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Simeprevir

Updated: January 18, 2018.

OVERVIEW

Introduction

Simeprevir is an oral, direct acting hepatitis C virus (HCV) protease inhibitor that is used in combination with other antiviral agents in the treatment of chronic hepatitis C, genotypes 1 and 4. Simeprevir has been linked to isolated, rare instances of mild, acute liver injury during treatment and to occasional cases of hepatic decompensation in patients with preexisting cirrhosis.

Background

The hepatitis C virus is a small RNA virus that is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma in the United States as well as worldwide. Various approaches to antiviral therapy of chronic hepatitis C have been developed, starting in the 1980s with interferon alfa which was replaced in the 1990s by long acting forms of interferon (peginterferon), to which was added the oral nucleoside analogue, ribavirin. Between 2010 and 2015, several potent oral, direct acting anti-HCV agents were developed and combinations of these found to have marked activity against the virus, allowing for highly effective therapy without use of interferon with treatment courses of 12 to 24 weeks only. These direct acting agents included HCV protease (NS3/4) inhibitors, structural replication complex (NS5A) inhibitors and the HCV RNA polymerase (NS5B) inhibitors. The HCV protease inhibitors block the activity of the viral encoded protease that is essential in the posttranslational modification of the viral polypeptide, cleaving it into a series of structural and nonstructural (NS: enzyme) regions. The HCV proteases that have been developed are polypeptide-like molecules, modified amino acids that that resemble the specific amino acid sequence that the protease cleaves and act as competitive inhibitors of the protease enzyme. At least four HCV protease inhibitors (all having the suffix: previrs) have been approved for use in the United States: boceprevir [2012], telaprevir [2012], simeprevir [2013] and paritaprevir [2014].

Simeprevir (sim e' pre vir) was the third HCV protease inhibitor to become clinically available for therapy of hepatitis C. Like other HCV protease inhibitors, simeprevir blocks the activity of the viral encoded protease (HCV nonstructural [NS] region 3/4) that is essential in the posttranslational modification of the viral polypeptide that is cleaved into a series of structural and nonstructural (enzyme) regions. When used by itself, it results in rapid inhibition of HCV RNA levels, but resistance develops rapidly in a high proportion of patients. When combined with peginterferon and ribavirin, it was shown to provide a sustained inhibition of HCV RNA with a low rate of antiviral resistance. When given for 24 to 48 weeks, triple therapy using simeprevir increased the sustained virological response (SVR) rate from 40% to 50% (peginterferon and ribavirin alone) to 65% to 75% in patients with genotype 1. Even higher rates of response were found when simeprevir was combined with the HCV polymerase inhibitor sofosbuvir in an all-oral, interferon free regimen for 12 weeks. Simeprevir was approved for use in the United States in 2013 for patients with chronic hepatitis C, genotypes 1 and 4, in

combination with peginterferon and ribavirin or as an all-oral regimen with sofosbuvir. Simeprevir is available in 150 mg capsules under the brand name Olysio (formerly TMC435), and the recommended dose is 150 mg once daily for 12 weeks. Common side effects include rash, photosensitivity, pruritus, nausea, headache, muscle aches and abdominal discomfort.

Hepatotoxicity

In large randomized controlled trials, simeprevir was not linked to an increased rate of serum enzyme elevations during treatment or with instances of clinically apparent liver injury. Simeprevir causes a mild increase in serum indirect bilirubin and some patients became visibly jaundiced, but the bilirubin elevations were generally mild, transient and not associated with changes in serum aminotransferase or alkaline phosphatase levels. After its approval and more wide scale use, however, simeprevir has been implicated in at least one case of an acute hepatitis (Case 1). The latency to onset was 7 weeks and pattern of injury was hepatocellular without immunoallergic or autoimmune features. Recovery was rapid and complete once therapy was stopped.

In addition, simeprevir, in combination with other agents, has been linked to instances of acute, seemingly spontaneous decompensation of HCV related cirrhosis. The role of simeprevir as opposed to the other HCV antivirals used in combination was often unclear. Rates of hepatic decompensation during simeprevir combination therapy of cirrhosis due to hepatitis C was approximately 2% to 3% when combined with peginterferon and ribavirin, and 0.5% to 1.0% when used with sofosbuvir. Because of the risk of decompensation, patients with cirrhosis who are treated with antiviral regimens (both all-oral and interferon based) should be monitored for evidence of worsening liver disease, particularly during the first 4 weeks of treatment. This complication is probably more common in patients with more advanced liver disease, Child's Class B cirrhosis and those with a previous history of liver decompensation.

Likelihood score: D (possible rare cause of clinically apparent liver injury in susceptible individuals).

Mechanism of Injury

The mechanism by which simeprevir might cause liver injury is not known. It is metabolized in the liver largely via the cytochrome P450 system, predominantly CYP 3A and it is an inhibitor of the drug transporters P-glycoprotein and OATP1Ba/3 and the efflux transporters MDR1, MRP2 and BSEP, perhaps accounting for the indirect hyperbilirubinemia that occurs in some patients. Simeprevir is associated with drug-drug interactions and it can raise levels of some statins. The decompensation that occurs with simeprevir combination therapy may be due to a direct effect of the agent, or else represent a usual complication of the rapid eradication of HCV infection. Finally, the episodes of decompensation may be incidental and unrelated to the antiviral therapy.

Outcome and Management

Combination antiviral regimens with peginterferon and ribavirin are now rarely used, largely because of the superior efficacy and better tolerance of all-oral regimens for hepatitis C. The oral regimen of sofosbuvir and simeprevir, while highly effective, is more expensive than other equally effective oral regimens. Because of the risk of hepatic decompensation in patients with preexisting cirrhosis, particularly those with a prior history of hepatic decompensation, regular monitoring is recommended for patients with hepatitis C related cirrhosis undergoing antiviral therapy, particularly during the first 4 weeks. Therapy should be suspended if signs or symptoms of hepatic failure arise such as marked rises in serum bilirubin (both direct and indirect) and any worsening of ascites, hepatic encephalopathy or prolongation of the prothrombin time. There is no evidence for cross sensitivity to liver injury among the various oral antiviral agents used to treat hepatitis C.

Drug Class: Antiviral Agents, Hepatitis C Agents, HCV Protease Inhibitors

CASE REPORTS

Case 1. Acute hepatitis during therapy of chronic hepatitis C with simeprevir, peginterferon and ribavirin.

[Modified from: Igawa T, Fushimi S, Matsuo R, Ikeda F, Nouso K, Yoshino T, Nakatsukasa H. Severe liver injury associated with simeprevir plus pegylated interferon/ribavirin therapy in a patient with treatment-naïve genotype 1b hepatitis C virus: a case report. Clin J Gastroenterol 2014; 7: 465-70. PubMed Citation]

A 65 year old Japanese man with chronic hepatitis C, genotype 1b, developed fatigue and abdominal bloating and was found to have worsening of serum aminotransferase levels 49 days after starting triple antiviral therapy with simeprevir [100 mg orally, once daily], peginterferon [100 µg subcutaneously, each week] and ribavirin [400 mg orally, twice daily]. Serum ALT which had fallen on antiviral therapy rose to 768 U/L with a serum bilirubin of 3.3 mg/dL, alkaline phosphatase 171 U/L, INR 1.2 and albumin 3.8 g/dL (Table). He had no previous history of liver disease other than hepatitis C which was attributed to a blood transfusion 45 years previously and for which he had not been previously treated. He also had a history of heavy alcohol use, but had stopped five years previously. His other medical conditions included diabetes for which he was taking voglibose (an alpha glucosidase inhibitor) and glimepiride (a sulfonylurea), and hyperuricemia for which he was taking allopurinol. All of his medications he had taken for more than a year and he denied use of other over-the-counter medications or nutritional or herbal supplements. Physical examination showed no evidence of fever or rash, and an eosinophil count was normal (1.2%). Tests for hepatitis A, B, C and E were negative as were tests for acute EBV and CMV infection. Both ANA and SMA were negative and serum globulins were not elevated. Imaging of the liver by ultrasound showed no evidence of biliary obstruction or masses. A liver biopsy showed evidence of acute hepatocellular injury superimposed upon on chronic hepatitis, but did not suggest autoimmune hepatitis. Antiviral therapy was suspended, and he improved rapidly. One month later, his symptoms had resolved and all liver tests, including ALT levels, were normal. He remained HCV RNA negative and was ultimately considered to have a sustained virologic response despite the early discontinuation of therapy.

Key Points

Medication:	Simeprevir, peginterferon and ribavirin
Pattern:	Hepatocellular (R ratio=18)
Severity:	Moderate (jaundice and hospitalization)
Latency:	7 weeks
Recovery:	1 month
Other medications:	Ursodiol, voglibose, glimepiride and allopurinol chronically

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	HCV RNA (IU/mL)	Other
Day 0	0	301	185	1.6	1.3 million	Therapy started
Week 4	0	23		1.7	None	Routine monitoring
Week 7	0	768	171	3.3	None	Admission
Week 12	5 weeks	20	166	1.1	None	Asymptomatic
Normal Values		**<40**	**<360**	**<1.2**	**None**	

Comment

A man with known chronic hepatitis C for many years developed an asymptomatic worsening of disease with ALT rising to 301 U/L, for which reason he was started on combination therapy of simeprevir with peginterferon and ribavirin, a regimen that was available and approved for use in Japan. He did well for the first six weeks of treatment and was HCV RNA negative when tested at 4 weeks. After 7 weeks, however, he developed nonspecific symptoms of fatigue and was found to have marked elevations in ALT and mild jaundice. Thorough evaluation found no evidence of other forms of liver disease and he was, indeed, still negative for HCV RNA. He improved rapidly once antiviral therapy was stopped and all liver tests had returned to normal one month later. Fortunately, his HCV infection did not relapse and he appeared to have achieved an SVR with other 7 weeks of treatment. This was a very convincing case of liver injury due to the antiviral therapy. Because he was receiving three agents, one cannot say for sure which one was responsible, but attributing it to simeprevir appears appropriate.

Case 2. Acute hepatic decompensation in a patient with chronic hepatitis C and cirrhosis during therapy with simeprevir and sofosbuvir.

[Modified from Case 1 in: Stine JG, Intagliata N, Shah NL, Argo CK, Caldwell SH, Lewis JH, Northup PG. Hepatic decompensation likely attributable to simeprevir in patients with advanced cirrhosis. Dig Dis Sci 2015; 60: 1031-5. PubMed Citation]

A 56 year old man with chronic hepatitis C, genotype 1a, and Child's Class B cirrhosis developed worsening fatigue, anorexia and jaundice 4 weeks after starting oral therapy with simeprevir and sofosbuvir. He had a history of excessive alcohol use, but had stopped drinking years before. He had been treated with peginterferon and ribavirin for hepatitis C on two occasions in the past, without a significant response and had undergone transjugular intrahepatic portosystemic stent shunting (TIPSS) two years previously because of refractory ascites and esophageal varices. He was evaluated for liver transplantation, having a MELD score of 17 with serum bilirubin 5.3 mg/dL, ALT 29 U/L, INR not given. He received approval for pretransplant, compassionate use therapy with the all oral antiviral regimen of sofosbuvir and simeprevir (doses not provided). He had a rapid virological response becoming HCV RNA negative by week 4. However, the total serum bilirubin level rose concurrently to 6.6 by week 2 and 28.0 mg/dL by week 4, at which point the antiviral drugs were stopped (Table). His MELD score subsequently rose to 36, the INR to 4.4 and he underwent successful emergency liver transplantation 4 weeks after stopping therapy. In follow up, he remained HCV RNA negative, suggesting a SVR despite therapy for only 4 weeks.

Key Points

Medication:	Simeprevir and sofosbuvir
Pattern:	Unknown (alkaline phosphatase not given)
Severity:	Fatal (liver transplantation)
Latency:	4 weeks
Recovery:	None
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	HCV RNA (IU/mL)	Other
Day 0	0	29	52	5.3	Present	Therapy started
2 Weeks	0			6.6		

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	HCV RNA (IU/mL)	Other
4 Weeks	0	90	229	28.0	None	
8 Weeks	4 weeks	Normal	Normal	14.2	None	Liver transplantation
Normal Values		**Not Provided**		**<1.2**	**None**	

Comment

A man with chronic hepatitis C and cirrhosis and a past history of alcoholism presented for a liver transplant evaluation and was found to have advanced liver disease with moderate decompensation (Child's Class B). He had HCV genotype 1a infection and a history of "null" responses to courses of peginterferon and ribavirin. He was started on an oral regimen of simeprevir and sofosbuvir, which in clinical trials had been shown to yield sustained virological response rates of 73% in patients with Child's B cirrhosis. Indeed, he rapidly became HCV RNA negative, but had worsening symptoms and jaundice with rises in serum ALT and INR, prompting emergent liver transplantation. Fortunately, the antiviral therapy was successful in eradicating HCV infection and he remained HCV RNA negative thereafter. While somewhat short on details, this case report was reasonably convincing as demonstrating liver injury due to antiviral therapy. The authors attributed the injury to simeprevir, but sofosbuvir was given concurrently making it difficult to attribute the episode to one versus the other agent. Another possibility was that the sudden decompensation was triggered by the rapid clearance of HCV infection, as occurs in some cases of chronic hepatitis B during initiation of antiviral therapy. Finally, the decompensation may have been coincidental and not related to the drugs or antiviral response at all. Several such instances of "spontaneous" hepatic decompensation arising during potent antiviral therapy have been described which argues for careful monitoring of patients with cirrhosis, particularly during the first few weeks of therapy. This case also shows that antiviral therapy of patients with advanced cirrhosis is best left to centers with expertise in managing end stage liver disease and where liver transplantation is available.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Simeprevir – Olysio®

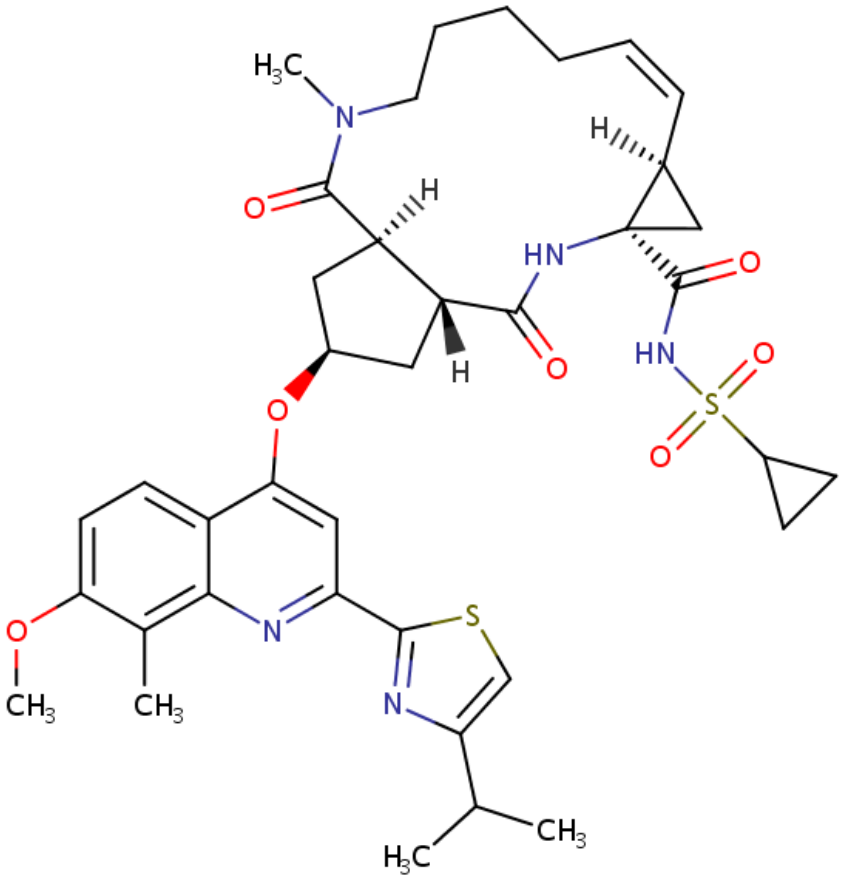
DRUG CLASS

Hepatitis C Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Simeprevir	923604-59-5	C38-H47-N5-O7-S2	

ANNOTATED BIBLIOGRAPHY

References updated: 18 January 2018

[Abbreviation used: HCV, hepatitis C virus; HBV, hepatitis B virus; SVR, sustained virological response; DDA, direct acting antiviral agent]

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Multi-authored textbook of hepatotoxicity published in 2013 does not discuss oral, direct acting antiviral agents used to treat hepatitis C).

Kim JL, Morgenstern KA, Lin C, Fox T, Dwyer MD, Landro JA, Chambers SP, et al. Crystal structure of the hepatitis C virus NS3 protease domain complexed with a synthetic NS4A cofactor peptide. Cell 1996; 87: 343-55. PubMed PMID: 8861917.

(Report of the crystal structure of the NS3/4 region of HCV with detailed description of the active serine protease catalytic site, the target for subsequent development of specific inhibitors of the HCV protease).

Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, Marcellin P, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. Hepatology 2013; 58: 1918-29. PubMed PMID: 23907700.

(Among 388 patients with chronic hepatitis C, genotype 1, randomized to 1 of 5 different regimens of simeprevir vs placebo combined with peginterferon and ribavirin for 24 or 48 weeks, SVR rates higher with simeprevir vs placebo [76% to 86% vs 66%], while side effects were similar in all groups and there were no concurrent increases in serum bilirubin and aminotransferase levels).

Hayashi N, Seto C, Kato M, Komada Y, Goto S. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naïve hepatitis C genotype 1-infected patients in Japan: the DRAGON study. J Gastroenterol 2014; 49: 138-47. PubMed PMID: 24005956.

(Among 92 Japanese patients with chronic hepatitis C, genotype 1, treated with simeprevir [50 or 100 mg] vs placebo for 12 or 24 weeks combined with peginterferon and ribavirin for 24 or 48 weeks, the SVR rates were higher with simeprevir [77% to 92% vs 46%], but adverse event rates were similar except for higher rates of mild bilirubin elevations and rash with simeprevir).

Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. Lancet 2014; 384(9956): 1756-65. PubMed PMID: 25078309.

(Among 167 patients with chronic hepatitis C, genotype 1, treated with sofosbuvir and simeprevir [with or without ribavirin] for 12 or 24 weeks, SVR rates were 90% to 94%; no mention of ALT elevations or hepatotoxicity).

Simeprevir (Olysio) for chronic hepatitis C. Med Lett Drugs Ther 2014; 56 (1433): 1-3. PubMed PMID: 24419295.

(Concise review of the efficacy, safety and costs of simeprevir shortly after its approval in the US as a part of combination therapy of chronic hepatitis C, genotype 1, mentions side effects of rash, photosensitivity, pruritus, nausea, fatigue and dyspnea; simeprevir can cause serum bilirubin elevations, but these are generally mild, transient and in the indirect(unconjugated) fraction and are not associated with ALT elevations or other evidence of liver injury).

Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. Liver Int 2014; 34 Suppl 1: 69-78. PubMed PMID: 24373081.

(Summary of safety and efficacy of various all-oral regimens for therapy of hepatitis C does not discuss hepatic decompensation, hepatotoxicity or ALT elevations during therapy).

Rosenquist Å, Samuelsson B, Johansson PO, Cummings MD, Lenz O, Raboisson P, Simmen K, Vendeville S, et al. Discovery and development of simeprevir(TMC435), a HCV NS3/4A protease inhibitor. J Med Chem 2014; 57: 1673-93. PubMed PMID: 24446688.

(Summary of the development of protease inhibitors for treatment of chronic hepatitis C including simeprevir [TMC435], a novel cyclopentane macrocyclic inhibitor identified by screening in HCV NS3 protease assays, application of structure based design and validation in HCV replicon systems).

Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, 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 1669-79. PubMed PMID: 24602923.

(Among 393 patients with previously treated chronic hepatitis C, genotype 1, who were treated with simeprevir vs placebo [12 weeks] combined with peginterferon and ribavirin [24 or 48 weeks], SVR rates were higher with simeprevir [79% vs 36%] and, except for hyperbilirubinemia and photosensitivity [3.5% vs 0], adverse event rates were similar).

Izumi N, Hayashi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, et al. Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies. J Gastroenterol 2014; 49: 941-53. PubMed PMID: 24626851.

(Among 155 patients with previously treated chronic hepatitis C, genotype 1, treated with simeprevir [12 or 24 weeks] and peginterferon with ribavirin [24 or 48 weeks], SVR rates ranged from 36 to 96%; one patient discontinued therapy because of "abnormal hepatic function" and one for erythema multiforme, but few details provided).

Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, Janczewska E, 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; 384: 414-26. PubMed PMID: 24907224.

(Among 324 patients with previously untreated chronic hepatitis C, genotype 1, treated with simeprevir vs placebo [12 weeks] combined with peginterferon and ribavirin [24 or 48 weeks], SVR rates were 81% with simeprevir vs 50% with placebo, while adverse event rates were similar except that simeprevir treated patients had higher rate of rash [24% vs 11%] and photosensitivity [4% vs <1%]).

Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014; 384: 403-13. PubMed PMID: 24907225.

(Among 394 previously untreated patients with chronic hepatitis C, genotype 1, treated with simeprevir or placebo [12 or 24 weeks] combined with peginterferon and ribavirin [24 to 48 weeks], SVR rates were higher with simeprevir [80% vs 50%], adverse event rates were similar and increases in ALT "were infrequent and similar between the treatment groups" and not associated with bilirubin elevations).

Kumada H, Hayashi N, Izumi N, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, et al. Simeprevir (TMC435) once daily with peginterferon-α-2b and ribavirin in patients with genotype 1 hepatitis C virus infection: The CONCERTO-4 study. Hepatol Res 2015; 45: 501-13. PubMed PMID: 24961662.

(Among 79 patients with chronic hepatitis C, genotype 1, treated with simeprevir [12 weeks] and peginterferon and ribavirin [24 or 48 weeks], SVR rates were higher in treatment naïve [92%] and relapse patients [100%] than in previous nonresponders [39%] and no serious liver related adverse events were recorded).

Dieterich D, Rockstroh JK, Orkin C, Gutiérrez F, Klein MB, Reynes J, Shukla U, et al. Simeprevir (TMC435) with pegylated interferon/ribavirin in patients coinfected with HCV genotype 1 and HIV-1: a phase 3 study. Clin Infect Dis 2014; 59: 1579-87. PubMed PMID: 25192745.

(Among 106 patients with chronic hepatitis C, genotype 1, and HIV coinfection treated with simeprevir [12 weeks] combined with peginterferon and ribavirin [24 or 48 weeks], the overall SVR rate was 74%, rash occurred in 16%, photosensitivity 2%, moderate bilirubin elevations 2%, but no patient had significant ALT elevations or clinically apparent liver injury).

Manns MP, Fried MW, Zeuzem S, Jacobson IM, Forns X, Poordad F, Peeters M, et al. Simeprevir with peginterferon/ribavirin for treatment of chronic hepatitis C virus genotype 1 infection: pooled safety analysis from Phase IIb and III studies. J Viral Hepat 2015; 22: 366-75. PubMed PMID: 25363449.

(In a pooled analysis of 5 clinical trials of simeprevir vs placebo combined with peginterferon and ribavirin for 24 to 48 weeks in 1464 patients with chronic hepatitis C, genotype 1 [11% with cirrhosis], bilirubin elevations occurred in 8.4% on simeprevir vs 2.8% on placebo, but none were accompanied by serum ALT elevations or evidence of hepatic injury; no liver related severe adverse events or deaths occurred nor any cases of DRESS or Stevens Johnson syndrome).

Stine JG, Intagliata N, Shah NL, Argo CK, Caldwell SH, Lewis JH, Northup PG. Hepatic decompensation likely attributable to simeprevir in patients with advanced cirrhosis. Dig Dis Sci 2015; 60: 1031-5. PubMed PMID: 25373453.

(Two men, ages 43 and 56 years, with chronic hepatitis C, genotype 1, and advanced cirrhosis developed progressive liver failure 2 and 4 weeks after starting sofosbuvir and simeprevir [bilirubin rising from 5.3 to 14.2 mg/dL and 9.5 to 25 mg/dL, ALT 90 and 53 U/L, Alk P not provided], one patient undergoing successful liver transplantation and the other dying, both remaining HCV RNA negative despite stopping therapy promptly).

Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's class A cirrhosis. Gastroenterology 2015; 148: 762-70. PubMed PMID: 25557952.

(Among 82 patients with chronic hepatitis C and compensated cirrhosis, genotype 1a, who were treated with sofosbuvir and either simeprevir vs peginterferon with ribavirin for 12 weeks, SVR rates were higher with simeprevir [93% vs 75%]; one patient on peginterferon developed hepatic decompensation, but there were no other liver related serious adverse events in either group).

Pungpapong S, Aqel B, Leise M, Werner KT, Murphy JL, Henry TM, Ryland K, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. Hepatology 2015; 61: 1880-6. PubMed PMID: 25722203.

(Among 123 patients with recurrent chronic hepatitis C, genotype 1, after liver transplant who were treated with simeprevir and sofosbuvir with or without ribavirin for 12 weeks, the overall SVR rate was 90% and severe side effects included acute pancreatitis, allergic lung injury and acute urinary obstruction; there were no ALT elevations above 5 times ULN or clinically apparent liver injury).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-1352. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 were attributed to antiviral agents, but all were antiretroviral agents and no case was attributed to the oral direct acting agents used to treat hepatitis C).

Gutierrez JA, Carrion AF, Avalos D, O'Brien C, Martin P, Bhamidimarri KR, Peyton A. Sofosbuvir and simeprevir for treatment of hepatitis C virus infection in liver transplant recipients. Liver Transpl 2015; 21: 823-30. PubMed PMID: 25825070.

(Among 61 patients with recurrent hepatitis C after liver transplantation who were treated with simeprevir and sofosbuvir for 12 weeks, the overall SVR rate was 93%; two patients with cirrhosis developed hepatic decompensation, but no patient died or had hepatic rejection).

Saxena V, Nyberg L, Pauly M, Dasgupta A, Nyberg A, Piasecki B, Winston B, et al. Safety and Efficacy of simeprevir/sofosbuvir in hepatitis C-infected patients with compensated and decompensated cirrhosis. Hepatology 2015; 62: 715-25. PubMed PMID: 26033798.

(Among 156 patients with chronic hepatitis C, genotype 1, and cirrhosis treated with simeprevir and sofosbuvir with or without ribavirin for 12 weeks, overall SVR rates were 91% in compensated vs 73% in decompensated cases, and hepatic decompensation in 20% vs 3%, one patient dying of liver failure, but rates of adverse events were said to be similar to those of matched, untreated subjects).

Collins JM, Raphael KL, Terry C, Cartwright EJ, Pillai A, Anania FA, Farley MM. Hepatitis B Virus Reactivation During Successful Treatment of Hepatitis C Virus With Sofosbuvir and Simeprevir. Clin Infect Dis 2015 Jun 16. [Epub ahead of print] PubMed PMID: 26082511.

(2 cases: 55 year old man with chronic hepatitis C, genotype 1, and HBsAg with low levels of HBV DNA [2300 IU/mL] developed jaundice 8 weeks after starting sofosbuvir and simeprevir [bilirubin 12.2 mg/dL, ALT 1495 U/L, INR 1.96, HBV DNA 22 million IU/mL], with resolution within 6 weeks of stopping HCV agents and starting tenofovir and emtricitabine [Case 2]; 57 year old man with chronic hepatitis C, genotype 1a, and anti-HBc without HBsAg developed rising levels of HBV DNA during therapy with sofosbuvir and simeprevir [Pre <20, 2 weeks 353 and 4 weeks 11,255 IU/mL], which fell to undetectable levels within 8 weeks of starting tenofovir with emtricitabine [Truvada], ALT values remaining normal during the episode).

Aqel BA, Pungpapong S, Leise M, Werner KT, Chervenak AE, Watt KD, Murphy JL, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 in patients with cirrhosis. Hepatology 2015; 62: 1004-12. PubMed PMID: 26096332.

(Retrospective review of course of 119 patients with chronic hepatitis C, genotype 1, and cirrhosis treated with sofosbuvir and simeprevir with or without ribavirin found overall SVR rate of 78%; bilirubin levels rose above 3 mg/dL in 4 patients, but none developed hepatic decompensation on therapy or had to discontinue treatment early because of liver related adverse events; one patient died of liver failure 6 weeks after completing treatment despite having cleared HCV RNA).

Bailly F, Pradat P, Virlogeux V, Zoulim F. Antiviral therapy in patients with hepatitis C virus-induced cirrhosis. Dig Dis 2015; 33: 613-23. PubMed PMID: 26159282.

(Review of the status of antiviral therapy of chronic hepatitis C with cirrhosis summarizing the high rate of adverse events including hepatic decompensation and death with peginterferon based regimens combined with boceprevir or telaprevir, and the more effective and better tolerated all oral regimens).

Ferenci P, Kozbial K, Mandorfer M, Hofer H. HCV targeting of patients with cirrhosis. J Hepatol 2015; 63: 1015-22. PubMed PMID: 26100497.

(Review of the status of antiviral therapy of chronic hepatitis C with cirrhosis, suggests that genotype 1 infected patients should receive an all-oral regimen such as the dual regimen of sofosbuvir with ledipasvir, daclatasvir or simeprevir or the triple combination of dasabuvir with ombitasvir and paritaprevir, the major issues being duration of therapy and the role of ribavirin).

Igawa T, Fushimi S, Matsuo R, Ikeda F, Nouso K, Yoshino T, Nakatsukasa H. Severe liver injury associated with simeprevir plus pegylated interferon/ribavirin therapy in a patient with treatment-naïve genotype 1b hepatitis C virus: a case report. Clin J Gastroenterol 2014; 7: 465-70. PubMed PMID: 26184030.

(65 year old man with chronic hepatitis C developed fatigue and serum ALT elevations 50 days after starting simeprevir, peginterferon and ribavirin [bilirubin 3.3 mg/dL, ALT 728 U/L, Alk P 171 U/L, INR 1.2], with rapid improvement on stopping therapy and persistent loss of HCV RNA despite early discontinuation).

Shiffman ML, James AM, Long AG, Alexander PC. Treatment of chronic HCV with sofosbuvir and simeprevir in patients with cirrhosis and contraindications to interferon and/or ribavirin. Am J Gastroenterol 2015; 110:1179-85. PubMed PMID: 26215530.

(Among 120 cirrhotic patients with chronic hepatitis C, genotype 1, treated with sofosbuvir and simeprevir for 12 weeks, the SVR rate was 83%, but 14 patients developed complications of cirrhosis including hyperbilirubinemia in 8, sepsis in 2 [1 dying of multiorgan failure], hepatocellular carcinoma in 2 and variceal hemorrhage in 2).

Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. J Med Case Rep 2015; 9: 164.

(59 year old woman with chronic hepatitis C, genotype 1, and anti-HBc without HBsAg or HBV DNA in serum, developed jaundice 11 weeks after starting sofosbuvir and simeprevir [bilirubin 9.1 mg/dL, ALT 2263 U/L, INR

1.9, HBV DNA 29 million IU/mL]; she was started on tenofovir, but developed progressive liver failure and underwent emergency liver transplantation 10 days after presentation).

Lawitz E, Jacobson IM, Nelson DR, Zeuzem S, Sulkowski MS, Esteban R, Brainard D, et al. Development of sofosbuvir for the treatment of hepatitis C virus infection. Ann N Y Acad Sci 2015 Jul 31. [Epub ahead of print] PubMed PMID: 26235748.

(Review of the development of therapy of hepatitis C, focusing upon sofosbuvir and the prelicensure studies that lead to its approval).

Modi AA, Nazario H, Trotter JF, Gautam M, Weinstein J, Mantry P, Barnes M, et al. Safety and efficacy of simeprevir plus sofosbuvir with or without ribavirin in patients with decompensated genotype 1 hepatitis C cirrhosis. Liver Transpl 2015 Sep 3. [Epub ahead of print] PubMed PMID: 26335142.

(Among 42 patients with chronic hepatitis C, genotype 1, with decompensated cirrhosis treated with simeprevir and sofosbuvir with vs without ribavirin for 12 weeks, the overall SVR rate was 74% and no patient developed worsening hepatic decompensation or required hospitalization).

European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015; 63: 199-236. PubMed PMID: 25911336.

(Guidelines for the antiviral therapy of chronic hepatitis C from the European liver disease research and academic society).

AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62: 932-54. PubMed PMID: 26111063.

(Guidelines for the antiviral therapy of chronic hepatitis C from the US liver and infectious diseases research and academic societies).

Lawitz E, Matusow G, DeJesus E, Yoshida EM, Felizarta F, Ghalib R, Godofsky E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A Phase 3 study (OPTIMIST-2). Hepatology 2015 Dec 24. [Epub ahead of print] PubMed PMID: 26704148.

(Among 103 patients with chronic hepatitis C, genotype 1, and cirrhosis treated with sofosbuvir and simeprevir for 12 weeks 103 [83%] had an SVR, and no patient developed liver failure or a treatment related serious adverse event).

Kamar N, Marion O, Rostaing L, Cointault O, Ribes D, Lavayssière L, Esposito L, et al. Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C virus infection after kidney transplantation. Am J Transplant 2015 Nov 20. [Epub ahead of print] PubMed PMID: 26587971.

(Among 25 kidney transplant recipients tih chronic hepatitis C, genotype 1, treated with sofosbuvir in combination with other antiviral agents, 22 [88%] had an SVR, and "no adverse event was observed").

Crittenden NE, Buchanan LA, Pinkston CM, Cave B, Barve A, Marsano L, McClain CJ, et al. Simeprevir and sofosbuvir with or without ribavirin to treat recurrent genotype 1 hepatitis C virus infection after orthotopic liver transplantation. Liver Transpl 2016 Feb 25. [Epub ahead of print] PubMed PMID: 26915588.

(Among 56 patients with recurrent hepatitis C after liver transplantation who were treated with sofosbuvir and simeprevir for 12 weeks, 49 [88%] had an SVR, and two died of liver failure).

Issa D, Eghtesad B, Zein NN, Yerian L, Cruise M, Alkhouri N, Adams R,et al. Sofosbuvir and simeprevir for the treatment of recurrent hepatitis C with fibrosing cholestatic hepatitis after liver transplantation. Int J Organ Transplant Med 2016; 7: 38-45. PubMed PMID: 26889372.

(Among 5 patients with recurrent hepatitis C and fibrosing cholestatic hepatitis after liver transplant who were treated with sofosbuvir and simeprevir for 24 weeks, 4 had an SVR with resolution of jaundice, and one developed hepatic decompensation and died).

Pillai AA, Wedd J, Norvell JP, Parekh S, Cheng N, Young N, Spivey JR, et al. Simeprevir and sofosbuvir (SMV-SOF) for 12 weeks for the treatment of chronic hepatitis C genotype 1 infection: a real world (transplant) hepatology practice experience. Am J Gastroenterol 2016; 111: 250-60. PubMed PMID: 26832650.

(Among 170 patients with chronic hepatitis C, genotype 1, treated with sofosbuvir and simeprevir with or without ribavirin for 12 weeks in routine clinical practice, 133 [78%] had an SVR; adverse events were not discussed).

Brown RS Jr, O'Leary JG, Reddy KR, Kuo A, Morelli GJ, Burton JR Jr, Stravitz RT, et al; Hepatitis C Therapeutic Registry Research Network Study Group. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: Real-world experience from the hepatitis C therapeutic registry and research network. Liver Transpl 2016; 22: 4-33. PubMed PMID: 26519873.

(Among 151 patients with recurrent hepatitis C after liver transplantation treated with sofosbuvir and simeprevir with or without ribavirin for 12 or 24 weeks, 133 [88%] had an SVR, and 8 [5%] developed hepatic decompensation and 3 paitients died, all of whom had cirrhosis).

Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, Morelli G, et al.; HCV-TARGET Study Group. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. Gastroenterology 2016; 150: 419-29. PubMed PMID: 26497081.

(Among 802 patients with chronic hepatitis C, genotype 1, treated with sofosbuvir and simeprevir with or without ribavirin for 12 weeks in clinical practices ["the real world"], 675 [84%] had an SVR, 44 [5.3%] had a serious adverse event, 10 [1.2%] hepatic decompensation and 2 [0.3%] died of liver failure).

Modi AA, Nazario H, Trotter JF, Gautam M, Weinstein J, Mantry P, Barnes M, et al. Safety and efficacy of simeprevir plus sofosbuvir with or without ribavirin in patients with decompensated genotype 1 hepatitis C cirrhosis. Liver Transpl 2016; 22: 281-6. PubMed PMID: 26335142.

(Among 42 patients with chronic hepatitis C, genotype 1, and decompensated cirrhosis treated with sofosbuvir, simeprvir and [n=35] ribavirin for 12 weeks, 31 [74%] had an SVR, and none developed decompensation requiring hospitalization).

Fontana RJ, Brown RS, Moreno-Zamora A, Prieto M, Joshi S, Londoño MC, et al. Daclatasvir combined with sofosbuvir or simeprevir in liver transplant recipients with severe recurrent hepatitis C infection. Liver Transpl 2016 Feb 17. [Epub ahead of print] PubMed PMID: 26890629.

(Among 97 liver transplant recipients treated with daclatasvir and either sofosbuvir or simeprevir with or without ribavirin for up to 24 weeks, 84 [87%] had an SVR, and 8 [8%] patients died, but none of the deaths were considered due to the antiviral therapy).

Dyson JK, Hutchinson J, Harrison L, Rotimi O, Tiniakos D, Foster GR, Aldersley MA, et al. Liver toxicity associated with sofosbuvir, an NS5A inhibitor and ribavirin use. J Hepatol 2016; 64: 753-4. PubMed PMID: 26325535.

(74 year old man and 36 year old woman with HCV related cirrhosis developed worsening hepatic decompensation within a few weeks of starting sofosbuvir, an NS5A inhibitor and ribavirin [peak bilirubin 23.4 and 30.5 mg/dL, ALT 65 and 96 U/L, Alk P 202 and 398 U/L], resulting in death in one and emergency liver transplant in the other [Case 1]).

Marchan-Lopez A, Dominguez-Dominguez L, Kessler-Saiz P, Jarrin-Estupiñan ME. Liver failure in human immunodeficiency virus - hepatitis C virus coinfection treated with sofosbuvir, ledipasvir and antiretroviral therapy. J Hepatol 2016; 64: 752-3. PubMed PMID: 26682727.

(Letter in response to Dyson [2016]: 49 year old man with chronic hepatitis C, cirrhosis [Child-Pugh class B] and HIV coinfection developed worsening hepatic decompensation 1 to 2 months after starting sofosbuvir and ledipasvir that worsened for two weeks after stopping [peak bilirubin 46.9 mg/dL, INR 3.17], and then resolved; he later tolerated reinitiation of antiretroviral drugs).

Dyson JK, McPherson S. Reply to "Liver failure in human immunodeficiency virus - Hepatitis C virus coinfection treated with sofosbuvir, ledipasvir and antiretroviral therapy". J Hepatol 2016; 64: 753-4. PubMed PMID: 26682725.

(Letter in reply to March-Lopez [2016] reporting another case of hepatic decompensation during sofosbuvir, ledipasvir and ribavirin therapy of a patient hepatitis C, cirrhosis and HIV coinfection, arising within 6 weeks of starting treatment [bilirubin 12.6 mg/dL, protime 17 sec], and leading to successful, emergency liver transplantation).

Welker MW, Luhne S, Lange CM, Vermehren J, Farnik H, Herrmann E, Welzel T, et al. Lactic acidosis in patients with hepatitis C virus cirrhosis and combined ribavirin/ sofosbuvir treatment. J Hepatol 2016; 64: 790-9. PubMed PMID: 26658684.

(Among 35 patients with chronic hepatitis C and advanced fibrosis or cirrhosis treated with sofosbuvir based regimens, 12 [34%] had a serious adverse event and 5 [14%] developed lactic acidosis, largely in those with Child-Pugh class B or C cirrhosis and in the context of hepatic decompensation, 2 of whom died).

Hoofnagle JH. Hepatic decompensation during direct-acting antiviral therapy of chronic hepatitis C. J Hepatol 2016; 64: 763-5. PubMed PMID: 26795828.

(Editorial in response to Welker [2016] discussing the occurrence of unexplained hepatic decompensation during antiviral therapy of hepatitis C and whether these episodes are coincidental, caused by hepatoxicity of the antiviral drugs, or are the paradoxical result of sudden eradication of the chronic viral infection).

Bersoff-Matcha SJ, Cao K, Jason M, Ajao A, Jones SC, Meyer T, Brinker A. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. Food and Drug Administration adverse event reporting system. Ann Intern Med 2017; 166: 792-798. 28437794. PubMed PMID: 28437794.

(FDA summary of 29 reports of HBV reactivation among patients with chronic hepaitits C being treated with DAAs, including, presenting 14 to 196 days after starting therapy, with various DAA regimens, 3 resulting in death, 19 from Japan, 5 from the U.S., many treated after a delay in identifying the cause of sudden worsening of liver disease).

Mahale P, Glenn JS, O'Brien TR. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus. Ann Intern Med 2017; 167: 759-760.29159388. PubMed PMID: 29159388.

(Letter in response to Bersoff-Matcha [2017] suggesting that some cases of sudden worsening of liver disease in HBsAg positive patients might be due to superinfections with hepatitis D [Delta] virus).

Bersoff-Matcha SJ, Cao K, Jason M, Jones SC, Brinker A. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus. Ann Intern Med 2017; 167: 760. 29159389. PubMed PMID: 29159389.

(Reply to the letter to the editor by Mahale [2017] by the authors).

Serper M, Forde KA, Kaplan DE. Rare clinically significant hepatic events and hepatitis B reactivation occur more frequently following rather than during direct-acting antiviral therapy for chronic hepatitis C: Data from a national US cohort. J Viral Hepat 2017 Aug 28. [Epub ahead of print] 28845882. PubMed PMID: 28845882.

(Analysis of the large VA Medical system database of 17,400 veterans with chronic hepaittis C as well as anti-HBc who received oral DAA therapy, identified only 2 cases of HBV reactivation with serum ALT elevations above 300 U/L among 97 HBsAg positive patients).

Aggeletopoulou I, Konstantakis C, Manolakopoulos S, Triantos C. Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C. World J Gastroenterol 2017; 23: 4317-4323. 28706414. PubMed PMID: 28706414.

(Reivew of the litrature on reactivation of HBV during antiviral therapy of chronic hepatitis C summarizing 7 cases in the literature).

Calvaruso V, Ferraro D, Licata A, Bavetta MG, Petta S, Bronte F, Colomba G, et al. HBV reactivation in patients with HCV/HBV cirrhosis on treatment with direct-acting antivirals. J Viral Hepat 2018; 25: 72-79. 28703895. PubMed PMID: 28703895.

(Among 104 patients with cirrhosis and chronic hepatitis C who were treated with DAAs, reactivation of HBV occurred in 3 of 4 HBsAg positive patients not on anti-HBV therapy, but none developed ALT elevations or clinically apparent acute liver injury).

Loggi E, Gitto S, Galli S, Minichiello M, Conti F, Grandini E, Scuteri A, et al. Hepatitis B virus reactivation among hepatitis C patients treated with direct-acting antiviral therapies in routine clinical practice. J Clin Virol 2017; 93: 66-70. 28654775. PubMed PMID: 28654775.

(Among 137 Italian adults with chronic hepatitis C treated with DAAs during a one-year period, reactivation [without ALT elevations] occurred in 1 of 2 subjects with HBsAg, but in none of 42 with anti-HBc without HBsAg).

Kawagishi N, Suda G, Onozawa M, Kimura M, Maehara O, Ito J, Nakai M, et al. Hepatitis B virus reactivation during hepatitis C direct-acting antiviral therapy in patients with previous HBV infection. J Hepatol 2017; 67: 1106-1108. 28438688. PubMed PMID: 28438688.

(Letter describing course of 5 of 84 patients with chronic hepatitis C and serologic evidence of previous HBV infection [anti-HBc without HBsAg] developed evidence of HBV reactivation during various DAA regimens that was not accompanied by ALT elevations, but was persistent after DAA treatment in two patients).

Belperio PS, Shahoumian TA, Mole LA, Backus LI. Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals. Hepatology 2017; 66: 27-36. 28240789. PubMed PMID: 28240789.

(Analysis of VA Medical Database of 62,920 veterans with chronic hepatitis C treated with oral DAAs of whom 9 had evidence of HBV reactivation, 8 in patients with HBsAg and 1 with anti-HBc without HBsAg in serum, but only 3 patients had ALT elevations above twice ULN).

Yeh ML, Huang CF, Hsieh MH, Ko YM, Chen KY, Liu TW, Lin YH, et al. Reactivation of hepatitis B in patients of chronic hepatitis C with hepatitis B virus infection treated with direct acting antivirals. J Gastroenterol Hepatol 2017; 32: 1754-1762. 28230928. PubMed PMID: 28230928.

(Among 64 patients with chronic hepatitis C and serologic evidence of ongoing or previous HBV infection who were treated with various DAA regimens, 4 of 7 HBsAg positive [57%] but none of 57 anti-HBc positive, HBsAg negative subjects developed HBV reactivation but all cases were subclinical, ALT elevations occurring in only one).

Londoño MC, Lens S, Mariño Z, Bonacci M, Ariza X, Broquetas T, Pla A, et al. Hepatitis B reactivation in patients with chronic hepatitis C undergoing anti-viral therapy with an interferon-free regimen. Aliment Pharmacol Ther 2017; 45: 1156-1161. 28206681. PubMed PMID: 28206681.

(Among 352 patients with chronic hepatitis C receiving DAA treatment, 5 of 10 [50%] with concurrent HBsAg and 1 of 64 with anti-HBc without HBsAg developed a 1 log IU/mL increase in HBV DNA levels, but elevations were modest and none developed ALT elevations or clinically apparent liver injury).

Kawagishi N, Suda G, Onozawa M, Kimura M, Maehara O, Ohara M, Izumi T, et al. Comparing the risk of hepatitis B virus reactivation between direct-acting antiviral therapies and interferon-based therapies for hepatitis C. J Viral Hepat 2017; 24: 1098-1106. 28632923. PubMed PMID: 28632923.

(Among 151 patients with chronic hepatitis C undergoing antiviral therapy, reactivation of HBV occurred in 1 of 4 patients with HBsAg in serum, and 5 of 151 with anti-HBc without HBsAg, but peak HBV DNA levels were low and all cases were without ALT elevations or symptoms and all 6 occurred in 79 patients receiving oral DAAs [8%] and none in the 72 who received interferon-based therapies [0%]).

Mücke VT, Mücke MM, Peiffer KH, Weiler N, Welzel TM, Sarrazin C, Zeuzem S, et al. No evidence of hepatitis B virus reactivation in patients with resolved infection treated with direct-acting antivirals for hepatitis C in a large real-world cohort. Aliment Pharmacol Ther 2017; 46: 432-439. 28627791. PubMed PMID: 28627791.

(Among 848 patients with chronic hepatitis C treated in the "real world" with DAAs, 5 of 9 patients with HBsAg developed HBV reactivation [3 ultimately requiring anti-HBV therapy] and 8 of 263 patients with anti-HBc without HBsAg had low, but detectable levels of HBV DNA during therapy but without ALT elevations).

In brief: Hepatitis B reactivation with direct-acting antiviral drugs for hepatitis C. Med Lett Drugs Ther 2016; 58(1506): 140. 27755511. PubMed PMID: 27755511.

(Brief summary of the FDA warning letter concerning HBV reactivation caused by DAA therapies of hepatitis C).