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The Quest For A Cure For Hepatitis C -The End Is In Sight

Marc G. Ghany, MD, MHSc[1], **Naveen Gara, MD**[2]

[1]Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Washington, DC

[2]Division of Gastroenterology, Washington Hospital Center, Washington, DC

Chronic hepatitis C virus (HCV) infection affects an estimated 170 to 200 million persons or ~2% to 3% of the global population.[1,2] Chronic HCV infection accounts for 30% of all cases of cirrhosis and 25% of hepatocellular carcinomas worldwide and over 350,000 deaths annually.[3] Successful eradication of HCV has been associated with a reduction in these adverse outcomes.[4] However, less than 50% of subjects infected with HCV genotype 1, the most common genotype in the world, could be cured with a regimen consisting of peginterferon alpha and ribavirin. The development of several new classes of antiviral compounds termed direct acting antivirals (DAAs) has revolutionized the treatment of chronic HCV infection. These agents target key steps in the viral life cycle and are potent inhibitors of viral replication. In 2011 the first two DAAs, boceprevir or telaprevir, were approved for use in combination with peginterferon and ribavirin for the treatment of chronic HCV genotype 1 infection. These two drugs are specific inhibitors of the HCV NS3/4A serine protease and are associated with improved response rates. When administered for 24 or 48 weeks, the duration depending on the initial response and severity of underlying disease, lead to sustained viral clearance in 66% to 75% of subjects with HCV genotype 1 infection.[5,6] However, the use of these first generation protease inhibitors are associated with significant side effects, greater than those attributable to peginterferon alpha and ribavirin alone, including death in patients with compensated cirrhosis. Moreover, the pill burden is high, the regimens are complex requiring intensive monitoring and they have numerous drug-drug interactions-factors that have limited their widespread use.

In a very short span of time, multiple new agents targeting other viral or host proteins critical for HCV replication have been developed that hold the promise for safer and more effective therapy for chronic HCV infection.[7] In *The Lancet*, results from two phase three trials of one such drug, simeprevir, are presented.[8,9] Simeprevir also belongs to the class of HCV NS3/4A serine protease inhibitors but has the advantage of once daily dosing. In the two studies that are presented, the same study design was utilized to assess the safety and efficacy of simeprevir. Previously never treated subjects with chronic HCV genotype 1 infection were randomized 2:1 to receive simeprevir or placebo plus peginterferon alpha and ribavirin for 12 weeks followed by peginterferon alpha and ribavirin for an additional 12 (total duration 24 weeks) or 36 weeks (total duration 48 weeks) in the simeprevir group,

Contact Information for Corresponding Author Marc G. Ghany, MD, MHSc, Staff Physician, Bldg 10, Room 9B-16, 10 Center Drive, MSC 1800, Bethesda, MD 20892-1800, USA, Tel 301-402-5115, Fax 301-402-0491, marcg@intra.niddk.nih.gov.

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based on how rapidly the virus was cleared at weeks 4 and 12 of therapy (response-guided therapy), or an additional 36 weeks in the placebo group (total duration 48 weeks). The primary endpoint of the trial was the proportion of subjects who had a viral level that was undetectable or <25 IU/ml target detectable 12 weeks after stopping therapy-so called sustained virological response at week 12 (SVR_{12}). The results of the studies were remarkably similar. In both trials the SVR_{12} rate with the simeprevir regimen was significantly higher compared to the control regimen of peginterferon alpha and ribavirin, 80% versus 50% in Quest1[8] and 81% versus 50% in Quest 2.[9] In addition, a majority of subjects in both studies qualified for the shorter duration of therapy, 80% in Quest 1 and 90% in Quest 2. Subjects who had baseline factors traditionally associated with a poorer response to peginterferon alpha and ribavirin, such as male gender, high baseline viral load (>800,000 IU/ml) and the less favorable genotype of IL28B gene (CT or TT) which encodes for interferon-lambda-3,[10] experienced higher SVR_{12} rates with the simeprevir regimen compared to the control regimen. Notably, the presence of a genetic polymorphism within the HCV NS3 region, Q80K, was associated with a reduced response to simeprevir in subjects with HCV subtype 1a with compared to those without the polymorphism, 58% versus 84% and to patients with HCV subtype 1b, 58% versus 85%. The presence of this polymorphism reduced the effectiveness of simeprevir among subtype 1a patients such that the SVR_{12} rate between patients with subtype 1a was similar to that of the control group that received peginterferon alpha and ribavirin, 58% versus 52%, respectively. Simeprevir was generally well tolerated in both trials and the incidence and severity of adverse events were similar to the peginterferon and ribavirin arm. The most common adverse events were headache, fatigue, pyrexia and influenza-like illness. Adverse events that were higher in the simeprevir group were mostly dermatological in nature and included pruritus, rash and photosensitivity and elevated indirect bilirubin levels. Two deaths occurred one related to colon cancer and one unknown that was suspected to be a pulmonary embolism.

On-treatment virological failure was observed in 7% to 9% and virological relapse in 9% to 13% of simeprevir treated patients in both trials. The majority of subjects (>92%) who failed a simeprevir-containing regimen developed viral variants that conferred resistance to simeprevir predominantly involving amino acid changes at positions 80, 122, 155, and 168 within the NS3 region. Long-term data on the persistence of these variants was not provided but long-term follow studies of patients who developed boceprevir or telaprevir resistance associated variants suggest that most are replaced by wild type virus over a period of one year.[11–14] A clinical study has demonstrated that prior boceprevir and telaprevir treatment failures could be successfully cured with a regimen consisting of a HCV polymerase inhibitor in combination with a NS5A replication complex inhibitor which suggests that simeprevir failures in theory could be rescued with a similar regimen.[15]

Based on the results of these two trials, and a third phase 3 trial, PROMISE, which evaluated simeprevir with peginterferon and ribavirin in previously treated patients who had responded and relapsed,[16] simeprevir gained regulatory approval in the U.S., Canada, Japan and Russia. It has received market authorization in Europe and is awaiting final approval from the European Commission. Simeprevir was approved as a component of a combination antiviral treatment regimen for previously untreated and treated subjects with chronic HCV infection meaning it could be combined with agents other than peginterferon and ribavirin.

The approved regimen dispensed with the need for response-guided therapy and instead two fixed durations were recommended based on prior treatment exposure.[17] Where does this regimen fit in our therapeutic armamentarium against hepatitis C? This regimen clearly represents an improvement over first generation protease-based therapy in that it is less complicated, appears to be well tolerated and has high efficacy. However, we have limited information on how this regimen will perform in patients who are more difficult to treat such as Blacks and those with cirrhosis as the trials only included 6% to 10% Blacks and 7% to 12% of subjects had cirrhosis. In addition, the regimen appears to have no advantage over peginterferon and ribavirin for genotype 1a subjects with baseline Q80K polymorphism. This is a particular issue for the U.S. population where the prevalence of the Q80K polymorphism is estimated to be around 48% among persons with HCV genotype 1a but less of an issue for the European population where the prevalence is estimated to be much lower, 5%.[18] A second regimen consisting of sofosbuvir, a NS5B polymerase inhibitor, in combination with peginterferon alpha and ribavirin, was approved around the same time as simeprevir in the U.S. and has a similar safety and efficacy profile with a duration of only 12 weeks.[19] Which of these interferon sparing regimens to recommend for a HCV genotype 1 subject should be left to the healthcare provider and patient to decide based on a through discussion of the risks and benefits of each regimen.

These advancements in therapy for HCV genotype 1 subjects are overshadowed by the rapid development of interferon free and ribavirin-free regimens. These regimens have virological cure rates in excess of 90% for most HCV genotypes regardless of which combinations of agents are used or the baseline characteristics of the patients and should be available by the end of 2014 and early 2015.[20–25] These therapies will have the advantage of much simpler schedules with once daily dosing without the need for complicated monitoring or response guided therapy, shorter duration of therapy and less side effects and will undoubtedly replace currently approved treatment. This should allow many more subjects who have contraindications to current regimens to receive therapy. Indeed, in the U.S. simeprevir is already being combined with sofosburvir either together or with ribavirin for a period of 12 or 24 weeks as off-label therapy for patients with HCV genotype 1 infection who require urgent therapy and have contraindications to or intolerance of peginterferon. Results of a small phase 2 trial of sofosbuvir and simeprevir have reported excellent tolerability and high efficacy ranging between 80%–100%.[26,27]

Excitement with the progress made in therapy must be tempered by the significant public health challenges that remain in order to reduce the burden of disease caused by chronic HCV infection. First and foremost of which is identifying the substantial number persons with undiagnosed infection and second getting patients access to care. Toward this end, the World Health Organization has issued its first ever guidance on the screening, care and treatment of persons with chronic HCV infection.[28] It is sobering to note that the majority of cases of chronic HCV infection reside in countries of the world with limited resources to diagnose and treat chronic HCV infection.[2] It would be ironic and a travesty of the health care system if patients who were not eligible for currently approved therapies because of substantial side effects remain ineligible to receive simpler, better tolerated treatment due to issues of access to care and cost. The challenge for policy makers will be how to bring affordable care to the persons who need them. This will require the coordinated effort of

many entities from both the public and private sectors. Steps are being taking toward this lofty goal and fortunately the quest for a simple, safe, pangenotypic cure is coming to an end.

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References:

1. Hepatitis C--global prevalence (update). Wkly Epidemiol Rec 2000;75:18–9. [PubMed: 10686829]
2. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333–42. [PubMed: 23172780]
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–128. [PubMed: 23245604]
4. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. Jama 2012;308:2584–93. [PubMed: 23268517]
5. Poordad F, McCone J Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195–206. [PubMed: 21449783]
6. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405–16. [PubMed: 21696307]
7. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. N Engl J Med 2013;368:1907–17. [PubMed: 23675659]
8. Jacobson IM, Dore GJ, Foster GF et al. Simeprevir (TMC 435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naive patients: The Phase 3, randomised, double-blind, placebo-controlled QUEST-1 trial. Lancet 2014.
9. Manns MP, Marcellin P, Poordad F et al. simeprevir (TMC 435) with peginterferon alpha-2a or alpha-2b/ribavirin for the treatment of chronic HCV genotype 1 infection in treatment-naive patienrs: QUEST-2, a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2014.
10. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399–401. [PubMed: 19684573]
11. Kieffer TL, De Meyer S, Bartels DJ, et al. Hepatitis C viral evolution in genotype 1 treatment-naive and treatment-experienced patients receiving telaprevir-based therapy in clinical trials. PLoS One 2012;7:e34372. [PubMed: 22511937]
12. Sullivan JC, De Meyer S, Bartels DJ, et al. Evolution of treatment-emergent resistant variants in telaprevir phase 3 clinical trials. Clin Infect Dis 2013;57:221–9. [PubMed: 23575197]
13. Barnard RJ, Howe JA, Ogert RA, et al. Analysis of boceprevir resistance associated amino acid variants (RAVs) in two phase 3 boceprevir clinical studies. Virology 2013;444:329–36. [PubMed: 23876458]
14. Susser S, Vermehren J, Forestier N, et al. Analysis of long-term persistence of resistance mutations within the hepatitis C virus NS3 protease after treatment with telaprevir or boceprevir. J Clin Virol 2011;52:321–7. [PubMed: 21924672]
15. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211–21. [PubMed: 24428467]
16. 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.
17. http://www.olysio.com/shared/product/olysio/prescribing-information.pdf. Accessed April 17th, 2014.

18. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM371623.pdf. Accessed April 17th, 2014.
19. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878–87. [PubMed: 23607594]
20. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. N Engl J Med 2014.
21. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483–93. [PubMed: 24725238]
22. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. N Engl J Med 2014.
23. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. N Engl J Med 2014.
24. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin. N Engl J Med 2014;370:1594–603. [PubMed: 24720703]
25. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin. N Engl J Med 2014;370:1604–14. [PubMed: 24720679]
26. Jacobson IMGR, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: the COSMOS study. Hepatology 2013;58:LB3.
27. Lawitz EGR, Rodriguez-Torres M, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype-1 prior null-responder/treatment-naive patients (COSMOS study): primary endpoint (SVR12) results in patients with METAVIR F3–4 (Cohort 2). Journal of Hepatology 2014;60.
28. http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1. Guidelines For The Screening, Care And Treatment Of Persons With Hepatitis C Infection April 2014. Accessed April 17th, 2014.