Public Health

EASL JOURNAL OF HEPATOLOGY

Optimizing HCV treatment – Moving beyond the cost conundrum

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Received 14 November 2015; received in revised form 28 January 2016; accepted 4 February 2016

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When is it appropriate to delay a potentially lifesaving treatment? Should treatment decisions be based purely on economic grounds? In the United States, these questions confront payers and government programs covering patients with hepatitis C virus (HCV) infection. New, highly effective oral treatments for this serious infection have recently received food and drug administration (FDA) approval in the U.S. but their list prices make immediate treatment of all infected patients infeasible. In response, many payers have instituted coverage policies that authorize treatment only for the sickest patients, putting off therapy for less severely ill patients. However, new data suggests that this approach may constitute a suboptimal policy, if not carefully executed. While not all patients require immediate treatment, an optimal strategy should treat patients before they progress too far towards end-stage disease; beyond the point when even highly effective treatments can confer only diminished benefit. Minimally invasive clinical markers of disease progression should be monitored to help guide when treatment should be initiated.

Hepatitis C is an infection of the liver caused by the HCV, which is generally transmitted by blood-to-blood contact. Historically, HCV was spread through blood transfusions but thanks to universal screening the current most frequent mode of infection relates to drug abuse and dirty needles [1–5]. HCV affects approximately 130–170 million persons worldwide [6] and roughly 2.7 million Americans [1,7,8].

Patients with chronic hepatitis C (CHC) are generally asymptomatic and so remain unaware of their illness until a diagnosis is made incidentally, or severe liver disease develops [9,10]. Approximately 20–30% of infected patients will develop cirrhosis after 20 years [6]. Once cirrhosis occurs, hepatocellular carcinoma (HCC) develops in approximately 4% of these patients per year [11]. Overall, liver complications represent a substantial public health burden. Although screening of the blood supply and drug abuse prevention efforts have helped to dramatically reduce the incidence of new hepatitis C infections, the aging population of already infected patients steadily experiences severe HCV complications such as cirrhosis, liver failure, hepatocellular carcinoma, and death [12–18].

Until 2014, treatment for HCV relied on interferon-alpha (IFN-α) based regimens, ordinarily including ribavirin and (more recently) a protease inhibitor – either boceprevir or telaprevir [19]. Those regimens had numerous unsatisfactory characteristics, including a long duration of treatment (often 24–48 weeks), and severe, nearly universal side effects such as fatigue, flu-like symptoms, and depression [20–22]. Needless to say, treatment completion rates were poor, with both dose reduction (35–42%) and discontinuation (14–19%) common [21,22]. Of those that did complete treatment, less than 50% achieved a sustained virologic response (SVR) [23]. Our recent analysis of data from the US Veterans Affairs health care system found that only 25% of HCV patients initiated therapy and only 16% of the treated patients achieved any viral response [24].

Beginning in 2014, novel oral treatment regimens with vastly superior characteristics became available. Unlike the IFN-α regimens, which rely on upregulating the patients' own immune system, these direct acting agents block various key stages of viral replication. Currently approved drugs include Harvoni (sofosbuvir/ledipasvir), Daklinza (daclatasvir), Olysio (simeprevir), Sovaldi (sofosbuvir), Technivie (ombitasvir, paritaprevir and ritonavir) and Viekira Pak (ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets) [25]. Specific treatment regimens vary, depending on factors such as HCV genotype, and may incorporate multiple drugs (potentially including ribavirin) [26]. Recommended treatment intervals are generally 12 weeks for patients without cirrhosis, and 24 weeks for cirrhotic patients. Side effects are much less common, and generally less severe [27,28]. Treatment success rates are also much higher: SVR rates achieved in FDA Stage 3 clinical trials generally exceeded 90%, although real-world rates may be somewhat lower [29,30]. Our previous study using VA data clearly documents that merely attaining an initial viral load response is associated with

reduced risk of complications associated with chronic HCV infection, such as cirrhosis, HCC, liver transplant, or death [31].

Unfortunately, the cost of these new drugs, at their U.S. Wholesale Acquisition Cost (i.e., list prices), creates both an affordability challenge, and a "value for money" dilemma. While the cost per treated patient remains roughly the same as with the previous interferon based regimens, demand for them is many times higher. The undiscounted price for a 12 week course of Solvaldi is $84,000; for Harvoni it is $95,000. Some regimens also require drug combinations that drive the price still higher. Even if we assume a discounted treatment cost, after price re-negotiation, of $50,000 per patient, treating every HCV positive patient in the U.S. would cost in the order of $200 Billion. This compares to total annual U.S. spending on all prescription drugs of around $300 Billion [32]. Of course, successful treatment should avert many late HCV complications, but even if treatment actually proves cost saving in the long run, it remains simply too expensive to treat all patients immediately.

This high upfront cost of treatment represents a key barrier, despite the fact that recent studies suggest treatment is generally quite cost-effective. Benefits also include an up to 80% reduction in progression to end-stage complications, such as liver failure, liver cancer, or liver transplantation [33]. Cost effectiveness studies suggest that for treatment naive patients with genotype 1 infections (the most common genotype), incremental cost effectiveness ratios (ICERs) range from cost saving (i.e., $0/per Quality Adjusted Life-Year (QALY)) up to $31,453/per QALY. Treatment for other genotypes and more complicated treatment scenarios appears less cost-effective, with ICERs often well in excess of $100,000/QALY. However, those ratios improve significantly when price discounts are incorporated [34]. In addition to the direct benefits, large scale HCV treatment should also significantly reduce the incidence of both new infections and re-infections by shrinking the pool of infectious persons who can transmit the disease through needle sharing or other blood-borne contact. One recent modeling study that considered both disease progression and transmission suggested that treating all diagnosed patients (assumed to be 50% of the total HCV infected population) provides the most net economic and health benefits over ten years – significantly exceeding the costs of treatment. Only treating the most severely affected patients, by comparison, generated negative net economic and health benefits. [35]

Both economic questions – treatment affordability and cost effectiveness – hinge on drug price. This cost conundrum is certainly not unique to HCV drugs. For example, a similar debate is now beginning over coverage for the new PCSK9 inhibitors for elevated cholesterol [36]. The issue is particularly acute in the United States, compared with Europe, given the decentralized structure of our drug markets, and higher average drug prices. The U.S. pricing market is neither transparent, nor efficient: In the U.S., healthcare payers represent a patchwork of private, not for profit, and various governmental entities. Each entity, or their contracted pharmacy benefits manager, must negotiate price discounts with pharmaceutical companies separately. Those price agreements are generally subject to confidentiality clauses. Equally significant, negotiations on price usually require granting that drug 'preferred' status, limiting the ability of payers to offer unrestricted access to more than one treatment option. A further complication is that some government entities, especially the Medicare program, are barred from any innovation which restricts open access to services including the implementation of competitive bidding systems. Fortunately, most Medicare part D plans which cover more than 37 million beneficiaries, can negotiate price individually, leading to significant variation in prices paid among the over 1,000 part D plans [37]. In short, while Europe has opted for more global price controls, the U.S. system constitutes a more piecemeal approach to negotiating prices and access. Since demand for drugs is generally quite inelastic (insensitive) to pricing, resulting U.S. drug prices are roughly double those in Europe [38].

Numerous solutions to the U.S. price issue have been proposed. For example, Schulman and colleagues [39], when considering the a potential impact on annual drug spending, suggest several options: mandating greater patient cost sharing; instituting direct government negotiation of prices; restricting the indications for covering a drug to only those patients most likely to benefit; adopting international reference (i.e., average) pricing; and promoting re-importation of drugs from lower cost countries. While space precludes a full discussion of each option, implementing any of them in the U.S. would require overcoming significant financial, regulatory, and political challenges.

The issue of when to treat is still further complicated by U.S. payers' incentives to 'cost shift'. This is driven by the fact that while the treatment costs needed to 'cure' a patient's HCV infection are incurred immediately, the health and economic benefits accrue much later. Patients often switch between health plans, driven by changes in employment, residence, and program eligibility [40]. This creates an incentive for payers to delay treatment for low risk patients – essentially betting that many will dis-enroll before becoming seriously ill. This is a common economic problem, not unique to drug treatment