EDITORIALS

Therapy for Hepatitis C — The Costs of Success

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Welcomed and exciting results from three large, controlled trials of different regimens of oral antiviral agents for chronic hepatitis C, genotype 1, have now been published in the *Journal*.[1-3] The regimens all included the combination of ledipasvir and sofosbuvir, two new direct-acting antiviral agents with potent activity against hepatitis C virus (HCV). The two drugs were given as a single tablet once daily for 8, 12, or 24 weeks, with or without ribavirin. The results were consistent and striking: the various regimens yielded rates of sustained virologic response of 93% to 99%. The combination of ledipasvir and sofosbuvir alone (without ribavirin) for 12 weeks was associated with response rates of 94% in the ION-2 study and 99% in the ION-1 study.[1,2] Extending therapy to 24 weeks increased the rate minimally (to 98% and 99%, respectively). In contrast, adding ribavirin provided no further benefit, regardless of duration. In previously untreated patients without cirrhosis, shortening the duration of therapy (without ribavirin) to 8 weeks did not lessen the rate of response (94%, vs. 95% with 12 weeks of therapy in the ION-1 study).[3] Importantly, the single-tablet regimen was easy to administer and had few side effects; among the 539 patients who received ledipasvir and sofosbuvir alone for 12 weeks in these three trials, only 2 stopped therapy early because of adverse events.

The rates of response to ledipasvir and sofosbuvir were virtually the same in all subgroups of patients, regardless of patients' age, sex, race, liver-enzyme levels, HCV genotype (1a vs. 1b), preexisting antiviral resistance variants, or host genetic factors. Even in the difficult-to-treat patients who had not had a sustained response to a previous course of the most effective interferon-based therapies,[4] the response rate at post-treatment week 12 was 94%. In this group of patients, the presence of cirrhosis was associated with a slightly lower response rate (88%, vs. 95% without cirrhosis), but with the longer course of treatment (24 weeks), these differences disappeared (100% in both groups).[2] Preliminary studies with interferon-free drug combinations in patients with other HCV genotypes (2 or 3) suggest that high rates of response can be expected with those HCV strains as well.[5]

The combined results of the three trials include 1952 patients, of whom 97% had a sustained virologic response. Among the 3% who did not have a response, almost half were lost to follow-up or withdrew consent. Only 2 patients did not have an undetectable level of HCV RNA that was maintained during treatment (on-treatment virologic failure). Furthermore, the relapse rate after stopping therapy was only 2%. Relapses were more common with shorter courses of therapy: 5% of patients who received 8 weeks of treatment had a relapse, as did 2% of those who received 12 weeks and 0.2% of those who received 24 weeks of treatment. Trials focusing on retreatment of these rare patients with relapse are ongoing and will provide important guidance.

Ledipasvir and sofosbuvir are not the only promising antiviral agents for hepatitis C on the near horizon. Several other all-oral antiviral regimens have performed similarly in phase 2 studies, with sustained response rates in the range of 90% or higher.[6,7] Thus, there are likely to be several options for oral therapy of hepatitis C within the next year.

The availability of effective, oral regimens of therapy for hepatitis C will lead to major changes in the management of this disease and probably affect both its morbidity and its mortality. Since the first use of antiviral therapy for chronic hepatitis C almost 30 years ago,[8] treatment has been based on alpha interferon and was limited by the common and sometimes serious side effects of this cytokine, as well as the need for up to a year of therapy and the limited response rates of 50% or less, even among carefully selected patients. In patients with coexisting conditions such as human immunodeficiency virus (HIV) infection, an autoimmune disorder, solid-organ transplant, active substance abuse, or serious heart, renal, or psychiatric disease, interferon was usually contraindicated and, if given, had a high rate of adverse events and was often not effective. In real-life situations, fewer than half the HCV-infected persons qualify for interferon therapy, many patients decline treatment, and response rates can be far lower than 50%.[9] Furthermore, the management of therapy requires physicians and health care staff with special expertise and experience. It is hardly surprising that, despite the availability of interferon-based therapy for more than 20 years, the mortality from hepatitis C in the United States has continued to increase and now exceeds that from HIV infection.[10]

The limitations and medical barriers to treatment, however, may now largely disappear. The ease of administration, short duration of treatment, and minimal side effects of all-oral regimens will probably mean that most persons will qualify for therapy. Collectively, these regimens promise to transform hepatitis C from a condition requiring complex, unsatisfactory therapies and specialist care to one that can be effectively treated and easily managed by a general physician with few contraindications and side effects.

Unfortunately, not all barriers to treatment will be lifted. The major limitation remaining will be economic. The current cost of a 12-week regimen of sofosbuvir alone is $84,000, or $1,000 per tablet.[11] The addition of ledipasvir will add to the costs, and these estimates do not include expenses for diagnostic assays, monitoring, and physician visits.

The predicted costs of the new oral antiviral agents are as breathtaking as their effectiveness. Chronic hepatitis C is estimated to affect 3.2 million Americans, half of whom may not be aware that they are infected.[12] Public health efforts are now under way to identify persons with HCV infection and to direct them to medical care.[13] With the present estimates of costs, however, treating even half the HCV-infected persons in the United States would add billions of dollars to an already overburdened medical care system. Costs alone cast a pall over the stunning success in achieving the long-hoped-for goal of a safe and effective therapy for hepatitis C.

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1. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-93.
2. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. DOI: 10.1056/NEJMoa1402454.
3. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. DOI: 10.1056/NEJMoa1402355.
4. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. N Engl J Med 2013;368:1907-17.
5. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013;368:34-44.
6. Suzuki Y, Ikeda K, Suzuki F, et al. Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options. J Hepatol 2013;58:655-62.
7. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 2014;370:222-32.
8. Hoofnagle JH, Mullen KD, Jones DB, et al. Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon: a preliminary report. N Engl J Med 1986;315:1575-8.
9. Kramer JR, Kanwal F, Richardson P, Mei M, El-Serag HB. Gaps in the achievement of effectiveness of HCV treatment in national VA practice. J Hepatol 2012;56:320-5.
10. 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. [Erratum, Ann Intern Med 2012;156:840.]
11. Sofosbuvir (Sovaldi) for chronic hepatitis C. Med Lett Drugs Ther 2014;56:51-6.
12. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med 2013;368:1859-61.
13. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. MMWR Recomm Rep 2012;61(RR4):1-32.

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