The Price of Shortening Anti-Hepatitis C Virus Therapy: Is This Truly Cost Saving?

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With the development of the new all-oral regimens for treatment of hepatitis C virus (HCV) genotype 1 (GT1), the question has become what is the most appropriate length of treatment for these patients, both clinically and economically? The current evidence suggests that for most patients with HCV GT1 (patients without cirrhosis and treatment-naïve), 12 weeks of treatment with all-oral regimens seems most appropriate. Furthermore, shortening treatment with one of the currently approved regimens to 8 weeks may be possible for a small group of treatment-naïve patients without cirrhosis with low viral load. In contrast, treatment-experienced patients with cirrhosis may require 24 weeks of treatment. The data suggest that the efficacy of the current all-oral regimens declines if a shorter course than the approved duration is provided. Because efficacy and cost data drive economic analyses, shortening treatment for most patients with HCV GT1 may potentially reduce drug costs but at the significant “cost” of lower efficacy. Therefore, until the availability of more robust evidence, shorter duration of treatment for most patients with HCV GT1 may not presently be prudent. Nevertheless, it is important that patients who qualify for 8 weeks duration of LDV/SOF receive this shorter course which should help with cost without compromising efficacy.

Treating Hepatitis C Genotype 1: A Journey from 48 Weeks to 8 Weeks Duration:

Historically, treatment for patients with HCV GT1 consisted of pegylated interferon (PEG-IFN), ribavirin (RBV), and first-generation protease inhibitors for 24 to 48 weeks with substantial side effects such as flu-like symptoms, anemia, cytopenias, neuropsychiatric complications, and others. The sustained virological response (SVR) for these regimens was less than 40% in the real-world setting.¹ The low SVR was attributed, in part, to

low adherence rates because of numerous negative side effects. These side effects also negatively impacted patient-reported outcomes (PROs), such as health-related quality of life, daily activities, and work productivity.²

In 2013, the true first generation of direct-acting antiviral agents (DAAs) for treatment of chronic hepatitis C was approved including a new NS5B polymerase inhibitor [sofosbuvir (Sovaldi); Gilead] in combination with PEG-IFN or RBV, or both. This combination taken for 12 weeks led to an SVR rate of more than 90% in treatment-naïve patients with GT1.³ Although the SVR rates were substantially higher, PROs were still negatively affected because of the use of PEG-IFN or RBV, or both.⁴ Shortly afterward, a second-generation protease inhibitor, simeprevir (Olysio; Janssen), in combination with sofosbuvir, was approved for treatment of HCV GT1 for 12 weeks.¹ Although the efficacy was significantly improved, data on PROs were not available.

In the subsequent year, another DAA, ledipasvir (LDV an NS5A protein inhibitor), was approved as part of a fixed-dose combination with sofosbuvir (SOF; HARVONI; Gilead) for HCV GT1. This regimen was the first IFN and RBV-free regimen with SVR rates of more than 90%. Presently, the recommended treatment for patients with GT1 with hepatitis C is the use of these medications for 8 to 24 weeks.⁵ In contrast with IFN +/- RBV-containing regimens, this regimen is not only well tolerated, but also is associated with improvement of PRO scores as early as 4 weeks into treatment, as well as after achieving SVR-12.⁶

After the marketplace introduction of ledipasvir/sofosbuvir (LDV/SOF), another all-oral combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir (VIEKIRA; AbbVie) was approved to treat HCV GT1. This combination has a greater than 90% efficacy and improved safety profile. The

Abbreviations: DAA, direct-acting antiviral agent; GT1, genotype 1; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; PEG-IFN, pegylated interferon; PRO, patient-reported outcome; RAV, resistance-associated variant; RBV, ribavirin; SVR, sustained virological response.

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recommended duration of treatment is 12 weeks for the majority of patients with HCV GT1. However, for patients with GT1a with compensated cirrhosis or a history of null response to previous treatment, 24 weeks of treatment with the addition of RBV is recommended, whereas for patients with GT1b compensated cirrhosis or a history of a null response to previous treatment, 12 weeks of treatment with the addition of RBV is recommended.^{7,8}

Shorter treatment periods, higher efficacy, improved side effect profiles, and simpler regimens have contributed to the advantages of these new regimens. These advantages may also lead to higher adherence, which in turn may lead to higher “cure” rates in the real-world setting, as well as improved PROs, higher worker productivity, and a lessened economic burden of HCV on the society.²

Furthermore, these high cure rates may potentially lead to decreases in HCV-related complications such as hepatocellular carcinoma, liver-related mortality, and the extrahepatic manifestations of HCV.⁹ Because these outcomes are associated with high direct (increased resource utilization) and indirect medical costs (decreased worker productivity), high cure rates may reduce future resource utilization and increased worker productivity, resulting in an economic benefit to the society.^{2,9-12}

In fact, several cost-effective analyses determined that the incremental cost per SVR or cost per quality-adjusted life-year gained determined that the new regimens, as recommended by their package insert instructions, are cost-effective.¹³⁻¹⁶ This improved cost-effectiveness is believed to be due to higher efficacy, fewer negative side effects, less monitoring, and better PROs for the all-oral regimens.¹³⁻¹⁶ Nevertheless, evidence supporting the impact of HCV cure as a result of the new treatment regimens on the all-cause mortality is currently lacking, which impacts economic analyses because they are reliant on mortality data to show evidence for cost-effectiveness. However, the benefits of SVR on mortality have been shown with older regimens, so a similar assumption with the newer regimens is reasonable. Therefore, the current economic analyses support the use of the recommended regimens for HCV GT1.

The question now is whether an even shorter (6- to 8-week) course of treatment for all HCV GT1 patients is advantageous both clinically and economically. The answer lies in the current evidence for the efficacy and cost savings of a shorter regimen. Given the very few side effects of these newer regimens, there does not appear to be much of a cost savings related to the required monitoring of patients treated for a shorter duration, so any cost savings may be primarily associated with the lower cost of medication as a result of a shorter course of treatment.

In contrast with the limited cost saving, there may be a significant downside to shortening treatment with the current regimens. In fact, the current data suggest that shortening the

duration of treatment with the current regimens may lead to higher relapse rates and more resistance-associated variants (RAVs) in patients with HCV GT1.^{1,3,5,7,8} Current studies on the new DAAs are finding that certain patients develop RAVs when treatment is shortened to less than 12 weeks. RAVs are associated with a significant decrease in the chance for cure with subsequent treatment.^{17,18} As a result of these new developments, further testing before starting treatment may be necessary, which will add additional costs to treatment and may, in turn, create “push back” from payers because they often request the shortest possible therapy.

In this context, a new challenge arises in shortening treatment: correctly identifying the patient who would benefit the most from a shorter treatment duration. Therefore, identification should not simply include the patient's HCV viral load but also an assessment for the presence of cirrhosis, history of prior treatment, and the potential for the presence and/or development of RAVs to NS5A inhibitors. These recommendations not only add complexity and cost but also may reduce the effectiveness and cost-effectiveness of these regimens if not followed.

Until these questions are answered, we believe taking a shorter duration of treatment to obtain lower drug costs will only address a short-term budgetary concern while not attaining the best clinical outcome for the patient, as well as potentially causing poorer societal economic outcomes in the long term. Furthermore, it is plausible that marketplace competition may push the pricing of the HCV drug regimens downward, making the impact of the cost of drug vis-à-vis duration of treatment less pertinent (i.e., cost per course of treatment or cost of drugs that can guarantee re-treatment of relapsers at no additional drug cost).

In summary, the present data do not support substantial clinical or economic gain by shortening the course of treatment for all patients with HCV GT1. It is possible that for some patients a shorter course may certainly be more cost-effective. However, for the largest group of patients with HCV GT1 receiving treatment, the currently approved regimens seem to be most cost-effective in line with the recommended durations. Finally, in the context of the newer and potentially shorter regimens that are in development, their efficacy, effectiveness, cost-effectiveness, and impact on PROs must be established before a recommendation is made to promote a shortened course for all patients. In this context, new data is encouraging that future powerful combinations of multiple DAAs may be developed to suppress the virus to undetectable level within hours of treatment. These regimens may provide an opportunity to shorten these future treatments without compromising efficacy. Until the time that these regimens are developed, it is prudent to follow the current guideline for duration of treatment for HCV genotype 1 patients.

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