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Boceprevir

Updated: March 10, 2016.

OVERVIEW

Introduction

Boceprevir 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, genotype 1. Boceprevir has not been linked to instances of acute liver injury during therapy but, when combined with peginterferon and ribavirin, has been associated with 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].

Boceprevir (boe se' pre vir) was one of the first direct acting agents developed as therapy of hepatitis C. Like other HCV protease inhibitors, boceprevir 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. Triple therapy with boceprevir, peginterferon and ribavirin, when given for 44 to 48 weeks, increased the sustained virological response (SVR) rate from 40% to 50% (peginterferon and ribavirin alone) to 65% to 75% in patients with genotype 1. Boceprevir was approved for use in the United States in 2012 for patients with chronic hepatitis C, genotype 1, in combination with peginterferon and ribavirin. Since that time, boceprevir has been largely replaced by more potent and better tolerated oral antiviral agents that can be given

without peginterferon, but it is still available under the brand name Victrelis as capsules of 200 mg. The recommended dose is 800 mg three times daily. The side effects of boceprevir are difficult to separate from those of the coadministered peginterferon and ribavirin, but the triple therapy is associated with a higher rate of many side effects, including anemia, fatigue, headache, nausea, itching, rash and neutropenia.

Hepatotoxicity

In large randomized controlled trials, triple therapy with boceprevir, peginterferon and ribavirin was associated with a high rate of adverse events that often required dose adjustments and led to early discontinuation in 5% to 20% of patients. However, serum ALT elevations and clinically apparent liver injury were not generally mentioned as adverse events of therapy. The exception to this occurred in patients with preexisting cirrhosis in whom de novo, seemingly spontaneous hepatic decompensation occurred in a proportion of treated subjects. The cause of the decompensation was not clear and the separate role of boceprevir from peginterferon and ribavirin and from what might happen even without therapy could not be easily defined. Nevertheless, in postmarketing studies of triple therapy of chronic hepatitis C with cirrhosis, decompensation was reported in 3% to 8% of patients and deaths from hepatic failure in 1% to 3%.

Likelihood score: E* (unproven but suspected cause of liver injury).

Mechanism of Injury

The mechanism by which boceprevir might cause liver injury is not known. It is metabolized in the liver largely via the cytochrome P450 system, predominantly CYP 3A4. It is also a substrate of P-glycoprotein (P-gp). It is susceptible to drug-drug interactions, but largely for those agents that have major effects or are highly dependent upon CYP 3A4 and P-gp for their metabolism. In addition, the other adverse effects of boceprevir, particularly when combined with peginterferon and ribavirin, may predispose to events that might lead to hepatic decompensation in a susceptible patient. Triple therapy is associated with a high rate of anemia, neutropenia, thrombocytopenia, infection, gastrointestinal upset, dehydration and rash, all of which might help precipitate hepatic decompensation in a patient with underlying cirrhosis or advanced fibrosis.

Outcome and Management

While triple therapy using boceprevir is currently rarely used, it must be considered inadvisable in patients with preexisting cirrhosis, particularly those with a prior history of hepatic decompensation. A similar high rate of decompensation of preexisting cirrhosis has been reported with triple therapy using telaprevir and simeprevir, two other HCV protease inhibitors. In fact, hepatic decompensation was also a reported complication of all-oral antiviral therapy of hepatitis C, although the rates reported with non-interferon and non-ribavirin containing regimens were quite low (<1%).

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Boceprevir – Victrelis®

DRUG CLASS

Hepatitis C Agents

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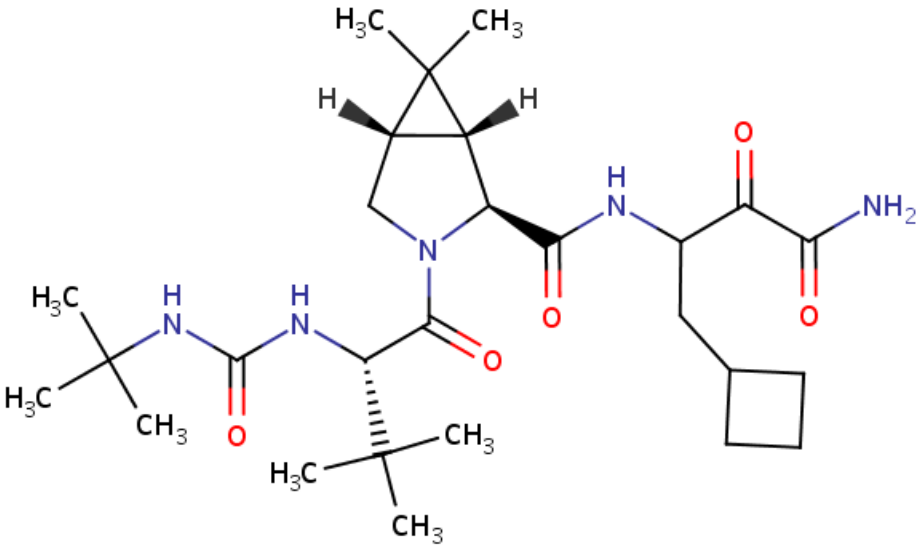
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Boceprevir	394730-60-0	C27-H45-N5-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 10 March 2016

[Abbreviation used: SVR, sustained virological response.]

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).

Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, et al.; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1195-206. PubMed PMID: 21449783.

(Among 1097 patients with previously untreated chronic hepatitis C, genotype 1, who were treated with peginterferon and ribavirin with vs without boceprevir for up to 48 weeks, SVR rates were higher with boceprevir [63-66% vs 38%], while serious adverse event rates were similar [11%-12% vs 9%] and there were no liver related serious events).

Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, et al.: HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1207-17. PubMed PMID: 21449784.

(Among 403 patients with previously treated chronic hepatitis C, genotype 1, who received peginterferon and ribavirin with vs without boceprevir for up to 48 weeks, SVR rates were higher with boceprevir [59% and 66% vs 21%], as were rates of serious adverse events [10% to 14% vs 5%], one patient on boceprevir developing hepatic encephalopathy).

Telaprevir (Incivek) and boceprevir (Victrelis) for chronic hepatitis C. Med Lett Drugs Ther 2011; 53: 57-9. PubMed PMID: 21778964.

(Concise review of the efficacy, safety and costs of boceprevir and telaprevir shortly after their approval for use as a part of triple therapy of chronic hepatitis C, genotype 1, in the US, mentions side effects of rash, anemia, fatigue, pruritus, nausea and anorectal pruritus and burning, but not ALT elevations or clinically apparent liver injury).

Bruno S, Vierling JM, Esteban R, Nyberg LM, Tanno H, Goodman Z, Poordad F, et al. Efficacy and safety of boceprevir plus peginterferon-ribavirin in patients with HCV G1 infection and advanced fibrosis/cirrhosis. J Hepatol 2013; 58: 479-87. PubMed PMID: 23183529.

(In a post hoc analysis of 178 patients with chronic hepatitis C, genotype 1, and advanced fibrosis or cirrhosis who were treated with peginterferon and ribavirin with or without boceprevir for up to 48 weeks in previous trials, serious adverse events occurred in 11-16% of patients and most "were associated with advancing chronic hepatitis C").

Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, et al.; CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme(ANRS CO20-CUPIC) - NCT01514890. J Hepatol 2013; 59: 434-41. PubMed PMID: 23669289.

(Among 497 patients with chronic hepatitis C, genotype 1, and cirrhosis treated in a French early access program with 48 weeks of peginterferon and ribavirin with either boceprevir or telaprevir, serious adverse events occurred in 197 patients [40%], hepatic decompensation in 12 [2.4%], severe infection in 24 [4.8%], and 6 patients died [1.5%], the serious complications typically arising in the first 12 weeks of therapy).

Sulkowski M, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, Rivero A, et al.; P05411 study investigators. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infect Dis 2013; 13: 597-605. PubMed PMID: 23768747.

(Among 98 patients with chronic hepatitis C, genotype 1, and HIV coinfection treated with peginterferon and ribavirin with vs without boceprevir for up to 48 weeks, SVR rates were higher with boceprevir [63% vs 29%], but serious adverse events rates were similar; no mention of liver related events or ALT elevations).

Coilly A, Roche B, Dumortier J, Leroy V, Botta-Fridlund D, Radenne S, Pageaux GP, et al. Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: a multicenter experience. J Hepatol 2014; 60: 78-86. PubMed PMID: 23994384.

(Among 37 patients with severe recurrent chronic hepatitis C, genotype 1, after liver transplant who were treated with peginterferon, ribavirin and either boceprevir or telaprevir for up to 48 weeks, 6 [16%] had an SVR, 10 [27%] a severe infection and 3 [8%] died).

Manns MP, McCone J Jr, Davis MN, Rossaro L, Schiff E, Shiffman ML, Bacon B, et al. Overall safety profile of boceprevir plus peginterferon alfa-2b and ribavirin in patients with chronic hepatitis C genotype 1: a combined analysis of 3 phase 2/3 clinical trials. Liver Int 2014; 34: 707-19. PubMed PMID: 24118703.

(Combined analysis of 3 trials of peginterferon and ribavirin with vs without boceprevir in 2095 patients with chronic hepatitis C, genotype 1, found similar rates of adverse events, but more anemia and dysgeusia with boceprevir).

Park C, Jiang S, Lawson KA. Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype 1: a meta-analysis. J Clin Pharm Ther 2014; 39: 14-24. PubMed PMID: 24237070.

(Analysis of efficacy and safety of telaprevir and boceprevir in triple therapy in 10 controlled trials of 4421 patients with chronic hepatitis C, genotype 1; serious adverse events were higher with triple therapy than with peginterferon and ribavirin alone).

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).

Vierling JM, Zeuzem S, Poordad F, Bronowicki JP, Manns MP, Bacon BR, Esteban R, et al. Safety and efficacy of boceprevir/peginterferon/ribavirin for HCV G1 compensated cirrhotics: meta-analysis of 5 trials. J Hepatol 2014; 61: 200-9. PubMed PMID: 24747798.

(Among 212 patients with cirrhosis due to chronic hepatitis C, genotype 1, treated with peginterferon and ribavirin with vs without boceprevir in 5 clinical trials, SVR rates were higher with boceprevir [55% vs 17%], but hepatic decompensation and/or sepsis occurred in 5 [2.5%] patients among whom 1 died).

Hézode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, De Ledinghen V, et al; CUPIC Study Group. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology 2014; 147: 132-142. PubMed PMID: 24704719.

(Among 511 patients with cirrhosis and chronic hepatitis C, genotype 1, and cirrhosis treated with triple therapy using telaprevir or boceprevir for 48 weeks, 91 [18%] patients had an SVR, severe adverse events occurred in 50%, including liver decompensation in 43 [8%], severe infections in 28 [5.5%] and death in 11 [2.2%]).

Burton JR, O'Leary JG, Verna EC, Saxena V, Dodge JL, Stravitz RT, Levitsky J, et al. A US multicenter study of hepatitis C treatment of liver transplant recipients with protease-inhibitor triple therapy. J Hepatol 2014; 61: 508-14. PubMed PMID: 24801415.

(Among 81 patients with recurrent hepatitis C, genotype 1, after liver transplant who were treated with triple therapy using peginterferon, ribavirin and either boceprevir or telaprevir, the overall SVR rate was 63%, the serious adverse event rate was not reported, but 27% required hospitalization, 15% early drug discontinuation and 7 patients [9%] died of liver failure).

Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Ramani A, Maliakkal B, et al; HCV-TARGET study group. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. J Hepatol 2015; 62: 286-93. PubMed PMID: 25218788.

(Among 2084 patients with chronic hepatitis C, genotype 1, treated in clinical practice with peginterferon, ribavirin and either boceprevir or telaprevir for up to 48 weeks, the overall SVR rate was 52%, serious adverse event rate 12%, while hepatic decompensation occurred in 3% and 5 patients [0.25%] died all from hepatic failure; rash was a common side effect [63% with telaprevir and 34% with boceprevir] and was graded as serious in 8 patients [0.5%], 2 [0.1%] with DRESS).

Verna EC, Saxena V, Burton JR, O'Leary JG, Dodge JL, Stravitz RT, Levitsky J, et al; CRUSH-C Consortium. Telaprevir- and boceprevir-based triple therapy for hepatitis C in liver transplant recipients with advanced recurrent disease: a multicenter study. Transplantation 2015; 99: 1644-51. PubMed PMID: 25715116.

(Among 54 patients with advanced, recurrent chronic hepatitis C, genotype 1, after liver transplantation, who were treated with peginterferon, ribavirin and either boceprevir or telaprevir for up to 48 weeks, the SVR rate was 50%, but hepatic decompensation arose in 24% and 6 patients [11%] died).

Neukam K, Munteanu DI, Rivero-Juárez A, Lutz T, Fehr J, Mandorfer M, Bhagani S, et al. Boceprevir or telaprevir based triple therapy against chronic hepatitis C in HIV coinfection: real-life safety and efficacy. PLoS One 2015; 10: e0125080. PubMed PMID: 25923540.

(Among 159 patients with chronic hepatitis C, genotype 1, treated in health care clinics in 5 European countries with peginterferon, ribavirin and either boceprevir or telaprevir for up to 48 weeks, the overall SVR rate was 63%, while 4 patients [2.5%] developed hepatic decompensation, one of whom died of hepatic failure).

Manolakopoulos S, Kranidioti H, Goulis J, Vlachogiannakos J, Elefsiniotis J, Kouroumalis EA, Koskinas J, et al. Boceprevir for chronic HCV genotype 1 infection in treatment-experienced patients with severe fibrosis or cirrhosis: The Greek real-life experience. Ann Gastroenterol 2015; 28: 481-6. PubMed PMID: 26423714.

(Among 25 Greek patients with chronic hepatitis C, genotype 1, and cirrhosis treated with peginterferon, ribavirin and boceprevir for up to 48 weeks, the SVR rate was 36%, but no patient developed hepatic decompensation or died).

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: 1340-52. 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).

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 dual therapy using sofosbuvir with ledipasvir or daclatasvir or the triple combination of dasabuvir with ombitasvir and paritaprevir, the major issues being duration of therapy and the role of ribavirin).

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).

Coilly A, Dumortier J, Botta-Fridlund D, Latournerie M, Leroy V, Pageaux GP, Agostini H, et al. Multicenter experience with boceprevir or telaprevir to treat hepatitis C recurrence after liver transplantation: when present becomes past, what lessons for future? PLoS One 2015; 10: e0138091. PubMed PMID: 26394142.

(Among 81 patients with recurrent hepatitis C after liver transplantation who were teated with peginterferon, ribavirin and either telaprevir or boceprevir, 38 [47%] had an SVR, 22 [27%] a serious adverse event, 10 [12%] acute rejection, and 4 [5%] died, largely of infectious complications; no mention of ALT elevations or hepatotoxicity).

Salmerón J, Vinaixa C, Berenguer R, Pascasio JM, Sánchez Ruano JJ, Serra MÁ, Gila A, et al; Alhambra Spanish Study Group. Effectiveness and safety of first-generation protease inhibitors in clinical practice: Hepatitis C virus patients with advanced fibrosis. World J Gastroenterol 2015; 21: 9163-74. PubMed PMID: 26290644.

(Among 1057 patients with chronic hepatitis C who were treated with peginterferon, ribavirin and either telaprevir or boceprevir at 38 Spanish hospitals, 635 [60%] had an SVR, and adverse events were largely hematologic; no mention of ALT elevations or hepatotoxicity).

Manolakopoulos S, Kranidioti H, Goulis J, Vlachogiannakos J, Elefsiniotis J, Kouroumalis EA, Koskinas J, et al. Boceprevir for chronic HCV genotype 1 infection in treatment-experienced patients with severe fibrosis or cirrhosis: The Greek real-life experience. Ann Gastroenterol 2015; 28: 481-6. PubMed PMID: 26423714.

(Among 26 patients with chronic hepatitis C, genotype 1, and severe fibrosis or cirrhosis who were treated with peginterferon, ribavirin and bocefprevir for 48 weeks, 9 [36%] had an SVR and side effects included anemia, thrombocytopenia, neutropenia, fatigue and diarrhea; no mention of ALT elevations or hepatotoxicity).

Hullegie SJ, Claassen MA, van den Berk GE, van der Meer JT, Posthouwer D, Lauw FN, Leyten EM, et al. Boceprevir, peginterferon and ribavirin for acute hepatitis C in HIV infected patients. J Hepatol 2015 Dec 12. [Epub ahead of print] 26689767. PubMed PMID: 26689767.

(Among 57 patients with acute hepatitis C, genotype 1, and HIV coinfection who were treated with a 12 week course of peginterferon, ribavirin and boceprevir, 49 [86%] had an SVR and no patient had a liver related serious adverse event or worsening of the acute hepatitis).

Ueda Y, Ikegami T, Soyama A, Akamatsu N, Shinoda M, Ishiyama K, Honda M, et al. Simeprevir or telaprevir with peginterferon and ribavirin for recurrent hepatitis C after living donor liver transplantation: A Japanese multicenter experience. Hepatol Res 2016 Feb 22. [Epub ahead of print] PubMed PMID: 26899352.

(Among 79 patients with chronic hepatitis C, genotype 1, after liver transplantation who were treated wtih peginterferon, ribavirin and either simeprevir [n=79] or telaprevir [n=36], the SVR rates were 56% vs 69%, serious adverse event rates 11% vs 25%, and immune mediated graft dysfunction occurred in 8% vs 11%).