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Cost/Benefit of Hepatitis C Treatment: It Doesn't End with SVR

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One of the greatest medical achievements of the past 20 years has been the development of direct-acting, all-oral, interferon-free antiviral therapy for chronic hepatitis C infection, which offers a chance for cure for the 170 million individuals worldwide estimated to have chronic HCV infections. Of the chronically infected, approximately 20–30% eventually develop cirrhosis and of the cirrhotic, 1–3% develop cancer or decompensation annually, resulting in millions of life-years lost. Direct-acting antiviral (DAA) therapy, using drugs that cure the infection (termed sustained virological response (SVR)) in > 95% of those treated with minimal adverse effects with a mere 8–12 weeks of treatment, reduces the likelihood of liver cancer and decompensation by 70–90% in patients with cirrhosis.

When first- and second-generation DAA therapies for hepatitis C were first commercially available, the associated drug acquisition costs resulted in widespread 'sticker shock', with some combination regimens priced at $94,500 – $150,000 per course. Almost immediately, payors including the Department of Veterans Affairs, developed stringent medication access criteria, largely restricting treatment to cirrhotic patients, a response which in turn generated vociferous protests by patients and providers. Not unexpectedly, a flurry of modeling studies, largely industry-supported (1–4), soon emerged to justify the massive costs associated with these novel therapies, attempting to demonstrate that novel antiviral therapies could be cost-effective at either at $50,000 or $100,000 cost per quality adjusted life year (QALY) willingness-to-treat threshold and/or reduce healthcare costs due to reduced future burdens-of-disease. A recent meta-analysis of 24 cost-effectiveness analyses of 2nd and 3rd generation DAAs using updated treatment cost estimates for 2014 and a willingness-to-treat threshold of $100,000 per QALY found that in 71% of simulations, 2nd generation DAA therapies would be cost-saving when used in cirrhotic and non-cirrhotic patients even if these treatments cost $120,000 per course (4).

A key assumption of nearly all these models is that SVR saves healthcare dollars. None of these modeling studies measured changes in post-SVR healthcare expenditures to support this assumption but rather relied on existing estimates of healthcare utilization prior to treatment. Most of the studies included in the recent meta-analyses focused only on liver-related, rather than global, expenditures, assumed that patients with none – severe fibrosis (F0-F3) patients who attained SVR would incur no further liver-related costs (1–3, 5), and

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utilized accounting-cost inputs that likely underestimated the cost of chronic disease care (3, 6, 7). Nevertheless, post-SVR liver-related costs may continue to accrue, related to incomplete attenuation of liver disease progression after SVR, concomitant alcohol misuse-related progression, and/or non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH)-related liver disease progression that progresses despite SVR. Clearly, valid estimates of real post-treatment costs should be included in the treatment cost-effectiveness analysis, yet few data exist to inform the field.

In this issue of *Digestive Diseases and Sciences*, Maier et al, based on the evaluation of a large cohort of patients treated with older interferon-based therapies alone or combined with DAAs for hepatitis C within the Veterans Administration medical system, the single largest provider of hepatitis C-related care in the United States, hypothesized that achieving SVR would indeed substantially save costs (8). To validate this hypothesis, they evaluated pre- and post-treatment costs of a cohort of ~ 2000 cirrhotic (33% SVR) and 12,500 non-cirrhotic patients (49% SVR) treated for hepatitis C over a nine years. Retrospectively evaluating all post-treatment healthcare costs of these patients, the authors found that sustained cost savings could only be demonstrated in cured hepatitis C patients with cirrhosis. Specifically, within the cirrhotic subgroup, cost savings was achieved in years 3–9 after treatment with a cumulative $15,705 cost-saving per patient with SVR. By contrast, within the non-cirrhotic subgroup, while cost savings were demonstrated in years 3–6, there was no cumulative cost saving in year 7–8 and by year 9 SVR patients incurred greater costs. To address the concern that reduced costs were attributable to higher death rates in the non-SVR group, the authors applied a survival adjustment that did not alter their prior observation. Two additional key methodological strengths of the study were 1) the application of a double robust estimator of average causal treatment effect to overcome limitations of applying parametric cost models to right-censored data; and 2) application of a propensity score to adjust for variables that could be associated with both the exposure (attainment of SVR) and the outcome (cost). These adjustments are critical for balancing baseline factors that could bias the findings. Thus, contrary to the initial hypothesis, SVR produced no long-term cost savings in non-cirrhotic individuals.

It is imperative to note that the cost of the treatment year was excluded from these analyses, and thus the cost of the antiviral regimen did not contribute to the cost estimates. All patients included were treated with interferon-based regimens, although some received interferon in combination with first- or second-generation DAAs. The costs captured were global and not liver-specific and likely to be comprehensive given the integrated nature of the VA health system. Finally, although first generation DAAs were less effective than current DAAs, the means by which SVR was achieved should not affect post-SVR monitoring data if the treatment groups are comparable.

The data presented contribute to a relatively small and conflicting literature related to studies directly measuring health care costs after HCV therapy. In a smaller study of a private health plan claims dataset, Gordon et al. (9) identified a cost savings of approximately $500 per patient per month among non-cirrhotic patients and a savings of approximately $1,500 per patient per month among decompensated cirrhotic patients; nevertheless, no significant cost differences were identified between treated and untreated compensated cirrhotic patients.

The impact of SVR was not determined and the median follow-up was quite short, ~ 2 years. Manos et al (10) measured costs in the Kaiser Permanente Medical Program for up to 5 years after antiviral therapy comparing SVR to non-SVR and found non-SVR status to be associated with $2,648 per year greater costs than SVR achievers due to reduced outpatient healthcare utilization but used only limited adjustments for baseline utilization-related confounders that could have impacted these costs. Specifically, the authors only compared SVR to non-SVR without adjusting for the 3-fold higher rate of cirrhosis in the non-SVR group, and they also did not include untreated patients as controls. The present data suggest over longer time horizons that early improvements in healthcare utilization costs might be lost with longer follow-up in non-cirrhotic patients, emphasizing the importance of post-SVR monitoring.

The present study, thus, forces the field to reconsider estimates of cost-effectiveness of DAAs in non-cirrhotic hepatitis C patients from a payor perspective. Nonetheless, higher long-term costs do not undermine the medical/societal rationale to treat patients with hepatitis C to reduce transmission, improve work productivity, and eliminate the stigma of infection. Furthermore, the ‘sticker price’ for DAAs and treatment duration have plummeted while SVRs have increased in the last year, reducing the cost while improving the benefit offsets. Although the argument that achieving SVR saves long-term healthcare costs in non-cirrhotic patients may not hold water for now, additional post-SVR experience with the more effective, cheaper, and safer DAAs might more strongly favor treatment for almost all HCV-infected individuals.

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