Making It Happen: Managed Care Considerations in Vanquishing Hepatitis C

John G. McHutchison, MD; Bruce R. Bacon, MD; and Glenda S. Owens, RPh, MHA, CDM

A substantial increase in the prevalence of chronic hepatitis C virus (HCV) infection is projected in decades to come, suggesting a future increase in the burden of HCV-related chronic liver disease with its attendant morbidity and mortality. Most cases of HCV were acquired during the 1960s to the 1980s, and infection is usually asymptomatic during both the acute and chronic phases. Symptoms usually only develop after the establishment of advanced stages of liver disease. The majority of currently infected individuals have not yet been diagnosed. As these baby boomers with asymptomatic infection advance in age, a proportion will likely develop clinical liver disease.

The economic burden of this will largely fall on managed care organizations (MCOs) and private insurers. HCV infection has not escaped the need to use newer and more expensive injectable antiviral agents. Optimizing the use of these agents, and the overall management of HCV infection, will be essential to assure that the best possible patient outcomes are achieved while long-term healthcare costs are minimized.

The objective of this review is to discuss the present medical and economic burden of HCV infection and projections for the future. Emphasis is placed on the medical and economic implications of these burdens for managed care. Methods to increase treatment efficacy and potentially lessen HCV-related costs are also discussed.

Health Burden: Liver-related

The Present. Cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC) are the most significant clinical sequelae of chronic HCV infection. Based on present data, about 20% of patients with chronic HCV infection will progress to cirrhosis after 20 to 30 years. Factors that have been shown to be associated with cirrhosis development are older age at time of infection, coinfection with human immunodeficiency virus (HIV) or hepatitis B virus, high levels of alcohol use, and male sex. Neither viral load nor HCV genotype has significantly affected the risk for progression of liver disease.

Each year, hepatic decompensation is seen in 3% to 6% of patients with HCV-related cirrhosis; these patients are potentially candidates for...
liver transplantation.\(^1\,^3\,^4\,^8\) In addition, HCC develops in up to 4% of patients with HCV cirrhosis.\(^1\,^3\,^8\) Overall, HCV infection is the most common indication for liver transplantation in the United States. It accounts for about one third of cases of HCC.\(^3\) Liver transplantation was performed in 1517 patients with HCV infection in 1998, with an increase in transplantation rates in subsequent years; however, the availability of cadaver livers has remained constant at only 4000 to 5000 per year.\(^4\,^8\)

Studies show a substantial and increasing use of healthcare resources by patients with chronic HCV infection.\(^9\) Outpatient visits and hospitalizations are now more frequent. From 1994 through 2001 in one study, HCV-related hospitalizations, deaths, and the costs incurred increased at average annual rates of greater than 20%, which were 3-fold higher than rates for all-cause hospitalizations.\(^9\) In 1998, there were 317,000 outpatient visits related to chronic HCV infection and an estimated 140,000 hospital discharges listing an HCV diagnosis.\(^4\,^8\) Each year, 10,000 to 12,000 deaths are attributed to HCV infection, although this is likely an underestimate.\(^3\,^8\) Deaths in association with HCV are more often related to decompensated cirrhosis as opposed to HCC.\(^3\)

In general, life expectancy is reduced in those chronically infected with HCV. In the average middle-aged adult receiving no treatment, life expectancy is estimated to decrease by 3 years and 9 years in those with mild and moderate hepatitis, respectively; for those with compensated cirrhosis, life expectancy falls by 16 years.\(^6\) Decompensated cirrhosis offers a much poorer prognosis, with a 28-year decrease in life expectancy, although liver transplantation in these patients can limit the decrement to about 22 years.\(^6\)

**The Future.** Trends toward steady increases in morbidity and mortality due to chronic HCV infection have already been shown during the period from 1980 to 2000, perhaps providing a hint of what can be expected in years to come. This included increases in HCV-related hospitalization, liver transplantation, and mortality.\(^1\,^4\,^3\,^8\) Hospitalization for HCV liver-related reasons also increased during this period in patients coinfected with HIV; in this group, 7.5 times as many patients were hospitalized in 2001 compared with 1994.\(^9\)

These trends may continue on an even greater scale in the future, presenting a major challenge to MCOs. Morbidity and mortality related to HCV liver sequelae are expected to double or even triple over the next 2 decades, because of the expected increase in the number of patients with mature HCV infection (ie, those acquired in the 1960s to 1980s).\(^1\,^6\,^8\,^10\,^11\) The need for liver transplantation will increase dramatically over this period, potentially overwhelming the capacity of transplant centers. An urgent need will be forthcoming to increase availability of transplant services through increased organ donation or alternative techniques,\(^10\) unless more effective treatments become available to eradicate HCV and prevent cirrhosis from developing.

With the use of Markov modeling, Davis and colleagues\(^10\) projected the HCV-related burden in the United States over the next 40 years (Table 1). In a more recent analysis, Deuffic-Burban et al\(^12\) projected the future disease burden associated with HCV infection in the United States by the use of the back-calculation model. Deaths from HCV-related liver disease and HCC were estimated to be 3,700 in 1998 and were projected to rise over the subsequent 25 years, peaking at 13,000 in 2030. It was estimated that future mortality from HCV will likely exceed that related to HIV. A caveat arising from studies that have projected disease burden is that methodology and techniques for estimating this burden have varied. Similarly, the studies varied with respect to inclusion or noninclusion of the beneficial effect of antiviral therapy in potentially reducing future disease complications and their costs. The confounding effects of therapy, such as accounting for those who are nonresponders or noncompliant, are also problematic in assessing costs and economic benefits.

Thus, the actual disease burden in the present or the future remains largely unknown. What is known with certainty, however, is that the burden will increase substantially over the next 20 years.

**Extrahepatic Complications.** Patients with chronic HCV infection can present with numerous extrahepatic complications, many of which are clinically significant.\(^3\,^8\) Some of these include glomerulonephritis, lichen planus, keratoconjunctivitis sicca, porphyria cutanea tarda, and various neuropathies.\(^3\,^8\) Although cryoglobulins are found in
the serum of up to 50% of HCV patients, the clinical disease associated with mixed cryoglobulinemia is infrequently observed.

Quality of Life. Health-related quality of life (HRQOL) is of major importance to patients with any chronic disease or disorder and is impaired in those with chronic HCV infection, as measured by generic and hepatitis-specific scales. Fatigue, depression, impaired social function, reduced vitality, and cognitive and other neuropsychiatric disorders are relatively common. Fatigue, which can be severe, occurs in about two thirds of infected patients. HRQOL impaired as a result of HCV infection does return to normal after successful viral eradication. It should be noted, however, that a history of intravenous drug use and alcohol abuse may contribute substantially to impaired HRQOL.

Similar to HIV infection, the cognitive and neuropsychiatric impairment in HCV infection has correlated with an increased choline/creatine ratio in the basal ganglia and white matter on cerebral proton magnetic resonance spectroscopy.

Economic Burden

Studies indicate that most privately insured individuals receiving employer healthcare coverage are enrolled in managed care, and MCOs will bear the burden of most costs related to treating HCV-related liver complications. For the year 1997, costs related to HCV infection in the United States were estimated at $5.5 billion; about one third of this was attributable to direct medical costs and two thirds to indirect costs. The total direct healthcare cost for HCV infection in 1998 was estimated at more than $1 billion. A US survey by the American Gastroenterological Association (AGA) indicated that the cost for outpatient physician services related to the more than 300,000 outpatient visits for hepatitis C in 1998 amounted to $24 million; this survey also found that about $530 million was spent on antiviral treatment during this year.

The economic burden imposed by HCV is similar to that reported in recent years for rheumatoid arthritis ($7 billion in 1994) and asthma ($5.8 billion in 1994); although less than that for HIV ($30 billion in 1992), HCV alone is projected to have an increasing disease burden relative to these other conditions.

When considering the expected rise in morbidity and mortality, one economic model projects direct medical costs of $10.7 billion over the period of 2010 to 2019. Societal costs are expected to reach $21 billion during this period, attributed to the projected 720,000 years lost because of decompensated cirrhosis and HCC, whereas indirect costs related to mortality are estimated to exceed $50 billion. These data do not consider the economic burden of HRQOL issues, including pain and suffering, or caregiver time. When considering these latter expenses, some investigators project a total economic burden of HCV infection of more than $180 billion between 2010 and 2019.

Per-patient Costs. Actual per-patient costs more effectively arm MCOs with the information needed to determine cost-effectiveness of available HCV treatments. In a retrospective review of a medical and pharmacy claims database of HCV-diagnosed patients in an MCO, the median annual total healthcare cost in those receiving interferon alfa was $4634, and the median annual total HCV-relat-

Table 1. Future Projections: Numbers of Patients With Chronic HCV Infection, Cirrhosis, and Complications Over Four 1-decade Intervals

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2010</th>
<th>2020</th>
<th>2030</th>
<th>2040</th>
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<td>HCV infection</td>
<td>2 940 678</td>
<td>2 870 391</td>
<td>2 681 556</td>
<td>2 433 709</td>
<td>2 177 089</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>472 103</td>
<td>720 807</td>
<td>858 788</td>
<td>879 747</td>
<td>828 134</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>66 294</td>
<td>103 117</td>
<td>134 743</td>
<td>146 408</td>
<td>142 732</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>7271</td>
<td>11 185</td>
<td>13 183</td>
<td>13 390</td>
<td>12 528</td>
</tr>
<tr>
<td>Liver-related death</td>
<td>13 000</td>
<td>27 732</td>
<td>36 483</td>
<td>39 875</td>
<td>39 064</td>
</tr>
</tbody>
</table>

HCV indicates hepatitis C virus.

Used with permission from Reference 10.
ed cost was $2472. Costs in patients receiving interferon alfa plus ribavirin were higher, with a median annual total healthcare cost of $6649 and median annual HCV-related total cost of $4303. This review found that total healthcare costs were substantially higher in HCV-infected patients with comorbid HIV infection.16 These costs would be even higher if the current standard of treatment, pegylated interferon (peginterferon) and ribavirin, were analyzed. Drug costs for a year of therapy are about $20 000.

In another analysis involving patients with confirmed HCV infection in a managed care population (N = 191), total medical costs amounted to about $75 million over a 3-year period, which translates into a mean annual cost of approximately $13 000 per patient.17 Of importance to health plans, the total healthcare costs in these latter 2 studies were larger than total costs related to HCV infection, emphasizing the cost burden due to healthcare needs above that due to HCV infection alone.16

**Implications for Managed Care**

Perhaps most important, hepatitis C is a disease that spans a long, indolent course. In addition, the aging of the large pool of individuals with asymptomatic infection will lead to increased morbidity, mortality, and attendant costs over the next 2 decades. The cornerstone of therapy is the use of injectable peginterferon preparations, which are expensive. Central questions to be addressed by MCOs are: Will the initial expense of such therapies be offset by cost savings from the prevention of future disease burden? If so, how can we be assured that we are providing the best care to patients with the most efficient use of healthcare resources? What methods can we use during treatment to further reduce total HCV costs? Finally, what can be done to ensure diagnosis and appropriate treatment of infected patients, which will reduce future health burden?

These questions require consideration of virologic efficacy, effects of this therapy on clinical outcomes, cost-effectiveness of antiviral regimens, and viable methods to enhance identification and treatment of HCV-infected patients and optimize prescribed antiviral therapy.

**Virologic Efficacy.** The current regimens of choice for chronic HCV infection are (1) weight-based subcutaneous (SC) peginterferon alfa-2b plus oral ribavirin or (2) fixed-dose SC peginterferon alfa-2a plus oral ribavirin.16-20 The dosages and cost of therapy of these combinations are shown in Table 2. These combination therapy regimens produce sustained virologic response (SVR—undetectable HCV RNA 6 months after therapy stops) rates of 54% to 56% overall, with rates of 42% to 52% in the less responsive genotype 1 and 76% to 84% in genotypes 2 and 3. They are more effective than pegylated interferon alfa alone or nonpegylated interferon alfa, either alone or combined with ribavirin, in producing SVR. However, compared with nonpegylated interferon alfa plus ribavirin, the greater virologic efficacy of peginterferon plus ribavirin comes at the expense of more adverse events, such as neutropenia.21

Although the ultimate goal of therapy is to prevent long-term complications of chronic HCV infection, attaining SVR is the initial and primary measurable goal.1 As virtually all patients achieving SVR after a course of therapy will remain so indefinitely, this in essence constitutes a cure of chronic infection, which is supported by histologic and virologic data.1,11

**Optimal Duration of Treatment.** Patients with genotype 1 should be treated with peginterferon alfa plus ribavirin for 48 weeks, using higher doses of ribavirin, whereas those with the more treatment-favorable genotypes 2 and 3 can receive a shorter duration of therapy with a lower ribavirin dose. The recommended duration for genotypes 2 and 3 is 24 weeks.3,18

**Twelve-week Virologic Response: A Clinical Milestone.** The early virologic response (EVR—undetectable HCV RNA or a 2-log drop) is a marker of eventual treatment success or failure. Clinical studies have shown that patients not achieving EVR by 12 weeks of treatment, defined as at least a 2-log reduction in HCV RNA levels, have only a small chance (≤3%) of achieving SVR at the end of a full course of therapy.1,11,22-24 This “12-week rule” is most important for patients with genotype 1, who typically require a 48-week course of therapy. In genotype-1 patients failing to achieve the 12-week EVR, discontinuation of therapy is indicated. This not only spares the patient of subsequent adverse events but also generates considerable cost savings.
Effects on Other Outcomes. The impact of peginterferon plus ribavirin on long-term outcomes is still forthcoming. The main difficulty in outcome assessment is the lengthy natural history of the disease—chronic HCV evolves slowly, extending to decades in many patients, and long-term follow-up in large studies of treated cases is needed. Most clinical trials have been of short duration, using SVR as the primary end point. The available data at present do, however, suggest liver complications can be reduced and survival prolonged after successful antiviral therapy.\textsuperscript{22,25} Reversal of liver fibrosis is also associated with SVR.\textsuperscript{11}

Data regarding a reduction in the risk and incidence of HCC are somewhat equivocal, although published and unpublished retrospective studies suggest this benefit, particularly in patients with sustained responses.\textsuperscript{20,22,25} There is no clear evidence at present to indicate a benefit of antiviral therapy with respect to increasing the time to liver transplantation or reducing the need for it.

Results of long-term trials, many of which are under way, will offer more definitive data regarding outcomes. However, most projections suggest that successful antiviral therapy will ultimately be shown to prevent cirrhosis, reduce mortality, reduce or prevent HCC, and minimize the need for liver transplantation.\textsuperscript{11}

Cost-effectiveness. The efficacy of a given treatment does not always correlate with cost-effectiveness. However, based on projections of the natural history of HCV disease and benefits of antiviral therapy in available clinical trials, most pharmacoeconomic analyses have concluded that peginterferon-ribavirin regimens for chronic HCV infection are indeed cost-effective, with cost-effectiveness being comparable to or better than other well-accepted clinical interventions.\textsuperscript{6,11,15,22,26-29} These cost-effective analyses agree that most costs associated with chronic HCV infection are justified considering the future cost savings generated by prevention of liver disease. Cost-effectiveness applies to patients in clinical trials as well as those with milder disease or persistently normal alanine aminotransferase levels.\textsuperscript{22,30,31} Combined therapy of peginterferon alfa plus ribavirin has also been shown cost-effective in patients with coexistent HCV and HIV infection.\textsuperscript{12}

From his review of pharmacoeconomic studies, Wong\textsuperscript{6} suggests that, in general, incremental cost-effectiveness ratios (ICERs) for antiviral treatment of chronic HCV infection fall below the widely cited $50,000 per quality-adjusted life-year (QALY)-gained threshold. From a societal perspective, this investigator indicates that the ICER of peginterferon alfa plus ribavirin therapy would, at most, be about $23,000 per QALY; this is almost identical to the value for an effective, 3-drug antiretroviral regimen employed in HIV infection.\textsuperscript{6} Wong concludes that most of the costs of antiviral therapy for HCV infection should be offset by the prevention of future liver disease.

Enhancing Patient Identification and Optimizing Therapy. The demonstrated cost-effectiveness of peginterferon alfa combinations does not guarantee a significant reduction in total treatment costs. First, these agents have to be prescribed to have benefit, and there is evidence of inadequacies in testing for HCV, diagnosing HCV, and providing treatment for those who are diagnosed. These inadequacies may have large implications for economic burden in the near future.\textsuperscript{5} In those given treat-

### Table 2. Peginterferons Combined With Ribavirin for Chronic HCV Infection: Dose and Cost of Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adult Dosage*</th>
<th>Cost of Therapy ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a (Pegasys®) plus:</td>
<td>180 mcg once weekly SC for 48 wk</td>
<td>21,913</td>
</tr>
<tr>
<td>Generic ribavirin</td>
<td>800-1200 mg PO daily for 48 wk</td>
<td>8534</td>
</tr>
<tr>
<td>Ribavirin as Copegus®</td>
<td>800-1200 mg PO daily for 48 wk</td>
<td>12,889</td>
</tr>
<tr>
<td>Peginterferon alfa-2b (PEG-Intron®) plus:</td>
<td>1.5 mcg/kg once weekly SC for 48 wk</td>
<td>20,831</td>
</tr>
<tr>
<td>Generic ribavirin</td>
<td>800-1200 mg PO daily for 48 wk</td>
<td>8534</td>
</tr>
<tr>
<td>Ribavirin as Rebetol®</td>
<td>800-1200 mg PO daily for 48 wk</td>
<td>13,964</td>
</tr>
</tbody>
</table>

*The 48-week regimen with full-dose ribavirin (1000-1200 mg) is indicated in patients with HCV genotype 1.\textsuperscript{18,20} A shorter course (24 weeks) and lower dose of ribavirin (800 mg) may be given to patients with genotypes 2 and 3 (see text). HCV indicates hepatitis C virus; SC, subcutaneously; PO, by mouth. Adapted with permission from Reference 20.
ment, difficulties exist in implementing the required 6- or 12-month regimens and maintaining their effective use for the duration of therapy.

Methods to enhance identification and treatment of affected patients are needed. Optimizing antiviral therapy is essential to assure that the intended goals of therapy are met, and to further reduce costs during therapy. Some considerations that relate to MCOs are presented here.

Specialists Versus Primary Care Providers. Referral of diagnosed patients to HCV specialists may assure MCOs of optimal impact and improved cost-containment from antiviral treatment. This is largely unrelated to quality of care in the primary care setting, which can also be optimal, but is a practical consideration. The high volume of patients seen by most primary care providers on a daily basis creates the potential for insufficient time to devote to the needs of HCV patients. In addition, specialists may have greater knowledge of available guidelines for treating HCV infection and more training to deal with its intricacies, such as appropriate dosing, patient follow-up, and patient education, as well as management of nonresponders, nonadherence, and adverse effects. Finally, many gastroenterology and hepatology practices have mid-level providers or nurses who can monitor treatment at less cost than physician monitoring.

Clearly, there are insufficient numbers of specialists and support staff to handle the future burden of HCV. For this reason, ongoing education for primary care providers is crucial to ensure more adequate identification and treatment of infected patients.

Clinician Education. Data accumulated from a large population-based claims study in a national MCO indicates substantial undertreatment of patients with chronic HCV infection, suboptimal use of baseline and follow-up testing, and the need for enhanced awareness of risk factors to increase HCV screening in those at risk. MCO-based educational programs to facilitate greater knowledge of current guidelines, and ongoing education to keep clinicians aware of recent advances in diagnosis and treatment, can positively impact clinical practice to counter the projected rise in burden of symptomatic liver disease. Earlier identification of HCV-infected patients enables intervention in high-risk groups, before the onset of cirrhosis or decompensation, and will ultimately reduce total costs, which will rise if suboptimal management continues.

An exemplary MCO model education program for physicians and other health professionals is available.

Patient Education and Adherence. Patient adherence to prescribed antiviral therapy enhances SVR rates and thus the opportunity to prevent advanced liver disease. Available data indicate that patients who are adherent and receive at least 80% of their total peginterferon alfa and ribavirin doses for at least 80% of the duration of treatment will have significantly higher rates of SVR than patients with lesser degrees of adherence.

Patient education is the key to adherence. Implementing system-wide patient education programs on all aspects of HCV, and drug therapy in particular, can maximize benefits of available therapy and help MCOs and health plans achieve optimal results with the limited resources available. Adverse effects serve as the major stumbling block to adherence. Patients must be informed of the potential adverse effects of interferon-based therapies, how frequently they occur, their severity, and ways they may be managed. Optimism should be emphasized, with encouragement that most adverse effects can be managed by dose reduction or other measures, such as treatment of interferon-related depression, rather than discontinuing therapy.

Patient education about chronic HCV disease in general and the importance of adherence in relation to long-term outcomes may also facilitate greater adherence. Other measures that may improve compliance are frequent clinic and telephone follow-up visits and the availability of support groups, printed materials, and self-monitoring devices.

Studies show that patients are more likely to adhere to and complete therapy when there is ongoing support by a clinical team. A multidisciplinary approach extending beyond the physician can also enhance patient educational efforts, and might include family, nurses, pharmacists, nurse practitioners, and physician assistants. The pharmacy, for example, can facilitate adherence by use of pill organizers, accessible refills, and reminders.

The specialty pharmacy offers a greater range of relevant services than the traditional pharmacy.
This type of pharmacy is increasingly playing an important role in providing injectable biologicals at lower cost and providing patient education and consultation regarding their proper and safe use. Most specialty pharmacies offer additional advanced services to ensure patient adherence to therapy, such as on-call assistance and monitoring and managing adverse effects of biologic agents. Many MCOs have contracted with specialty pharmacies as a means of assuring optimal use of antivirals and reducing long-term costs.

The prescriber or other healthcare professional should assess the patient for comorbidities or contraindications to therapy. A critical first step is to educate the patient about depression and substance abuse, since these are frequent roadblocks to successful antiviral therapy. Major depression or psychiatric symptomatology can be contraindications to interferon alfa therapy, and in addition to contributing to nonadherence, the depression commonly seen during interferon alfa therapy has been associated with lower response rates. Alcohol or use of illicit drugs may also compromise outcomes by reducing response rates or increasing the risk of antiviral toxicity.

Management of Adverse Effects Begets Adherence. Managing adverse effects to peginterferon alfa plus ribavirin therapy is critical to maintain or improve adherence. Preventing or correcting a complication of therapy can promote adherence in the patient who might not adhere otherwise, and may improve virologic response rates. Depression is seen in about one third of patients during therapy and is one of the most prevalent reasons for discontinuing therapy in large clinical trials. Anti-depressants may be useful, such as the selective serotonin reuptake inhibitors, and their liberal use is increasing in clinical practice to maintain adherence. However, discontinuation of antiviral therapy and psychiatric intervention is indicated if depression is severe and unresponsive to treatment. Influenzalike symptoms can usually be managed with acetaminophen or nonsteroidal anti-inflammatory agents.

Bone marrow suppression induced by interferon alfa regimens has been increasingly treated with either granulocyte colony-stimulating factor or epoetin alfa. In one review, 9% to 17% of patients receiving peginterferon alfa were also receiving one of these growth factors. However, these agents are expensive and the cost-effectiveness of this practice has not been clearly demonstrated. Dose reduction of interferon alfa is preferred and most often will obviate the need for growth factors.

The hemolytic anemia that may accompany oral ribavirin is typically more problematic, potentially resulting in anginal symptoms or myocardial infarction in susceptible patients. Dose reduction, discontinuation of therapy, or even blood transfusion may be indicated. Similar to the response to interferon-induced marrow suppression, the use of epoetin alfa or darbepoetin alfa has increased in the clinical setting to enable patients to continue their peginterferon plus ribavirin regimen, and to sustain the ribavirin doses needed to maximize chances for SVR. Although one study has suggested the cost-effectiveness of darbepoetin for ribavirin-induced anemia, another analysis showed that the incremental cost of treating HCV infection increased by 5.7% in genotype-1 patients and 34% in genotype-2 and -3 patients with use of epoetin for this complication, but decreased by using the strategy of ribavirin dose reduction or discontinuation.

Monitoring and the 12-week Stop Rule. Monitoring of antiviral therapy with peginterferon plus ribavirin is crucial to assure that the maximal benefit is being achieved and that complications that might interfere with outcomes are avoided. This should include examination, determination of HCV RNA levels, questioning in regard to adherence, and assessment for adverse effects. The AGA recommends that clinical and virologic monitoring be conducted at intervals ranging from once monthly to once every 3 months. Hematologic monitoring is indicated to detect anemia, neutropenia, or thrombocytopenia. Determination of thyroid-stimulating hormone is also indicated to identify hyper- or hypothyroidism. Close monitoring for clinical signs of depression, with appropriate intervention, is of particular importance.

As discussed earlier, assessment of EVR at 12 weeks (12-week stop rule) can identify those patients likely or unlikely to achieve SVR. This practice should be incorporated into all treatment
plans for chronic HCV infection. In patients receiving peginterferon alfa plus ribavirin who demonstrate a poor EVR at this time, especially genotype-1 patients, therapy may be discontinued. In addition to avoidance of adverse effects from continued therapy, health-system drug costs are thereby reduced substantially. Cost savings are greatest in patients with HCV genotype 1, who receive a 48-week course of treatment.

Economic analyses have shown decreases in lifelong antiviral drug costs of about 45% with use of the 12-week stop rule in patients receiving peginterferon alfa plus ribavirin. In treatment-naive patients receiving this regimen, savings of approximately $16 000 have been realized. Virologic assessment at the end of therapy is essential. The AGA recommends use of a highly sensitive assay (lower limit of 50 IU/mL or less) or use of a qualitative HCV RNA assay to document response at the end of therapy or an SVR 6 months or more after therapy has been completed.

Summary of Managed Care Implications. Analysis of available data regarding virologic efficacy, impact on outcomes, and cost-effectiveness in chronic HCV infection should offer encouragement to MCOs, in that initial costs for antiviral treatment appear justified. Most costs of therapy should be offset by the prevention of future liver disease. Peginterferon alfa-2a or -2b combined with ribavirin, the current standard of care, is effective in producing SVR in about half of patients with chronic HCV infection overall. This antiviral therapy will likely reduce hepatic complications and is considered cost-effective, even in patients with normal liver function tests.

Greater identification and effective treatment of HCV-infected patients, which would also reduce future HCV-related costs, may be facilitated by well-planned education programs for primary care providers; specialists may be more able to assure effective treatment and follow-up. Implementation of methods to assure optimization of therapy can help achieve therapy goals and lessen long-term treatment costs. These include measures to enhance adherence to therapy, close monitoring, and use of the 12-week stop rule. Enlisting the services of a specialty pharmacy is a further avenue to maximizing efforts of health plans to bring patients to SVR, with reduced long-term complications.

Prevention and Future Needs and Strategies. In the absence of a vaccine, primary prevention of HCV infection is directed at identifying cases and reducing transmission. Although it might seem an absolute necessity, mass screening for hepatitis C would pose an intolerable economic burden. Targeted screening is, however, indicated in those at risk, and specific populations in this category are presented elsewhere in this supplement. Injectable drug use is the main risk factor. This type of screening is likely cost-effective. For example, testing injectable drug users in a sexually transmitted disease (STD) clinic has been shown highly cost-effective. In addition to HCV screening, prevention considerations in subjects at risk include education about HCV, risk-reduction counseling, and substance abuse treatment.

Primary prevention education should be considered by MCOs and health plans, because any effort to identify those infected may lead to effective treatment that can help minimize the sizable proportion of HCV-infected patients projected to develop liver disease and attendant sequelae.

For patients with diagnosed hepatitis C, counseling to reduce HCV transmission to others is paramount. Immunization with hepatitis A and hepatitis B vaccines should be offered. A selective strategy of immunization with hepatitis A and B vaccines, based on immunity determined by blood testing, was considered cost-effective in one economic model—more cost-effective than a universal vaccination strategy with these vaccines.

Vaccination is considered to be the most important tool in the prevention of chronic viral infections, and the development of a hepatitis C vaccine is one of the major considerations in HCV research efforts. Understanding of host-viral interaction in HCV infection has been limited in general by lack of effective cell-culture systems and small-animal models. Intensified efforts to develop reliable, reproducible, and efficient cell-culture systems are essential for vaccine development. A number of therapeutic vaccines that may benefit patients with chronic HCV by stimulating immune responses have been under investigation. However, well-conducted clinical trials are now needed.

Re-treatment of patients who have failed on interferon plus ribavirin is a focus of ongoing research. By re-treating such patients with usual
doses of peginterferon alfa plus ribavirin, up to 20% have achieved SVR; however, this response rate suggests there is much room for improvement and additional trials of re-treatment are required, including the use of higher doses of the combination, re-treatment of patients with advanced cirrhosis or fibrosis, and use of newer therapeutic agents under development. 40-44

Of significant importance to managed care is more up-to-date information on the true prevalence, healthcare costs, morbidity, and mortality of hepatitis C, and ongoing assessment of these parameters, particularly in high-risk populations and patients with comorbidities. 4 Such research is vital for formulating healthcare policies and effectively allocating resources.

Newer approaches to drug pricing and payment for treatment are in the offing and may impact MCOs. Payment by results for expensive new agents is one such approach, in which a money-back guarantee would be in effect if these agents did not live up to expectations after a given course of treatment. 45 Future application of this paradigm to expensive HCV therapies could alter payment schedules significantly.

Conclusions

The health and economic burden of HCV infection promises to increase in the decades to come. MCOs and private insurers will share a large portion of costs for the new wave of symptomatic patients, and health plans need to consider the most practical, efficient, and cost-effective ways to manage this impending situation. Greater clinician awareness of available guidelines, patient education, close monitoring of antiviral therapy, emphasis on adherence to therapy, and swift and effective management of adverse effects of this therapy may increase the number of patients that are effectively treated, and maximize outcomes. The 12-week stop rule is one specific measure that can minimize costs in patients who do not achieve EVR. Specialty pharmacies can extend the reach of the clinician to help maintain adherence and intended outcomes of therapy. Newer ways of payment for treatment with biologic agents, now being discussed, are in line with managed care goals of assuring the intended effects of costly therapy, and may ultimately apply to HCV.

REFERENCES


