Effectiveness Research in the Evolving HCV Landscape

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As antiviral therapy for chronic hepatitis C virus (HCV) infection continues to evolve, understanding the effectiveness of antiviral regimens is critical for making informed treatment decisions for HCV management. While the terms “efficacy” and “effectiveness” are often used interchangeably, they hold different meanings: Efficacy is a measure of the capacity of a treatment to produce the desired effect in a controlled environment, such as in a randomized controlled trial whereas effectiveness describes the actual effect of the treatment in practice [1]. In HCV antiviral clinical trials, like other clinical trials, patients are screened using stringent predetermined criteria, closely monitored, and any treatment deviations must follow detailed protocols. As such, information provided in traditional randomized clinical trials is often limited when applied to clinical practice where variation of patient characteristics, setting, care coordination, and management cannot be controlled. These elements are likely to influence the magnitude of the effect in practice depending on who is treated, how they are treated, which conditions are being treated and other nuances. Effectiveness studies, which examine effects (outcomes) in actual practice, provide practical information to address the “where,” “how,” and “for whom” a treatment might be recommended depending on the questions addressed, patient population, groups compared, setting, and measured outcomes. Though the

randomized controlled trial is often held up as the “gold standard” for medical decision making, truly informed decision making requires information obtained from clinical practice.

In this issue of *Digestive Diseases and Sciences*, Price et al. [2] examine real-world treatment outcomes in a comparative effectiveness study of boceprevir and telaprevir in an insured US HCV-infected population. In this large integrated care setting, those undergoing treatment initiation were frequently cirrhotic and treatment-experienced groups, groups usually underrepresented in clinical trials of boceprevir and telaprevir. Almost a third of patients in this study discontinued treatment prematurely, most often patient-initiated and commonly related to adverse effects. Sustained virological response (SVR) rates were notably lower than reported in clinical trials: 48–54 % for boceprevir-based regimens and 31–67 % for telaprevir-based regimens depending on prior HCV treatment experience and stage of liver disease. The findings underscore the differences between “real-world” HCV care experiences and clinical trials. The observed SVR rates serve as further documentation of the decrement in effectiveness when moving from the clinical trial to clinical practice.

With current advances in HCV treatment and approval of newer, better tolerated, and less complex regimens, the use of boceprevir and telaprevir regimens is expected to be greatly reduced. Yet, results from this study and other comparative effectiveness studies are still useful. The differences observed in this study with regards to patient characteristics, early treatment discontinuations, adverse effects, and lower SVR rates reflect the differences between clinical trials and clinical practice. Perhaps more importantly, it demonstrates that providers, patients, and payers need to appropriately temper expectations about

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outcomes when new medications are approved and used in real-world settings.

This study brings to light another essential issue regarding for whom HCV treatment is being initiated. Compared to the overall pool of treatment-eligible patients in this cohort, those that initiated treatment were more likely to be cirrhotic, which the authors suggest was due to treatment prioritization based partly on illness severity. Despite the urgency to treat patients with more advanced HCV disease in clinical practice—and the reality that this population represents a substantial proportion of those who are actually being treated—clinical trials often include very few such patients and thus applicability of clinical trial outcomes to these key populations is limited. For example, in clinical trials of currently approved direct-acting antivirals for genotype 1 infection, cirrhosis was present in only 4–17 % of sofosbuvir patients enrolled, 10–15 % of simeprevir patients, 9–11 % of boceprevir patients, and 6–23 % of telaprevir patients, with most study arms having less than 30 cirrhotic patients included [3–10]. Effectiveness studies may thus provide the only data needed to predict outcomes in these challenging populations where clinical trial data is lacking.

Results of this effectiveness study and other similar studies further highlight difficulties of completing HCV treatment in “real-world” settings. Without the additional resources that generally accompany clinical trial participation, patients, and providers may be less willing or able to endure adverse effects, complex treatment regimens, and frequent clinic visits, culminating in a lower threshold for stopping therapy. This has been particularly true for those with cirrhosis who are more likely to experience adverse effects and less likely to tolerate therapy, thus leading to early treatment discontinuation [11, 12]. So few patients with advanced HCV disease have been included in HCV antiviral clinical trials, the extent of adverse effects, and poor tolerability in patients with cirrhosis had not been recognized before these effectiveness studies.

Consistently lower SVR rates have been reported in real-world cohorts with peginterferon/ribavirin-based regimens and with boceprevir- and telaprevir-based regimens. Historically, SVR rates in genotype 1 patients treated with peginterferon/ribavirin dual therapy in actual clinical practice have been 15–25 % lower than reported in clinical trials [13, 14]. As reported by Price et al. and noted in other “real-world” cohorts evaluating boceprevir- and telaprevir-based regimens, overall SVR rates were 4–20 % lower than those reported in clinical trials [15–18]. The observed differences in SVR rates likely reflect the diverse HCV-infected population treated in “real-world” practice, many of whom would never meet stringent clinical trial screening criteria and would never qualify for clinical trial enrollment due to existing comorbidities, laboratory abnormalities, or

social issues. Such factors highlight the challenges associated with HCV treatment in routine clinical practice and may explain why clinical trial results do not always translate to other HCV care settings. Thus, providers, patients, and payers should have realistic expectations that SVR rates may be lower than predicted from clinical trials and recognize that comparative effectiveness outcomes may better reflect the outcomes that will be attained in the populations actually being treated.

Given the extraordinary costs of newer agents and the associated burden on the healthcare system, adjusting cost-effectiveness models based on these comparative effectiveness data could potentially identify specific patient populations where boceprevir or telaprevir regimens may be comparable to newer HCV antiviral regimens. This may be particularly relevant as payers grapple with economic realities which may necessitate continued use of boceprevir or telaprevir, particularly in resource-constrained settings. It is conceivable that insurers may use tiered systems for managing costs which could include boceprevir- or telaprevir-based regimens.

The rapidly changing environment surrounding HCV antivirals and the FDA breakthrough therapy designation granted to several HCV agents including sofosbuvir, sofosbuvir/ledipasvir, daclatasvir, asunaprevir, and the triple drug direct acting combination ABT-450/r-ombitasvir and dasabuvir, means medications are being approved much more quickly and on the basis of preliminary clinical evidence. In such an environment, providers, patients, and payers will often be faced with making decisions on the basis of small or incomplete clinical data. By the time sufficient numbers of patients receiving a particular regimen can be accrued in clinical practice in order to assess effectiveness, that regimen will be supplanted by newer medications. We have seen this already with boceprevir and telaprevir regimens. With the imminent expected approval of new agents, we are likely to see this same phenomenon with simeprevir and some sofosbuvir-based regimens as well. Given this rapid pace and the number of HCV antiviral agents currently under investigation, not to mention appealing off-label combinations, it will be difficult to produce timely comparative effectiveness data before the field has moved on. By the time comparative effectiveness data can be evaluated, many will view it as outdated. Yet, “real-world” experiences are essential to provide practical information that may better inform HCV treatment decisions in this highly segmented drug market.

In summary, the comparative effectiveness study by Price et al. represents an important high-quality evaluation that explores outcomes with direct-acting agents in a “real-world” community-based setting. It highlights practical experiences, key issues, and outcomes that are not always sufficiently examined in clinical trials but will continue to

be relevant to future HCV regimens. It provides the opportunity to assess cost-effectiveness more accurately given the economic realities with newer HCV agents that may preclude their use. These results serve as a reminder to the HCV community that since efficacy and effectiveness are not interchangeable, the differences between clinical trials and clinical practice are many, are important, and should not be overlooked.

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Conflict of interest None.

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