A Cure for the High Cost of Hepatitis C Virus Treatment

Chronic infection with hepatitis C virus (HCV) affects more than 170 million persons worldwide, 350 000 of whom die annually from complications of end-stage liver disease or hepatocellular carcinoma (1). Viral eradication is associated with a reduction in adverse outcomes and liver-related death in patients with advanced chronic HCV infection (2). Although therapy with pegylated interferon–ribavirin has been available for more than a decade, only about one third of persons with chronic HCV infection have been referred for care and 7% to 10% have received therapy (3). The major reasons for the low treatment rates were the debilitating adverse effects, the presence of contraindications to therapy, and the lengthy treatment course (1 year). Patients and physicians preferred to wait for the promise of safer and more effective therapy because of the generally good short-term prognosis.

The wait is over. The advent of several classes of direct-acting antivirals (DAAs)—potent antiviral agents that inhibit key enzymes in the viral life cycle—has revolutionized chronic HCV therapy. Unlike pegylated interferon–based therapies, combinations of these drugs are safe and well-tolerated and cure more than 90% of patients in just 12 weeks or less, regardless of disease severity, race, or viral genotype (4). This is truly a remarkable achievement that allows chronic HCV infection to be viewed as an infectious disease with the prospect of global eradication.

These developments have generated great excitement. However, when the retail price of sofosbuvir, an important backbone of several of the regimens, was announced ($1000 per pill, or $84 000 for a 12-week course) (5), it became evident that cost would pose a major barrier to cure. The high cost of treatment has come to the forefront of discussions about therapy among patients, physicians, health policy analysts, and third-party payers. From the patient and physician perspectives, the benefits of new treatments are evident. Therapy that is both effective and safe can now be offered to all patients, including those who previously did not respond to, could not tolerate, or were too sick for interferon-based therapy. Advocates of treatment with DAAs also argue that population-level cure could, in the long run, reduce costs of managing complications of end-stage liver disease and prevent new infections. However, the projected cost of treating all patients in the United States is staggering: more than $300 billion.

From the payer and policymaker perspective, the new therapies present a unique challenge because the costs are incurred over a short period. Payers justifiably claim that treatment of the entire HCV-infected population would seriously compromise funding of life-saving therapies for other diseases. Is this a reasonable allocation of health care resources for a disease that kills fewer than 1% of infected persons annually? This is obviously a difficult question, and the answer depends on one's perspective. In such situations, a cost-effectiveness analysis can be helpful.

Instead of simply putting a price tag on each treatment, cost-effectiveness analysis aims to quantify the relative cost of each intervention as a function of its contribution to the quality and number of life-years gained. Although cost-effectiveness analysis has inherent limitations, when applied appropriately it is a useful tool to objectively evaluate the economic impact of competing treatment alternatives for a specific indication. In addition, the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) allows for comparison of the net value of different types of interventions across medical disciplines. The metric used to assess the value of an ICER is generally the willingness to pay from a societal perspective.

In this issue, Linas and colleagues estimate the cost-effectiveness of all-oral regimens compared with pegylated interferon–ribavirin or no therapy for HCV genotype 2 or 3 infection in the United States (6). The primary finding was that, at its current price, sofosbuvir-based therapy is cost-effective in patients with HCV genotype 2 or 3 infection only if they have previously not benefitted from treatment with pegylated interferon–ribavirin or have underlying cirrhosis. However, in treatment-naive patients without cirrhosis, the ICER exceeded $100 000 per QALY, the generally accepted threshold at which the net benefit gained with therapy does not justify the cost. These results are not surprising when 3 important assumptions used to construct the model are taken into account. First, most patients with HCV infection do not have and will not progress to cirrhosis during their lifetime, even without treatment. Second, HCV infection does not substantially affect quality of life or health care expenditure until the development of cirrhosis. Third, treatment with pegylated interferon–ribavirin in patients with HCV genotype 2 or 3 infection is relatively short (24 weeks) and achieves high response rates (an average of 80%).

Conclusions from this study do not apply to genotype 1 infection, which is more prevalent. Two additional studies provided similar analyses for HCV genotype 1, 2, and 3 infection (7, 8). Although conclusions from these studies on treatment of genotype 2 or 3 infection were similar to those of Linas and colleagues, several all-oral regimens were found to be cost-effective in treatment-naive patients with HCV genotype 1 infection without cirrhosis.

These analyses raise important questions about how we should approach HCV treatment. Should DAA regimens be permitted only for patients who have advanced disease or have not benefitted from interferon-based therapy? Should others receive interferon-based therapy or wait for the cost of DAAs to decrease? Prioritizing treatment for those at highest risk for complications of HCV infection certainly makes sense in a

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cost-constrained environment, and most state Medicaid programs and third-party payers have adopted this approach. But what about the millions who could benefit from DAA-based therapy? Is it ethical to require these patients to wait? Who decides who gets treatment and when? These are difficult issues for which there are no easy solutions. Of note, in all 3 cost-effectiveness analyses, the drug prices were the most important variable driving cost-effectiveness. Therefore, the simplest solution would be to reduce the price of the new drugs. Hopefully, in a free market environment, competition will eventually drive down costs. However, this will happen too late for some patients, and costs will remain prohibitive in some settings. Medicine does not often have the potential to eradicate a disease with significant public health burden. Results from the studies discussed here offer a price that would make these treatments cost-effective, but is society willing to pay even the reduced price?

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References

1. **Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al.** Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095-128. [PMID: 23245604] doi:10.1016/S0140-6736(12)61728-0
2. **van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al.** Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308:2584-93. [PMID: 23268517] doi:10.1001/jama.2012.144878
3. **Holmberg SD, Spradling PR, Moorman AC, Denniston MM.** Hepatitis C in the United States. N Engl J Med. 2013;368:1859-61. [PMID: 23675657] doi:10.1056/NEJMp1302973
4. **Liang TJ, Ghany MG.** Therapy of hepatitis C–back to the future [Editorial]. N Engl J Med. 2014;370:2043-7. [PMID: 24795199] doi:10.1056/NEJMe1403619
5. Sofosbuvir (Sovaldi) for chronic hepatitis C. Med Lett Drugs Ther. 2014;56:5-6. [PMID: 24457562]
6. **Linas BP, Barter DM, Morgan JR, Pho MT, Leff JA, Schackman BR, et al.** The cost-effectiveness of sofosbuvir-based regimens for treatment of hepatitis C virus genotype 2 or 3 infection. Ann Intern Med. 2015;162:619-29. doi:10.7326/M14-1313
7. **Najafzadeh M, Andersson K, Shrank WH, Krumme AA, Matlin OS, Brennan T, et al.** Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. Ann Intern Med. 2015;162:407-19. doi:10.7326/M14-1152
8. **Chhatwal J, Kanwal F, Roberts MS, Dunn MA.** Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med. 2015;162:397-406. doi:10.7326/M14-1336

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