, with a cost-effectiveness ratio of less than $50,000 per QALY for all genotypes, and an incremental cost-effectiveness ratio of $11,600 per QALY compared with no therapy. Monotherapy in patients intolerant of ribavirin was also cost-effective.

Hornberger et al used a Markov model performed from a US societal perspective to report that pegylated interferon is cost-effective compared with nonpegylated interferon or no therapy in patients with HCV and HIV coinfection. Pegylated interferon/ribavirin increased QALYs by 0.73 compared with interferon/ribavirin, and by 0.94 years compared with no therapy, with an incremental cost-effectiveness ratio of $2082 and $5187 per QALY gained, respectively (2004 US dollars).

The timing of therapy is also important, with evidence of greater cost-effectiveness when therapy is provided at the mild stage of the disease rather than the moderate stage for patients less than 65 years of age.

Cost Utility of Current Treatments

The current gold standard in treatment of chronic HCV infection is 24 to 48 weeks of pegylated interferon/ribavirin. Although 2 forms of pegylated interferon are available, a head-to-head trial comparing pegylated interferon-alfa-2a to pegylated interferon-alfa-2b in treatment-naive patients with genotype 1 HCV infection demonstrated similar SVR rates and safety profiles. However, patients in the standard pegylated interferon alfa-2a group experienced a higher relapse rate (31.5%) than those in the standard-dose pegylated interferon alfa-2b group (23.5%) or low-dose pegylated interferon alfa-2b group (20%).

Although pegylated interferon is more expensive than regular interferon, it has a higher sustained response rate, longer half life, and less-frequent dosing. Thus, in several studies, pegylated interferon was shown to be more cost-effective than interferon/ribavirin combination therapy.

Buti et al used a Markov model to assess 4 therapeutic strategies with pegylated interferon alfa-2b/ribavirin or interferon alfa-2b/ribavirin. The incremental cost-effec-
tiveness ratio of a fixed-dose pegylated combination was €8478 per life year (LY) saved and €3737 per QALY gained compared with interferon alfa-2b/ribavirin. Ensuring patient compliance and using weight-adjusted doses of ribavirin reduced the incremental cost-effectiveness ratio to €1636 per LY saved and €721 per QALY gained, leading the authors to suggest that weight-based pegylated interferon alfa-2b/ribavirin was the most cost-effective strategy, assuming good patient compliance.56

An analysis of data from 2 trials comparing pegylated interferon/ribavirin with interferon/ribavirin determined that the pegylated interferon combination reduced the relative risk of remaining infected by 17% compared with interferon, with an SVR of 55%. The incremental discounted cost per QALY gained for 48 weeks of dual therapy with pegylated interferon/ribavirin was £12,123 compared with interferon/ribavirin, making it cost-effective.57

Several studies have assessed cost differences between pegylated interferon alfa-2a and alfa-2b. Malone et al used a decision analysis model to compare flat ribavirin dosing regimens for each or a weight-based ribavirin regimen with pegylated interferon alfa-2b in a hypothetical cohort of 100 patients with chronic HCV infection (75% of whom had genotype 1 virus). The analysis was conducted from a managed care perspective. There were no significant differences in SVR rates between the groups for patients with genotype 1. However, patients with genotype 1 virus in the pegylated interferon alfa-2a/flat ribavirin dose group had a higher early virologic response rate at 12 weeks (81%) than the pegylated interferon alfa-2b/flat ribavirin dose group (71%) and the pegylated interferon alfa-2b/weight-based ribavirin group (74%). Thus, more patients in the pegylated interferon alfa-2a group continued to receive treatment without additional benefit, which increased the cost for this cohort.58 This resulted in a 19.4% cost reduction per successful treatment (defined as SVR) in the pegylated interferon alfa-2b/ribavirin flat dosing cohort ($37,638) (2004 US dollars) compared with the pegylated interferon alfa-2a/ribavirin cohort ($46,717).

Brixner et al used a retrospective database analysis to compare treatment persistence and cost of therapy between the 2 pegylated interferons in patients with HCV infection in a large US health plan. Their analysis demonstrated an 18% lower rate of adherence to pegylated interferon alfa-2b at 48 weeks (P = .013), with mean all-cause costs and HCV-related costs at 6 months significantly lower in the pegylated interferon alfa-2a/ribavirin cohort (P = .0368 and P <.0001, respectively). Annualized mean costs for all causes and for HCV-related causes were also significantly lower in the pegylated interferon alfa-2a cohort (P = .0060 and P = .0167, respectively).59

Sullivan et al used a Markov model to evaluate the cost-effectiveness of peginterferon alfa-2a or alfa-2b combination therapy with ribavirin from a US healthcare payer perspective using genotype to guide treatment duration. More patients given peginterferon alfa-2a with genotypes 1 or 2/3 HCV infection achieved an SVR than those given peginterferon alfa-2b (46% vs 76% and 36% vs 61%, respectively). In patients with genotype 1, peginterferon alfa-2a plus ribavirin increased QALY by 0.70 a year compared with interferon alfa-2b plus ribavirin, with a cost-effectiveness ratio of $2600 per QALY gained. The QALY increase in patients with genotype 2/3 was 1.05 with peginterferon alfa-2a compared with interferon alfa-2b plus ribavirin. The incremental cost-effectiveness ratio never exceeded $16,500 per QALY, making peginterferon alfa-2a more cost-effective than peginterferon alfa-2b in this model.60

A German Federal Ministry of Health and Social Security health technology assessment of the effectiveness and cost-effectiveness of initial combination therapy with pegylated interferon/ribavirin in patients with chronic HCV used data from 9 randomized clinical trials, 2 health technology assessments, 1 Cochrane review, 2 meta-analyses, and 7 economic evaluations. It concluded that pegylated interferon/ribavirin was superior in terms of efficacy (as measured by SVR rates) to interferon/ribavirin or interferon monotherapy, and reduced the number of non-SVR cases by 17%. Combination interferon/ribavirin was cost-effective compared with interferon monotherapy, while pegylated interferon/ribavirin resulted in an incremental cost-effectiveness ratio of €9800 (2002 euros) per QALY gained.61

Similar studies in other countries produced comparable results—pegylated interferon/ribavirin is a cost-effective therapy for treatment-naïve patients with chronic HCV when compared with interferon/ribavirin.62,65

The adverse effects of combination therapy and impact on quality of life, however, should also be considered. Perrillo et al evaluated the impact of pegylated interferon alfa-2a monotherapy or interferon alfa-2b/ribavirin on HRQoL, work productivity, and medical resource utilization. During 48 weeks of therapy, patients in the monotherapy cohort experienced less impairment across all measures of work functioning and productivity, required fewer prescription drugs for adverse effects, and were more adherent to therapy than those in the combination cohort.66

Hassanein et al found higher HRQoL in patients receiving combination therapy with pegylated interferon than with combination non-pegylated interferon, although
patients receiving pegylated interferon alfa-2a monotherapy experienced less impairment in HRQoL.\(^6\) Current guidelines recommend evaluation of patients on combination therapy at 12 weeks to assess viral response and minimize antiviral-related morbidity and costs.\(^1\) In an analysis of the efficacy and cost-effectiveness of such assessments, Wong et al found they reduced the duration of antiviral therapy by 40% to 44%, resulting in antiviral cost savings of 44% to 45% compared with 48-week dosing in patients with genotype 1 HCV infection. There were no differences in costs or outcomes, however, in patients with genotype 2 or 3 infection.\(^6\)

**Looking to the Future**

Although cost-effective and moderately efficacious therapies are currently available to manage chronic HCV infection, none are ideal in terms of efficacy and safety, and all have significant barriers to use.\(^6\)\(^4\)\(^9\)\(^7\) The introduction of newer therapies, including the protease inhibitors, has the potential to shift the natural history of chronic HCV infection by triggering much higher SVR rates in treatment-naïve patients, nonresponders to previous therapies, and those who have relapsed following therapy.\(^7\)\(^1\)\(^-\)\(^4\) As of publication time, none of these new agents were approved for use in HCV infection, so drug costs are not available. Therefore, it is not possible to assess their cost-effectiveness over the lifetime course of chronic HCV infection. Nonetheless, a predictive analysis suggests that using these new agents in half of those currently infected with HCV could reduce the risk of cirrhosis by 15.2% after 10 years; treating all patients currently infected could lead to a 30.4% risk reduction. New agents could also result in significant reductions in the number of patients with decompensated liver disease and HCC. Such reductions may provide significant cost benefits in managed care settings (Figure).\(^5\)

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**Figure.** Estimated Reductions in Cirrhosis (A) and Liver-Related Death (B) by 2020 Assuming Incremental Treatment of Zero to 100 Percent of Infected Persons and Sustained Viral Response Rates of 40%, 60%, and 80%\(^5\)

REFERENCES


