HCV/HIV Co-infection: Risks and Treatment Options

OVERVIEW

Liver disease is the leading cause of non-AIDS related death among persons infected with human immunodeficiency virus (HIV).[1] An important cause of liver-related mortality in this population is hepatitis C virus (HCV) co-infection, which affects an estimated 4-5 million people worldwide, including more than 250,000 persons in the United States.[2,3] Patients with HCV/HIV co-infection have a 35% higher risk of mortality compared to persons with HIV monoinfection,[4] and among persons with HCV infection who have an AIDS diagnosis, the relative risk of mortality increases to 50%.[5]

Hepatitis and hepatic fibrosis progress more rapidly among patients with HCV/HIV co-infection compared with patients who have HIV mono-infection, which increases the risk of cirrhosis, end-stage liver disease, hepatocellular carcinoma, and liver-related death in the absence of transplantation.[6,7] Although sustained virologic response (SVR) is the goal of HCV treatment, patients with HCV/HIV co-infection often have low rates of SVR when treated with the standard HCV therapy of pegylated interferon plus ribavirin (pegIFN/ribavirin).[8-12] However, there has been a rapid emergence of new therapies for both HCV mono-infection and HCV/HIV co-infection.[13] A number of clinical trials of direct-acting antiviral agents for HCV and HCV/HIV are underway or have recently reported clinically significant results.[14-19]

The epidemiology of HCV also is evolving. Although injection drug use remains the primary mode of transmission, sexual transmission – once considered rare for HCV – has increased, particularly among certain subgroups of HIV-positive men who have sex with men (MSM).[19-22] A recent retrospective study reported a 1.6% annual incidence of HCV/HIV co-infection among MSM, the highest rate ever reported by studies of MSM in the United States.[23] Molecular studies indicate that HCV/HIV co-infected patients have higher rates of T-cell activation and exhaustion compared with persons who are healthy or mono-infected with either virus, and this difference may account for increased levels of HCV viremia seen in persons with HIV infection.[24,25] It is thought that increased viremia, in turn, increases the likelihood of HCV transmission during high-risk sexual activities.[19,25]

Clinicians must stay abreast of changes in the epidemiology and treatment of HCV/HIV co-infection to be able to best diagnose and treat this condition. However, studies indicate that substantial knowledge and practice gaps persist among clinicians who treat HCV and HCV/HIV co-infection. This continuing medical education program will educate physicians, pharmacists, nurses, and other health care professionals about the prevalence, pathology, risk factors, current therapies, and new drug development efforts for patients co-infected with HCV and HIV.

RESEARCH REVIEW (EXCERPT)

From 1998 until recently, pegIFN/ribavirin was the standard treatment for HCV infection.[26] However, therapeutic outcomes have been suboptimal for many patients with HCV/HIV co-infection due to therapeutic contraindications, low rates of treatment initiation, and reported SVR rates of approximately 14-30%.[9-13,27-29]

In the past several years, direct-acting antiviral agents have shown promise for the treatment of both HCV mono-infection and HCV/HIV co-infection.[14] However, these protease inhibitors also are associated with adverse events and drug interactions in co-infected patients, and more data are needed on their potential to achieve SVR in this population.

Multiple direct-acting antivirals are being investigated for HIV/HCV co-infection. Notable findings from these studies and ongoing late-stage trials of interest are summarized here.

Boceprevir

- Boceprevir targets the nonstructural NS3 protease of HCV, which plays major role in virus replication.[30]

- In May 2011, boceprevir was the first protease inhibitor approved by the FDA to be used in combination with pegIFN/ribavirin for the treatment of chronic HCV genotype 1 infection.[31]

- In April 2012, the FDA recommended against co-therapy with boceprevir and certain ritonavir-boosted HIV protease inhibitors due to the risk of decreased efficacy secondary to CYP3A4/5 inhibition.[32]

- In a phase IIa study, 98 patients with HIV/HCV were randomly assigned to 4 weeks of pegIFN/ribavirin followed by 44 weeks of combination therapy of 800 mg boceprevir every 8 hours (n = 64) or placebo (n = 34) plus pegIFN/ribavirin.[14,33] The results showed that 12 weeks after ending boceprevir plus pegIFN/ribavirin therapy, 61% of patients with HIV/HCV co-infection had SVR (defined as undetectable HCV RNA), compared with 27% of patients receiving pegIFN/ribavirin only. Virologic breakthrough occurred in 9% of patients during treatment with boceprevir, and relapse occurred in 5% of patients after therapy ended.

- An interim analysis was reported in March 2013 of a phase II trial to assess the efficacy and safety of efficacy and safety of boceprevir plus pegIFN/ribavirin in HCV/HIV co-infected patients who previously failed pegIFN/ribavirin therapy.[18] Researchers reported that up to week 16, response rates and tolerability profiles were similar between the two therapies.

- Boceprevir is associated with higher rates of anemia and gastrointestinal symptoms in patients with HCV and HIV compared to HCV-monoinfected patients.[34]

GAP ANALYSIS (EXCERPT)

Practice Gap	Type of Gap	Learning Objective	Desired Outcome
Health providers must understand risk factors for progression of HCV disease in order to evaluate and select appropriate treatments.[35] Providers lack current data on the pathology and progression of HCV/HIV co-infection and do not believe study findings apply to their own patients.[36]	Knowledge	Describe the pathology of HCV/HIV co-infection and its effects on progression of hepatic disease, severity, and mortality.	Clinicians understand the importance of early diagnosis of HIV/HCV co-infection and the need to educate patients about appropriate disease management.

REFERENCES

1. Price JC, Thio CL. Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol. 2010 Dec;8(12):1002-12.
2. Curry M. HIV and hepatitis C virus: special concerns for patients with cirrhosis. J Infect Dis. 2013 Mar;207 Suppl 1:S40-4.
3. WHO. Factsheet 164: Hepatitis C. 2012.
4. Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. Clin Infect Dis. 2009;49:1605–15.
5. Branch AD, Van Natta ML, Vachon ML, Dieterich DT, Meinert CL, Jabs DA; Studies of the Ocular Complications of AIDS Research Group. Mortality in hepatitis C virus-infected patients with a diagnosis of AIDS in the era of combination antiretroviral therapy. Clin Infect Dis. 2012 Jul;55(1):137-44.
6. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology 1999;30:1054-8.
7. Seeff LB. Natural history of chronic hepatitis C. Hepatology. 2002;36:S35-S46.
8. Núñez M, Miralles C, Berdún MA, et al; PRESCO Study Group. Role of weight-based ribavirin dosing and extended duration of therapy in chronic hepatitis C in HIV-infected patients: the PRESCO trial. AIDS Res Hum Retroviruses. 2007;23:972-82.
9. Shire NJ, Welge JA, Sherman KE. Response rates to pegylated interferon and ribavirin in HCV/HIV coinfection: a research synthesis. J Viral Hepat. 2007;14:239-48.
10. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004;351:438-50.
11. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004;292:2839-48.
12. Chung RT, Andersen J, Volberding P, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004;351:451-9.
13. Sulkowski MS. J Infect Dis. Current management of hepatitis C virus infection in patients with HIV co-infection. 2013 Mar;207 Suppl 1:S26-32.
14. Dieterich D, Soriano V, Nelson M, Rockstroh J, Arasteh K, Bhagani S, Talal A, Tural C, Vinisko R, Kort J. STARTVerso 4: High Rates of Early Virologic Response in Hepatitis C Virus Genotype 1/HIV Co-infected Patients Treated with Faldaprevir + Pegylated Interferon and Ribavirin. Conference on Retroviruses and Other Opportunistic Infections; Atlanta, GA. March 3-6 2013, [Paper #40LB]
15. Martel-Laferriere V, Brinkley S, Bichoupan K, Posner S, Stivala A, Perumalswami P, Schiano T, Sulkowski M, Dieterich D, Branch A. On-treatment Responses to Telaprevir-based Hepatitis C Treatment Are Similar in HIV/Hepatitis C Virus Co-infected and Hepatitis C Virus Mono-infected Patients. Conference on Retroviruses and Other Opportunistic Infections; Atlanta, GA. March 3-6 2013, [Paper #679]
16. Benito JM, Bichoupan K, Soriano V, Maida I, Branch A, Sanchez C, Rallon N, Aguilera A, Barreiro P, and Dieterich D. Triple Combination Therapy for Hepatitis C with Telaprevir Exhibits Higher Early Antiviral Potency than with Boceprevir Regardless HIV Status. Conference on Retroviruses and Other Opportunistic Infections; Atlanta, GA. March 3-6 2013, [Paper #676]
17. Poizot-Martin I, Bellissant E, Piroth L, Renault A, Quertainmont Y, Rosenthal E, Alric L, Guyader D, Bourliere M, Molina JM, and ANRS-HC27 BOCEPREVIH Study Group. ANRS-HC27 BocepreVIH Interim Analysis: High Early Virologic Response with Boceprevir + Pegylated Interferon + Ribivirin in Hepatitis C Virus/HIV Co-infected Patients with Previous Failure to Pegylated Interferon + Ribivirin. Conference on Retroviruses and Other Opportunistic Infections; Atlanta, GA. March 3-6 2013, [Paper #37]

18. Dieterich DT, Rockstroh J, Orkin C, Gutierrez F, Klein M, Reynes J, Jessner W, Lenz O, Peeters M, Beumont-Mauviel M. Simeprevir with Pegylated Interferon/Ribavirin in Patients Co-infected with Chronic Hepatitis C Virus and HIV-1: Week-24 Interim Analysis of the TMC435-C212 Study. Conference on Retroviruses and Other Opportunistic Infections; Atlanta, GA. March 3-6 2013, [Paper #154LB]
19. Centers for Disease Control and Prevention (CDC). Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men--New York City, 2005-2010. MMWR Morb Mortal Wkly Rep. 2011 Jul 22;60(28):945-50.
20. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS 2007; 21:983–91.
21. Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS 2009; 23:F1–7.
22. Matthews GV, Pham ST, Hellard M, et al. Patterns and characteristics of hepatitis C transmission clusters among HIV-positive and HIVnegative individuals in the Australian trial in acute hepatitis C. Clin Infect Dis 2011; 52:803–11.
23. Garg S et al. Prevalent and incident hepatitis C virus infection among HIV-infected men who have sex with men engaged in primary care in a Boston community health center. Clin Infect Dis, online edition, 2013.
24. Feuth T, Arends JE, Fransen JH, Nanlohy NM, van Erpecum KJ, Siersema PD, Hoepelman AI, van Baarle D. Complementary role of HCV and HIV in T-Cell activation and exhaustion in HIV/HCV coinfection. PLoS One. 2013;8(3):e59302.
25. Matthews-Greer JM, Cladito GC, Adley SD, et al. Comparison of hepatitis C viral loads in patients with or without human immunodeficiency virus. Clin Diagn Lab Immunol 2001;8:690-4.
26. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335-74.
27. Thomas DL. The challenge of hepatitis C in the HIV-infected person. Annu Rev Med 2008;59:473-8.
28. Mehta SH, Lucas GM, Mirel LB, et al. Limited effectiveness of antiviral treatment for hepatitis C in an urban HIV clinic. AIDS 2006;20:2361-9.
29. Mehta SH, Genberg BL, Astemborski J, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health 2008;33:126-33.
30. Njoroge FG, Chen KX, Shih NY, Piwinski JJ. Challenges in modern drug discovery: a case study of boceprevir, an HCV protease inhibitor for the treatment of hepatitis C virus infection. Acc Chem Res. 2008 Jan;41(1):50-9.
31. FDA. Prescribing and labeling information for Victrelis (boceprevir). Accessed April 10, 2013. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails
32. FDA Drug Safety Communication: Updated information on drug interactions between Victrelis (boceprevir) and certain boosted HIV protease inhibitor drugs. Accessed April 10 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm301616.htm
33. Sulkowski MS, Pol S, Cooper C, Fainboim H, Slim J, Rivero A, Laguno M, Thompson S, Wahl J, Greaves W. Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV-coinfected patients: end of treatment (week 48) interim results. Conference on Retroviruses and Other Opportunistic Infections; Seattle, WA. March 5-8 2012, [Abstract #47]
34. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364:1195-1206.
35. Tran TT. Overview of epidemiology, diagnosis, and disease progression associated with hepatitis C. Am J Manag Care. 2012 Dec;18(14 Suppl):S335-9.
36. Lekas HM, Siegel K, Leider J. Challenges facing providers caring for HIV/HCV-coinfected patients. Qual Health Res. 2012 Jan;22(1):54-66.