

VIEWPOINT

New Expensive Treatments for Hepatitis C Infection

Troyen Brennan, MD, MPH

CVS Caremark,
Woonsocket,
Rhode Island.

William Shrank, MD, MSHS

CVS Caremark,
Woonsocket,
Rhode Island.



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Treatment of infection with hepatitis C virus (HCV) has changed substantially in the last 3 years, with new therapies now reaching cure rates (defined by sustained virologic response) higher than 95%. As little as 3 years ago, treatment involved an arduous course of pegylated interferon and ribavirin, which caused serious adverse effects in more than 80% of patients; less than 50% of patients could finish the treatment course. Because HCV infection can be indolent, with slowly developing liver injury in the form of scarring and fibrosis, many patients were so-called warehoused by their physicians, followed up closely while waiting for more promising treatments.¹

In 2011, introduction of the first generation of protease inhibitors, particularly telaprevir and boceprevir, heralded change. When combined with interferon and ribavirin, these medications produced much higher sustained viral responses in the HCV genotype 1 subclasses.¹ However, these agents were much more expensive than standard therapy, at a cost of more than \$80 000 per course of therapy, and were associated with high levels of viral resistance development if patients did not strictly adhere to therapy.

In 2014, the introduction of polymerase inhibitors set a new standard. The first in this class, sofosbuvir, manufactured by Gilead, has shown significant effectiveness when combined with ribavirin and interferon in patients with genotype 1 HCV. Sofosbuvir also can be combined with another new protease inhibitor, simeprevir, to treat patients in whom interferon-based therapy has failed. These regimens provide interferon-free treatment protocols that are shorter and well tolerated and have 80% to 95% cure rates.¹ This fall, an oral combination of sofosbuvir and ledipasvir will be introduced that inhibits both the NS5B polymerase and NS5A polymerase and has been shown to reduce treatment to an 8-week course with cure rates of more than 95%.² Now, a chronic disease that affects millions of Americans can be cured by well-tolerated oral medications.

Perhaps surprisingly, most media coverage of this important development in HCV treatment has not focused on the cure rates but, rather, on cost. The price of sofosbuvir is essentially \$1000 per pill, or \$84 000 for a standard 12-week course. The fact that pricing in the United Kingdom for a similar regimen is \$54 000, and perhaps as low as \$900 in Egypt and other developing countries,³ indicates that the pricing in the United States is a purely financial decision by Gilead and has outraged many. Indeed, some pharmacy benefit managers are calling on their clients to boycott these products until alternatives are available late in 2014.⁴

But is the pricing unfair? This question can be considered from at least 2 perspectives—"return on invest-

ment" and "value driven." In a market-driven health care system such as that in the United States, the manufacturer, Gilead, should be able to recoup its costs of development (ie, return on investment). With sofosbuvir, this is fairly straightforward. The medication was identified and initially tested by a different firm, Pharmasset, which Gilead bought in 2012 for \$11 billion.⁵ Although there were additional drug development costs, assume that sofosbuvir cost \$11 billion to develop. If all of the approximately 3 million HCV carriers in the United States were treated with sofosbuvir at current prices, Gilead would net more than \$250 billion dollars, or better than a 20-to-1 return on its investment, suggesting that pricing is inappropriately high. However, not all HCV-infected persons will be treated with sofosbuvir. A half dozen major competing medications are in development and expected to come to market in the next 4 years; as this occurs, price competition will likely drive down costs and the return for Gilead.

A value-driven approach to pricing focuses on how treatment with sofosbuvir compares with other treatments for HCV infection. For instance, according to the average wholesale price from Medi-Span, the cost of a 12-week course of sofosbuvir plus pegylated interferon and ribavirin is \$116 910.72.⁶ This price is expensive, but the cost of a 24-week course of the first-generation protease inhibitor telaprevir plus pegylated interferon and ribavirin is \$111 606.48, and the 48-week course that many patients need is \$143 827.92.⁶

Average wholesale price is only part of the equation. Value also has to consider the efficacy of treatment and requires more sophisticated cost-effectiveness analyses, such as the incremental cost-effectiveness ratio, representing the added cost of an additional quality-adjusted life-year. The evidence documenting the effectiveness and tolerability of the newer sofosbuvir regimens, and the expected reductions in downstream costs associated with averted progression of disease, suggest that these newer expensive medications may represent a relatively good "deal" by typical cost-effectiveness thresholds. Indeed, the cost per additional quality-adjusted life-year may be quite comparable with other therapies.

Perhaps the controversy about sofosbuvir is really about the increasing total cost of specialty medications, considering both cost and prevalence of treatment targets. While a daily oral medication that costs \$1000 per pill gains attention, the more important issue is the number of people eligible for treatment. With broader screening, the pool of eligible patients may be as high as 3 million in the United States alone.⁷ The simple math is that treatment of patients with HCV could add

Corresponding Author: Troyen Brennan, MD, MPH, CVS Caremark, One CVS Dr, Woonsocket, RI 02895 (troyen.brennan@cvscaremark.com).

\$200 to \$300 per year to every insured American's health insurance premium for each of the next 5 years. Thus sofosbuvir is not really a per-unit cost outlier but is a "total cost" outlier because of its high cost *and* very large population eligible for treatment—a beacon for costs of specialty medications generally.

These costs will be especially burdensome over the next year. Presently, Gilead has a monopoly, and its investors expect it to make a profit during this period. However, it is anticipated that by December, another highly effective oral regimen will become available.⁸ Pharmaceutical manufacturers know that monopolies are evanescent. With HCV treatment, that lesson is very recent: the manufacturers of telaprevir and boceprevir priced their products high and were profitable for 15 to 18 months, but now their products are essentially replaced by the new polymerase inhibitors.

Given this context, how should costs be managed? In some state Medicaid programs, the new medications have not been added to the formulary, despite the new practice guidelines. Physicians for whom the drug is denied by the state are going to Gilead, and, by report, the company is quietly subsidizing the costs—there is an official assistance program offered by Gilead.⁹ In states where managed care plans provide the Medicaid benefit, many are not adding sofosbuvir to their formulary until they convince the state to renegotiate or consider "carving out the drug"—ie, having the state pay directly for the therapy outside the capitated payment agreement.

Some private insurers have added sofosbuvir to the formulary and are absorbing the costs but also are taking steps to ensure ap-

propriate utilization by developing prior authorization programs based on practice guidelines. Some insurers are asking physicians to treat only patients who absolutely need therapy now. Delaying treatment for some patients promises lower future costs, as competition generated by new drugs will likely cause prices to decrease as pharmacy benefit managers negotiate for best prices on behalf of health insurers and employers. This approach has been countenanced recently by expert panels.¹⁰

The ultimate approach to cost will be lower prices, which will occur as more products create competition. However, it will likely entail narrower formularies, in which the physician choice of a particular medication is limited by the deals negotiated by insurers and pharmacy benefit managers. Even then, the costs could still be very high—restrictive formularies have led to discounts of 30% to 40% for branded medications, not the greater than 95% discounts that occur when drug patents expire and generic competitors enter.

In summary, the health care system is adjusting quickly, but perhaps not quickly enough, to compensate for the high prices of HCV medications and, more importantly, the high cost of treating all HCV-infected individuals. However, this is not an isolated phenomenon; other expensive specialty medications are in development, many with large potential pools of targeted patients. Effective approaches to control costs for high-priced medications need to be developed and evaluated to ensure broad, equitable, and appropriate use of these new interventions in an already stressed health care system.

ARTICLE INFORMATION

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