THE OREGON STATE DRUG REVIEW©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter

August 2014 Volume 4, Issue 6

New Hepatitis C Antiviral Therapies: How should they be used in clinical practice?

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Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and death from liver disease in the United States.[1] The goal of treatment is reduction of cirrhosis, hepatocellular carcinoma, decompensated hepatic disease, liver failure, liver transplant and mortality.[2] Since the 2013 approval of sofosbuvir (SOF) (Solvaldi®) and simeprevir (SMV) (Olysio®), there has been active debate about which patients should receive them due to their high cost. The purpose of this newsletter is to provide evidence for efficacy and safety of these new agents, and identify who is most likely to benefit from treatment.

Progression of HCV is generally slow, but varies significantly among individuals. Over 20 to 30 years, approximately 5% to 20% of individuals who develop chronic HCV infection will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer. [2] Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis. Patients with cirrhosis are at risk of progressing to decompensation, hepatocellular carcinoma or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease and prolonging graft survival in liver transplant recipients. For high risk patients, SOF and SMV show the most benefit in terms of liver events avoided.[3]

Prior standard of care (pegylated interferon (PEG)-based treatment) had lower efficacy rates, high risk for adverse events, difficult administration and high patient burden. Newer treatments were developed to alleviate these limitations. However, this added benefit comes at a significant cost. The wholesale acquisition cost (WAC) of SOF was set at $1,000 per tablet, which translates into $84,000 for 12 weeks of treatment and $168,000 for 24 weeks of treatment.[4] Although therapeutic regimens for other diseases can be just as costly, the sheer number of people afflicted with hepatitis C infection magnifies the issue of cost. Policymakers and clinicians alike are waiting to see if these known and possible other benefits outweigh the cost to the healthcare system.

Sofosbuvir and Simeprevir

Treatment response is measured by the absence of virus (sustained virological response) for 24 weeks (SVR24) or 12 weeks (SVR12) after stopping treatment. SVR has been associated with reduction of virus-related morbidity and mortality and there is evidence that a SVR is equivalent to HCV infection cure.[5,6] HCV genotype 1 (G1) comprises 73% of U.S. chronic HCV cases and has a lower response rate to therapy than genotypes 2 and 3.[7] Short term evidence has shown improved response rates with SOF and SMV compared to previous standard of care (Table 1) in the treatment naive.[2] Still, there is limited evidence directly comparing newer regimens to the older.

Table 1: Response Rates of Hep C FDA Approved Treatment Regimens[2]

Virus Genotype	Treatment Regimen	Response Rate*
Genotype 1	PEG/RBV Dual Therapy x 48 weeks	45%
	PEG/RBV + BOC or TVR Triple Therapy	65-70%
	SOF + PEG + RBV x 12 weeks	89%
	SOF + RBV x 24 weeks	68%
	SOF + SMV +/- RBV 12-24 weeks	90-100%
Genotype 2	PEG/RBV x 24 weeks	75%
	SOF + RBV x 12 weeks	82-95%
Genotype 3	PEG/RBV x 24 weeks	75%
	SOF + RBV x 24 weeks	84%

PEG-pegylated interferon, RBV-ribavirin, BOC-boceprevir, TVR-telaprevir, SOF-sofosbuvir, SMV-simeprevir, *SVR-sustained virological response (12 or 24 wks post tx)

The Oregon Center for Evidence-based Policy recently evaluated the efficacy and safety of SOF for chronic HCV treatment.[2] The available evidence is comprised of ten studies; eight published and two unpublished. However, the majority of the studies are non-comparative and all but one was found to have a high risk of bias. Studies were small, and included few patients that were of clinical interest with less than 14% having cirrhosis and around 10% of African American ethnicity. None of the trials compared SOF to standard of care in HCV G1 patients, and they excluded those patients under 18 years of age, patients with HIV or HBV co-infection, significant alcohol or drug use in the past year, current excessive alcohol use, significant renal (eGFR <60 mL/min), cardiac, pulmonary, or uncontrolled chronic diseases (hypertension and diabetes). The SVR rates in these studies may be strongly influenced by a majority of study of patients having favorable prognostic factors. The relapse rate was not always reported, and trials were not consistent with how they defined relapse. Relapse rates ranged from 5% to 28%, including patients who were fully treated with the SOF regimen.[2]

To date, there are no studies looking at the long-term side effects associated with SOF.[2] The current safety of SOF treatment is based on small studies of short duration with healthier patients than those found in the general HCV population. The adverse events most commonly reported were nausea, fatigue, headache, rash, insomnia, and pain. Overall, discontinuation of active treatment due to adverse events was relatively low in clinical studies (1.4% in patients treated with SOF + RBV).[2] Longer and larger studies or post-marketing follow up data are needed to accurately assess safety.

SMV is a direct-acting-antiviral (DAA) with the same mechanism of action as BOC and TVR, but offers the advantage of being dosed once daily and posing less significant safety concerns. SMV is only FDA approved for use as a triple therapy regimen including PEG and RBV. SMV demonstrated SVR rates ranging from 60-86% and recent studies have shown that SMV triple therapy results in a higher SVR rate compared to PEG plus RBV dual therapy in chronic HCV G1 patients.[8,9] However, with the pipeline of regimens moving away from PEG-based treatment due to side effects, higher discontinuation rates and disease progression, the place in therapy of SMV triple therapy seems limited.

The combination of SMV and SOF has been evaluated and is supported by expert opinion based guidelines.[10] Currently, this recommendation is based on only one small, open-label, randomized, poor quality phase IIa study (COSMOS) evaluating the combination in previous null responders and treatment naïve HCV G1 patients (n=167) with METAVIR F0-F2 fibrosis (Cohort 1) or F3-F4 (Cohort 2).[11] SVR 12 rates in Cohort 1 ranged from 79.2% to 100%, and from 92.6% to 100% in Cohort 2, regardless of whether or not the patient received RBV. More randomized controlled trials evaluating this off-label combination are needed to adequately assess the efficacy and safety in this patient population.

Readiness Assessment and Patient Education

Due to the complexity of the disease and treatment regimens, many psychosocial factors can potentially interfere with treatment adherence, and effectiveness, therefore incurring unnecessary and significant costs. There are higher rates of psychiatric and substance use disorders and cognitive impairment (risk factors for non-adherence) in persons with chronic HCV infection than in the general population.[12] Mental health issues, particularly depression and anxiety disorders, and treatment of addiction should be assessed and managed before initiating treatment. In addition, HCV treatment side effects often result in early treatment discontinuation which reduces rates of cure. The term "readiness" is highlighted as an important concept in an individual's decision-making to undergo treatment, but there is little consensus on its definition.

The use of an initial assessment for readiness to treat has been studied. However, most of the literature occurs in the prison setting[13–15] or in those

with HCV/HIV co-infection.[16–18] Still, standardized protocols or treatment guidelines are lacking. Primary care providers can assess if a patient with chronic HCV is ready for referral to a specialist, as well as identify areas for readiness improvement while waiting to start treatment. The primary topics to address include alcohol and substance use, mental health, and life stability and/or major life events. Validated screening tools such as the SBIRT (http://www.sbirtoregon.org/screening.php) can be used. In addition, it is valuable to assess the willingness of a patient to comply with treatment and all related screening and appointments through a patient consent program.

Key patient educational points include the following: 1) Avoid using alcohol, 2) Avoid using illicit drugs, 3) Get vaccinated for Hepatitis A and B, 4) Talk to your healthcare provider before taking any medications, including over-the-counter and vitamins, 5) Eat a healthy diet, and 6) Work with your healthcare provider in controlling all underlying comorbid illnesses including psychiatric issues. Providing patients with moderate behavioral changes to protect liver health will enable them to be prepared for treatment when it is appropriate.

Ideal Candidates for New Hepatitis C Antiviral Therapy

New guidelines recommend the prioritization of HCV patients for treatment based on disease severity, including those patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations.[19,20] Since the next generation of all oral hepatitis C therapy will be available soon, the goal is to identify those patients who need treatment with the current regimens in the next 6-12 months in order to avoid poorer outcomes if treatment is delayed. The Oregon evidence-based policy report recommends using the study inclusion and exclusion criteria to help select patients who are more likely to respond.[2] Common exclusion criteria included decompensated cirrhosis, significant alcohol or drug use within the past 12 months, significant cardiac or pulmonary disease. However, this is based on a lack of evidence in these populations and clinical opinion might help fill in some of these gaps.

Based on clinical expertise from local hepatologists, patient groups who are at higher risk if not treated includes cirrhotic patients (Fibrosis stage 4) without ongoing progressive decompensation (MELD score between 8 and 11), HCV/HIV co-infected patients with cirrhosis (Stage 4), patients with extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulinemia, lymphoma), and HCV infection in the transplant setting (post-transplant with stage 4 fibrosis and pre-transplant in those who it is essential to eradicate the virus). However, there is a lack of evidence in these patient populations so an analysis of risk versus benefit, as well as cost should be involved in the treatment determination. The Oregon prior authorization criterion that prioritizes these high-risk groups can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html.

Conclusion

The slow course of disease progression for those at a lower baseline risk provides ample time for clinicians to select those patients that are most likely to respond and get value from a treatment response with SOF and SMV. Though these recently approved regimens seem to have improved efficacy, much is not known about their safety and their effectiveness in a more heterogenous population than in the clinical trials. The pipeline of medications for the treatment of HCV is extremely robust with newer PEG-free and SOF containing combination therapies expected to be approved in 2014 and 2015. The evidence gaps along with the high cost of these regimens make it prudent to adequately assess patients for readiness to treat and prioritize treatment based on disease severity and risk of progression.

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References

1. Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R. *Treatment for Hepatitis C Virus Infection in Adults*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. Available at: http://www.ncbi.nlm.nih.gov/books/NBK115347/. Accessed July 18, 2013.
2. Leof A, Thielke A, King V. Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.
3. Van der Meer AJ, Hansen BE, Fattovich G, et al. Reliable prediction of clinical outcome in patients with chronic HCV infection and compensated advanced hepatic fibrosis: a validated model using objective and readily available clinical parameters. *Gut*. 2014. doi:10.1136/gutjnl-2013-305357.
4. U.S. Food and Drug Administration Approves Gilead's Sovaldi™ (Sofosbuvir) for the Treatment of Chronic Hepatitis C | Gilead. Available at: http://www.gilead.com/news/press-releases/2013/12/us-food-and-drug-administration-approves-gileads-sovaldi-sofosbuvir-for-the-treatment-of-chronic-hepatitis-c. Accessed July 16, 2014.
5. Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med*. 2013;158(2):114-123.
6. Pearlman, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis*. 2011;52(7):889-900.
7. Zeuzem S. Heterogeneous virologic response rates to interferon-based therapy in patients with chronic hepatitis C: who responds less well? *Ann Intern Med*. 2004;140(5):370-381.
8. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir With Peginterferon and Ribavirin Leads to High Rates of SVR in Patients With HCV Genotype 1 Who Relapsed After Previous Therapy: A Phase 3 Trial. *Gastroenterology*. 2014;146(7):1669-1679.e3. doi:10.1053/j.gastro.2014.02.051.
9. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2014. doi:10.1016/S0140-6736(14)60538-9.
10. American Association for the Study of Liver Diseases / Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014. Available at: http://www.hcvguidelines.org/full-report-view.
11. Jacobsen I. ABSTRACT: SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1treatment-naïve and prior null responder patients: The COSMOS study. *Hepatology*. 2013;6(58):1379A-1380A.
12. Weiss JJ. (2012) Psychosocial Readiness Evaluation and Preparation for Hepatitis C Treatment: PREP-C. Oral Presentation at the Seventh International Conference on HIV Treatment and Prevention Adherence, Miami, Florida. www.iapac.org.
13. Post JJ, Arain A, Lloyd AR. Enhancing assessment and treatment of hepatitis C in the custodial setting. *Clin Infect Dis*. 2013;57 Suppl 2:S70-74. doi:10.1093/cid/cit265.
14. Yap L, Carruthers S, Thompson S, et al. A descriptive model of patient readiness, motivators, and hepatitis C treatment uptake among Australian prisoners. *PLoS ONE*. 2014;9(2):e87564. doi:10.1371/journal.pone.0087564.
15. Lloyd AR, Clegg J, Lange J, et al. Safety and effectiveness of a nurse-led outreach program for assessment and treatment of chronic hepatitis C in the custodial setting. *Clin Infect Dis*. 2013;56(8):1078-1084.doi:10.1093/cid/cis1202.
16. Wagner G, Osilla K, Garnett J, et al. Provider and patient correlates of provider decisions to recommend HCV treatment to HIV co-infected patients. *Journal of the International Association of Physicians in AIDS Care*. 2012;11(4):245-51. doi:http://dx.doi.org/10.1177/1545109712444163.
17. Osilla K, Wagner G, Garnett J, et al. Patient and provider characteristics associated with the decision of HIV coinfected patients to start hepatitis C treatment. *AIDS Patient Care & Stds*. 2011;25(9):533-8. doi:http://dx.doi.org/10.1089/apc.2011.0048.
18. Wagner G, Ryan G. Hepatitis C virus treatment decision-making in the context of HIV co-infection: the role of medical, behavioral and mental health factors in assessing treatment readiness. *AIDS*. 2005:190-8.
19. European Association for the Study of the Liver (EASL). Recommendations on Treatment of Hepatitis C. 2014.
20. World Health Organization. Guidelines for the Screening, Care and Treatment of persons with Hepatitis C Infection. April 2014.