Hepatitis C: The End of the Beginning and Possibly the Beginning of the End

Not since the initial cloning of the hepatitis C virus (HCV) in 1989 and the subsequent development of assays to detect silent carriers (1) and protect the blood supply (2) have data on this infection been so exciting. Before 1990, HCV was an incurable, prevalent chronic infection and had only a 10% cure rate with early interferon monotherapy. Sustained virologic response (SVR) rates—which are tantamount to cure—increased to approximately 25% by adding ribavirin and 45% when pegylated interferon was combined with ribavirin (3). In 2011, the first HCV-specific protease inhibitors were licensed after clinical trials showed that these drugs, combined with pegylated interferon and ribavirin, could achieve close to 70% SVR for patients with genotype 1 infections (4, 5). Further, a small clinical trial that added a polymerase inhibitor (quadruple therapy) achieved 90% SVR (6). More amazing, a Japanese trial that used only 2 oral agents (protease plus NS5A inhibitor) also demonstrated a 90% cure rate, albeit in only 10 patients (7). Such dramatic cure rates for genotype 1 infections far exceed prior expectations and portend a paradigm shift in HCV therapy that may eventuate in interferon-sparing regimens with low toxicity and high compliance.

These unprecedented outcomes result from 2 decades of brilliant basic science that developed crystal structures of key viral enzymatic sites and then generated inhibitors to engage these sites (8). These basic studies coalesced into 2 licensed protease inhibitors and at least 40 drugs in the pipeline that additionally target the NS5b polymerase and NS5a proteins. Other nonenzymatic targets, such as entry and assembly sites, are also being studied.

What do these findings mean to the average patient with HCV, high-risk cohorts, patients with severe chronic liver disease, and society? Will the costs of new treatments be justified and sustainable? Can we afford not to treat when cure rates are so high? What factors best predict response? Is prediction less important when cure rates are high? How will we identify the large number of persons who are unaware of their infection and likely to be cured if identified?

Because traditional pegylated interferon–ribavirin therapy has considerable adverse effects and less than 50% sustained efficacy, treatment decisions have been highly variable. Generally, patients with normal alanine aminotransferase levels or minimal fibrosis were not offered treatment and asymptomatic patients often opted out of recommended treatment because the complications are so difficult to endure. Estimates suggest that only 10% to 20% of patients known to be infected with HCV accept therapy and complete a full therapeutic course (9). Newly licensed triple therapy that incorporates protease inhibitors will not alleviate the adverse effects of interferon and will, in fact, impose some new toxicities. However, triple therapy increases efficacy to 70% and shortens treatment duration, so it will be more frequently recommended and more likely accepted. When cure rates approach 90%, as they appear to do with quadruple therapy or with combinations of oral direct-acting antivirals, it is probable that nearly all identified patients will be offered therapy and that acceptance will be high. However, this optimism comes with some caveats. First, the adverse effects associated with triple therapy are difficult to manage. Second, many factors diminish treatment response, including black race, obesity, HIV coinfection, and established cirrhosis. In addition, viral genotype and specific host polymorphisms in the interleukin (IL)-28B gene strongly influence treatment response. Of note, all of these predictors of response are based on classic dual therapy. Data from clinical trials with protease inhibitors suggest that, as overall efficacy increases, predictors of response become less important; potency appears to trump negative confounders (10). What will these new regimens cost and, more important, will the costs be worth the benefits? In this issue, Liu and colleagues (11) report the cost-effectiveness of universal triple therapy (interferon plus ribavirin and a protease inhibitor) compared with a strategy that used IL-28B genotyping to guide therapeutic decisions. Patients with the favorable IL-28B CC genotype would receive pegylated interferon plus ribavirin, whereas patients with unfavorable genotypes would also receive a protease inhibitor. They estimate that, compared with IL-28B–guided therapy, universal triple therapy costs $102 600 per quality-adjusted life-year (QALY) for patients with mild fibrosis and $51 500 per QALY for patients with advanced fibrosis and that, compared with standard therapy, it costs $70 100 and $36 000 per QALY, respectively. Of note, protease inhibitors fell within a range typically considered to be cost-effective, whichever strategy was used. We hypothesize that, as efficacy increases with future regimens, cost-effectiveness will improve and the advantages of IL-28B testing will diminish.

As innovative treatments for hepatitis C follow their now-destined progression, the most burning question will not be whether to treat, but rather how to identify the many chronic HCV carriers who are unaware of their infection and are at risk for cirrhosis, end-stage liver disease, or hepatocellular carcinoma. This concern was a major emphasis of a recent Institute of Medicine report (9). Another article in this issue, by Ly and associates (12), emphasizes that a minimum of 15 000 persons in the United States died of HCV-related events in 2007 and that HCV now exceeds HIV as a cause of mortality in the United States. Hepatitis C virus–related mortality is anticipated to increase as the infected population ages and as the incidence of hepatocellular carcinoma increases, proportionate to the duration of infection (13).

Identification of persons with asymptomatic HCV infection presents a continuing dilemma. It is estimated that

50% to 75% of persons with HCV are unaware of their HCV status (14). Persons who are at risk, such as those who use intravenous drugs, are not often engaged in regular medical care. Further, most persons with HCV are not addicted to drugs, but rather those who experimented with drugs for a limited time in their youth. These bygone experiences do not often connote risk to the affected persons nor serve as a reason to seek testing. Public health campaigns to encourage such individuals to be tested have not been sufficiently effective. Recommendations that physicians routinely ask questions about HCV risk have fallen victim to brief clinical encounters and the awkwardness of addressing sensitive issues. A new approach is needed that shifts the focus from the person to a more global context.

The Centers for Disease Control and Prevention and its collaborators (15) have proposed a clever strategy that targets the highest-risk birth cohorts. Hepatitis C virus infection has been shown to be most prevalent among persons born between 1945 and 1965. In this issue, Rein and colleagues (15) report an analysis of the cost-effectiveness of birth-cohort screening in U.S. primary health care settings. Compared with the status quo, birth-cohort screening for anti-HCV identified 808 580 additional cases of chronic hepatitis C at a screening cost of $2874 per identified case. If birth-cohort screening were followed by treatment with pegylated interferon plus ribavirin, screening would result in an incremental cost-effectiveness ratio of $15 700 per QALY gained. This is a phenomenal incremental cost-effectiveness ratio and will only improve as sustained treatment efficacy increases with newer regimens. It must be emphasized that—as opposed to HIV and hepatitis B virus, where the infecting virus is integrated into the host genome, necessitating lifetime treatment—HCV is nonintegrative and eradicable after only 6 to 12 months of antiviral therapy. Thus, birth-cohort screening seems practical and cost-effective and should be implemented as a national health policy. We must also directly target high-risk cohorts because every effectively treated high-risk individual diminishes the infectious pool and the likelihood of secondary transmission.

In summary, treatments for chronic hepatitis C are evolving at such a rapid pace that in 5 years, interferon-free, oral, direct-acting antiviral regimens may achieve close to 90% cure rates across viral genotypes and regardless of IL-28B allele status. What is currently lacking in this optimistic perspective is a national "find-and-treat" policy aimed at achieving maximum identification of HCV carriers and providing new-generation therapies to a large proportion of those identified cases. The individual and societal benefits of such a strategy are substantial and the costs are in step with other well-established public health measures. The goal to prevent fibrosis progression and cancer evolution in patients with HCV infection is now achievable if our collective will can evolve as rapidly as our pharmacologic skill.

Harvey J. Alter, MD
T. Jake Liang, MD
National Institutes of Health
Bethesda, MD 20892

Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-0093.

Requests for Single Reprints: Harvey J. Alter, MD, Department of Transfusion Medicine, National Institutes of Health, Building 10/Room 1C-711, 10 Center Drive, Bethesda, MD 20892; e-mail, halter@dtm.cc.nih.gov.

Current author addresses are available at www.annals.org.

Ann Intern Med. 2012;156:317-318.

References

1. **Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M.** Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989;244:359-62. [PMID: 2523562]
2. **Alter HJ, Purcell RH, Shih JW, Melpolder JC, Houghton M, Choo QL, et al.** Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med. 1989;321:1494-500. [PMID: 2509915]
3. **Hoofnagle JH, Seeff LB.** Peginterferon and ribavirin for chronic hepatitis C. N Engl J Med. 2006;355:2444-51. [PMID: 17151366]
4. **Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al; SPRINT-2 Investigators.** Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364:1195-206. [PMID: 21449783]
5. **Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al; REALIZE Study Team.** Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364:2417-28. [PMID: 21696308]
6. **Zeuzem S, Buggisch P, Agarwal K, Marcellin P, Sereni D, Klinker H, et al.** The protease inhibitor GS-9256 and non-nucleoside polymerase inhibitor tegobuvir alone, with RBV or peginterferon plus RBV in hepatitis C. Hepatology. 2011. [PMID: 22006408]
7. **Chayama K, Takahashi S, Toyota J, Karino Y, Ikeda K, Ishikawa H, et al.** Dual therapy with the NS5A inhibitor BMS-790052 and the NS3 protease inhibitor BMS-650032 in HCV genotype 1b-infected null responders. Hepatology. 2011. [PMID: 21987462]
8. **Pawlotsky JM, Chevaliez S, McHutchison JG.** The hepatitis C virus life cycle as a target for new antiviral therapies. Gastroenterology. 2007;132:1979-98. [PMID: 17484890]
9. **Mitchell AE, Colvin HM, Palmer Beasley R.** Institute of Medicine recommendations for the prevention and control of hepatitis B and C. Hepatology. 2010;51:729-33. [PMID: 20186842]
10. **Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB; American Association for Study of Liver Diseases.** An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54:1433-44. [PMID: 21898493]
11. **Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD.** New protease inhibitors for the treatment of chronic hepatitis C. A cost-effectiveness analysis. Ann Intern Med. 2012;156:279-90.
12. **Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD.** The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156:271-8.
13. **Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW.** Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138:513-21, 521.e1-6. [PMID: 19861128]
14. **Culver DH, Alter MJ, Mullan RJ, Margolis HS.** Evaluation of the effectiveness of targeted lookback for HCV infection in the United States-interim results. Transfusion. 2000;40:1176-81. [PMID: 11061852]
15. **Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al.** The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. Ann Intern Med. 2012;156:263-70.

Current Author Addresses: Dr. Alter: Department of Transfusion Medicine, National Institutes of Health, Building 10/Room 1C-711, 10 Center Drive, Bethesda, MD 20892.

Dr. Liang: Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Drive, Room 9B16, Bethesda, MD 20892.