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

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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

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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.

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