Treatment of hepatitis C in patients with HIV

Published Online
July 10, 2015
http://dx.doi.org/10.1016/S2352-3018(15)00128-9
See Online/Articles
http://dx.doi.org/10.1016/S2352-3018(15)00114-9

An estimated 185 million people worldwide and 3·2 million people in the USA are infected with chronic hepatitis C virus (HCV),[1] which remains a leading cause of progressive liver disease, cirrhosis, hepatocellular cancer, and liver transplantation in the USA.[2] During the next decade, deaths related to HCV are predicted to increase, and the proportion of patients with cirrhosis is expected to rise.[3] Recently, treatment for HCV has shifted to highly effective combination all-oral, interferon-free directly acting antiviral therapy characterised by short treatment durations of 8–24 weeks, low pill burdens, and few side-effects.[4,5] Because of shared routes of transmission, HCV is more common in patients with HIV infection than in those without. Co-infection is associated with high HCV viral loads, high rates of cirrhosis and decompensated liver disease, high mortality, poor response to interferon-based treatment (achieving lower rates of sustained virological response [SVR]), and more adverse reactions than is HCV monoinfection.[6,7]

In the past year, several phase 2 and 3 studies have shown that with interferon-free directly acting antiviral therapy, patients with HIV can be treated for HCV as effectively as patients without HIV. The NIAID ERADICATE (in treatment-naive patients with HCV genotype 1, without cirrhosis) and ION-4 (in treatment-experienced patients with HCV genotypes 1 and 4, with or without cirrhosis) trials showed efficacy of 12 weeks of ledipasvir (NS5A inhibitor) plus sofosbuvir (NS5B inhibitor)—a regimen free of both interferon and ribavirin.[8,9] TURQUOISE-1, another phase 3 trial, assessed the efficacy of ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), ritonavir, dasabuvir (NS5B polymerase inhibitor), and ribavirin.[10] Finally, ALLY-2 assessed 12 weeks of sofosbuvir plus daclatasvir (NS5A inhibitor) in patients with HCV genotypes 1–4.[11] These studies have paved the way to expansion of HCV treatment eligibility for patients with HIV and HCV co-infection.

In *The Lancet HIV*, Jürgen Rockstroh and colleagues[12] report the findings of the C-EDGE CO-INFECTION trial. In this open-label, single-arm, multicentre study, 12 weeks of treatment with the pan-genotypic fixed-dose combination tablet of grazoprevir, a second-generation NS3/4A protease inhibitor, and elbasvir, an NS5A inhibitor, achieved SVR 12 weeks after the end of therapy (SVR12) in 210 (96%) of 218 patients with HIV and HCV genotype 1, 4, or 6 infection (97% per protocol). This regimen further expands the range of directly acting agents for effective treatment of HCV in patients with HIV co-infection. Notably, grazoprevir plus elbasvir has been investigated in two other studies: one in patients with chronic kidney disease stage 4 or 5, and another that included a small cohort of patients with HCV genotype 3 infection. Both studies reported SVR12 rates of more than 90%, suggesting that a wide range of patients could benefit from this regimen.[13,14]

Despite the high rates of SVR reported with all these regimens, the major restriction in the treatment of patients with HIV and HCV co-infection remains the drug interactions between antiretroviral therapy (ART) and directly acting antiviral agents: in the C-EDGE trial, only specific combincations of ART were allowed. This limitation leaves clinicians with the unresolved challenge of how to best treat their patients on different ART regimens. Furthermore, most clinical trials, including C-EDGE, have treated patients with mean CD4 counts of more than 500 cells per µL with complete HIV suppression. The US Centers for Disease Control and Prevention estimates that only 30% of people living with HIV in the USA are virally suppressed;[15] therefore, a more likely scenario for most community clinicians is a patient with less well controlled HIV but in need of HCV treatment. With the necessary support, even individuals with less than well controlled HIV disease might successfully engage and complete HCV therapy based on directly acting antiviral agents. Should we, as clinicians, consider initiation of HCV therapy for newly diagnosed patients even before ART initiation? This approach would certainly represent the next frontier in the treatment of patients with HIV and HCV co-infection worldwide.

In summary, the pan-genotypic efficacy, ribavirin-free, and favourable renal profile makes grazoprevir plus elbasvir a welcome addition to the treatment options for HCV. The availability of greater choice is crucial at a time when health-care policy makers worldwide are attempting to address the conundrum of universal access to HCV drugs. The findings of the C-EDGE trial augment those of others, in that they support the similar efficacy of directly acting antiviral agent

regimens for treatment of all patients irrespective of HIV status. Perhaps the time has come for all future clinical trials of HCV therapy based on directly acting antiviral agents to integrate patients with HIV co-infection.

*Lydia Tang, *Shyam Kottilil*
Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD 21201, USA
skottilil@ihv.umaryland.edu

We declare no competing interests.

1 Mohd Hanafiah K, Groeger J, Flaxman AD, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; **57:** 1333–42.
2 Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144:** 705–14.
3 Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138:** 513–21.
4 Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370:** 1889–98.
5 Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014; **370:** 1983–92.
6 Thomas DL, Astemborski J, Vlahov D, et al. Determinants of the quantity of hepatitis C virus RNA. *J Infect Dis* 2000; **181:** 844–51.
7 Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001; **33:** 562–69.
8 Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA* 2015; **313:** 1232–39.
9 Naggie S, Cooper C, Saag M, et al. Ledipasvir/sofosbuvir for 12 weeks in patients coinfected with HCV and HIV-1. Annual Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; Feb 23–26, 2015. Abstract 152LB.
10 Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA* 2015; **313:** 1223–31.
11 Wyles D, Ruane P, Sulkowski M, et al. Daclatasvir in combination with sofosbuvir for HIV/HCV coinfection: ALLY-2 study. Annual Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; Feb 23–26, 2015. Abstract 151LB.
12 Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised open-label trial. *Lancet HIV*; published online July 10. http://dx.doi.org/10.1016/S2352-3018(15)00114-9.
13 Roth D, Nelson D, Bruchfeld A, et al. C-SURFER: grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. 50th Annual Meeting of the European Association for the Study of the Liver; Vienna, Austria; April 22–26, 2015. Abstract LP02.
14 Poordad F, Lawitz E, Gutierrez J, A, et al. C-SWIFT: Grazoprevir/elbasvir + sofosbuvir in cirrhotic and noncirrhotic, treatment-naive patients with hepatitis C virus genotype 1 infection, for durations of 4, 6, or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. 50th Annual Meeting of the European Association for the Study of the Liver; Vienna, Austria; April 22–26, 2015. Abstract O-006.
15 Centers for Disease Control and Prevention. Vital signs: HIV diagnosis, care, and treatment among persons living with HIV—United States, 2011. *MMWR Morb Mortal Wkly Rep* 2014; **63:** 1113–17.