Sticker Shock and the Price of New Therapies for Hepatitis C: Is it worth it?

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The new era of antiviral therapy for hepatitis C holds great promise to finally reign in a public health nightmare, but at what expense? It has been estimated that a 12 week course of therapy could cost in excess of $84,000. Much has been written in the lay press regarding the price of these newer therapies which has led to concerns about the ability of our health care system to effectively implement and deliver these treatments to those in greatest need.[1] Can we justify these costs? To better understand this, it is necessary frame the discussion in the context of the economic burden of chronic liver disease against the retail cost of therapy. Product price also reflects drug development and productions expense; however this is very difficult to access.

What is success and what is it worth? According to Oxford dictionary, success is the accomplishment of an aim or purpose.[2] In medicine, success can be hard to define. However, when it comes to hepatitis C therapy, sustained viral response (SVR) is a well-established surrogate for treatment success, and has been equated with a cure. Not only is SVR durable, with a less than 1% chance for late relapse, SVR has been associated with lower rates of liver cancer, cirrhosis, transplant and all-cause mortality. It leads to improved quality of life, lower risk of metabolic complications such as insulin resistance, improves glycemic control in those that are diabetic and recovers neurocognitive function. It is difficult to argue this is not success- both for the patient as well as society. How much is this worth? What is the price of prevention?

HCV is generally asymptomatic (and thus not a significant economic burden) until advanced liver disease occurs. This was confirmed by a recent study that

compared the economic burden for U.S. patients with chronic hepatitis C, stratified by severity of liver disease, in a large private health insurance claims database from 2003 to 2010. The database included claims for all prescription medications and all medical services submitted for payment. Researchers examined claims from 53,796 patients with chronic hepatitis C: 41,858 (78%) without cirrhosis, 3,718 (7%) with compensated cirrhosis, and 8,220 (15%) with end-stage liver disease. Overall, the annual health care costs were estimated to be $24,176 for patients with chronic hepatitis C infection. However, when examined by disease stage, advanced disease consumed a substantially larger proportion of the total. Average annual costs were $17,277 for patients with no cirrhosis, $22,752 among patients with well-compensated cirrhosis, and $59,995 among patients with end-stage liver disease - most of which was driven by inpatient care.[3] Patients with compensated cirrhosis may live for over a decade, accruing (by this model) over $270,000 in expense prior to developing end-stage liver disease. When HCV disease progresses to decompensated cirrhosis, transplant offers the best long-term prognosis, but this is not cheap. According to the United Network for Organ Sharing (UNOS)' Transplant Living Web site, the estimated U.S. average of billed charges per liver transplant in 2011 was $577,100.[4, 5]

Despite the risk of progression to advanced disease, most patients remain untreated. Based on two large US cohorts (Chronic Hepatitis Cohort Study: CHeCS and the National Health and Nutrition Examination Survey: NHANES) analyzed by the Division of Viral Hepatitis at the Centers for Disease Control and Prevention (CDC) only 13-18% of individuals chronically infected with HCV receive treatment.[6] Other studies support this abysmal treatment uptake. In another recent interrogation of a large healthcare payer database showed that only 10.9% of 57,084 HCV infected patients have received HCV therapy.[7]

It is possible that many of these patients are simply waiting for better treatment options. A common quandary is when to begin therapy. Traditionally, it is felt that

a cirrhotic patient has the most to gain from viral eradication, as SVR is associated with a lower risk of hepatic decompensation, liver cancer and need for transplantation.[8,9] Yet, at least with 2011 triple therapy, patients with cirrhosis are more likely to experience treatment-related side effects, early termination, and are least likely to attain SVR.[10] This experience is likely to improve with newer therapies. Alternatively, treating all patients with minimal fibrosis could prevent progression to advanced disease. This subset has a high probability of cure; yet, these patients are also least likely to develop HCV induced complications in the immediate future and some may never develop advanced disease. Predicting disease progression would be ideal, and baseline factors do contribute to the risk of disease progression. However, the absence of these factors cannot guarantee disease stability.

Still, it is well recognized that SVR can mitigate disease complications and, theoretically, the cost of end stage liver disease. Traditional interferon-based therapy has never been inexpensive. HCV therapy has evolved from standard interferon-alfa for 24 weeks, which offered a 6% SVR rate and would cost less than 20 thousand dollars today, to peginterferon and ribavirin (PEG/RBV) for 48 weeks, with SVR rates increasing to 40-60%[11], but also with doubled the price. With the approval in 2011 of HCV protease inhibitor direct-acting antivirals (DAA), efficacy improved, but the cost increased substantially to over 70 thousand dollars. Still, this price tag is out of context. When the <u>total cost</u> of therapy to achieve SVR is considered, including management of complications, the price of treatment actually increases to $172,889 to $188,859 per SVR.[11,12] The treatment cost *per SVR* may therefore be the most reasonable way to estimate the total cost impact of a new therapy. Those patients who relapse (become HCV negative but the disease recurs once treatment is discontinued) therefore cost the most - as they experience the longest duration of therapy for the least return.

The next wave of therapy (simeprevir and sofsbuvir) has again increased treatment efficacy, but the price tag is daunting. These agents shorten therapy

and are much more tolerable, but are only approved in combination with PEG and RBV for genotype 1. They are expected to accumulate some additional cost driven by side effects but monitoring and management of adverse events will likely be attenuated. Sofosbuvir is also available as an all oral therapy in combination along with RBV for genotype 2 and 3, and those genotype 1 that are interferon intolerant. But the longer duration necessary for many will further increase the treatment cost.

Is this cost exorbitant?

The price of medical care in the United States has never been a bargain. According to the World Health Organization (WHO), total health care spending in the U.S. was 17.9% of its GDP in 2011, the highest in the world [14] Of each dollar spent on health care in the United States, 31% goes to hospital care, 21% goes to physician/clinical services, and only 10% to pharmaceuticals.[15] Still prescription drug prices are higher in the U.S. than anywhere else in the world, and the pharmaceutical industry remains a highly profitable business.[16] Manufacturing costs do not drive drug prices, as the cost of producing a drug (exclusive of development) is relatively low. Companies typically price a medication based on development costs and demand, but largely demand. The logic is circular in that the escalated cost helps offset drug development and clinical trials. Investing in drug development ultimately saves money by saving lives and preventing hospitalizations.[17]

Although HCV treatment induces a fair amount of sticker shock, other approved medications are equally costly. HIV therapy averages 2000-5000 dollars a month, and given that it is a lifelong treatment, lifetime drug costs are more than one-half million dollars.[18] Several other drugs, including treatment for multiple sclerosis and anti-neoplastic agents, “cost more than a car”. However, the majority of these high-end agents are used for niche indications such as rare enzyme defects (Gaucher Disease) or uncommon conditions such as Hunter Syndrome and paroxysmal nocturnal hemoglobinuria.[19]

So how can appropriate costs be determined? The cost-effectiveness of an intervention can be calculated by applying a well-being scale, where a unit of health status expresses the output of a health intervention in the number of years and the health-related "quality of life" produced by a treatment.[20] Understanding both cost-effectiveness, as well as impact on the quality of life, is imperative for health policy and cost containment. Although this measure has not been performed for current HCV therapy, evaluation of other medical and surgical procedures suggest that *very cost-effective* interventions typically include those procedures costing less than $20,000; those ranging from $20,000 to $100,000 are *moderately cost-effective*; and interventions costing more than $100,000 are *possibly cost-effective*, but expensive for society.[21] It is difficult, however, to justify an intervention simply by a price tag. Some treatments may be equally effective but toxicity and complexity may make one a much better value.

Can we negotiate a better price? Although consumers have little ability to impact drug prices, drug companies do negotiate with payers and pharmacy benefit plans. Medicaid also negotiates lower prices, which is then offset by the manufacturer by increasing retail prices. Although other federal agencies can bargain with drug companies, by design Medicare is not permitted to negotiate prices.[22] In addition, Medicare participants often assume some out of pocket expense. Other payers receive rebates from companies, effectively lowering the price of the medication. Rebates are not reported, but they are one factor that explains the difference between a company's gross sales and net sales. There is no standardization for rebates, but the average size is approximately 30% of gross sales. Naturally, rebates are larger for drugs close to patent expiration or those with more significant competition.[23]

Most consumers are fortunate if their insurer negotiates a better price for them, and then, based on their plan, provides coverage for the medication with affordable co-pays and premiums. For consumers without insurance, or those who cannot afford their portion of the charges, assistance programs and co-pay

coupon programs often exist. [(www.MySupportPath.com)]

Still, it remains unanswered if the new agents are worth their price. In some conditions, first line therapy may be a less effective agent that is escalated to a superior but more expensive therapy if it fails to control the disease. When treating viral hepatitis, this strategy is irresponsible. As described above, patients who relapse or fail a course acquire the most cost. They pay for a full course of therapy and experience all of the side effects, but fail to clear the infection. Although we have learned to use interferon and ribavirin effectively, these agents have side effects that can be life threatening. Failing therapy may also make future treatment more difficult, either through possible viral resistance or lack of approved treatment options. Cost is important, but effective safe therapy is paramount.

HCV therapy is most effective if there is adequate treatment uptake, but several barriers exist in addition to the price tag. Patients and providers do not want interferon-based therapy. Until an all-oral-option is widely available, access to physicians willing to treat HCV will be a barrier. Even if a doctor is interested in prescribing interferon, the inevitable availability of all-oral options is widely publicized and patients will be resistant to starting older stigmatized treatments.

The primary consumer of HCV therapy will shift as birth cohort screening increases HCV recognition. Most baby boomers will be insured through Medicare, which is financed through U.S. Treasury trust funds, payroll taxes, income taxes and funds authorized by congress (again tax dollars) .[24] HCV is also more prevalent in lower socioeconomic groups which are either uninsured or insured through Medicaid- also a tax burden. The University of Alabama recently undertook a massive screening project in their emergency room. Here HCV testing was offered to all birth cohort ER customers who were unaware of their HCV status. After the first 1287 subjects, they found a 12% prevalence of positive anti-HCV of which 72.5% were HCV RNA positive. They also found that the prevalence was much higher in those either uninsured or insured with

public/Medicaid (17% for each). Those with Medicare had an 11% prevalence where as those privately insured had only a 4% prevalence. They hope to screen over 7000 individuals and identify over 800 with positive HCV antibody.[25] It is easy to see how this will be a financial burden on our health care system. But if these individuals fail to be linked to a provider willing to administer HCV therapy, or if HCV therapy is out of reach due to barriers such as cost, the potential health care burden in the long run is even higher.

Thus, although DAA therapy may be $1000 a pill, SVR is arguably priceless.

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