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A SPECIAL MEETING REVIEW EDITION

Updates in the Treatment of Hepatitis C Virus Infection From EASL 2012

The 47th Annual Meeting of the European Association for the Study of the Liver

April 18–22, 2012 • Barcelona, Spain

Special Reporting on:

- Safety of Telaprevir or Boceprevir in Combination with Peginterferon α/ Ribavirin in Cirrhotic Nonresponders. First Results of the French Early Access Program (ANRS CO20-CUPIC)
- SVR in Prior Peginterferon/Ribavirin (PR) Treatment Failures After Re-treatment with Boceprevir + PR: The PROVIDE Study Interim Results
- Futility Rules in Telaprevir Combination Treatment
- Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients: End-of-Treatment (Week 48) Interim Results

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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VICTRELIS plus peginterferon alfa/ribavirin (PR) vs PR

AN ADDED EDGE AGAINST CHRONIC HEPATITIS C VIRUS (HCV) GENOTYPE 1 (G1)



INDICATIONS AND USAGE

VICTRELIS is indicated for the treatment of chronic HCV G1 infection, in combination with PR, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

The following points should be considered when initiating VICTRELIS for treatment of chronic HCV infection:

- VICTRELIS must not be used as monotherapy and should only be used in combination with PR
- VICTRELIS efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes VICTRELIS or other HCV NS3/4A protease inhibitors
- VICTRELIS in combination with PR has not been studied in patients documented to be historical null
 responders (<2-log₁₀ HCV-RNA decline by Treatment Week 12) during prior therapy with PR. The clinical
 studies included subjects who were poorly interferon responsive. Subjects with <0.5-log₁₀ HCV-RNA decline
 in viral load at Treatment Week 4 with PR alone are predicted to have a null response (<2-log₁₀ viral load
 decline at Treatment Week 12) to PR therapy
- Poorly interferon responsive patients who were treated with VICTRELIS in combination with PR have a lower likelihood of achieving a sustained virologic response (SVR), and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to PR



Visit http://www.victrelis.com or scan this QR code to go there directly



An added edge that nearly tripled virologic cure (SVR)^a rates



• VICTRELIS, in combination with PR, has not been studied in patients documented to be historical null responders (<2-log₁₀ HCV-RNA decline by Treatment Week 12) during prior therapy with PR

RESPOND-2 study design. A randomized, parallel-group, double-blind, Phase 3 study in previously treated patients with chronic HCV G1 infection (N=403). Subjects had demonstrated interferon responsiveness (as defined historically by a decrease in HCV-RNA viral load \geq 2-log₁₀ by Treatment Week 12, but never achieved SVR [partial responders] or undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma [relapsers]). All subjects received a 4-week lead-in of PR (peginterferon alfa-2b 1.5 µg/kg/week subcutaneously plus weight-based ribavirin 600 to 1400 mg/day orally BID), followed by either: a response-guided regimen that consisted of 32 weeks of triple therapy with PR + VICTRELIS 800 mg orally TID, followed by 12 additional weeks of PR if virus not cleared by Treatment Week 8 (VICTRELIS RGT); 44 weeks of triple therapy (VICTRELIS PR48); or 44 weeks of PR + placebo (PR48). Primary study end point = SVR.¹ All subjects with detectable HCV-RNA in plasma at Treatment Week 12 were discontinued from treatment. SVR was defined as plasma HCV-RNA undetectable at follow-up Week 24. Plasma HCV-RNA results at follow-up Week 12 were used if plasma HCV-RNA results at follow-up Week 24 were missing.

SELECTED SAFETY INFORMATION

- All contraindications to PR also apply since VICTRELIS must be administered with PR
- Because ribavirin may cause birth defects and fetal death, VICTRELIS in combination with PR is contraindicated in pregnant women and in men whose female partners are pregnant. Avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy; have monthly pregnancy tests; and use 2 or more forms of effective contraception, including intrauterine devices and barrier methods, during treatment and for at least 6 months after treatment has concluded. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS and concomitant ribavirin
- VICTRELIS is contraindicated in coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. VICTRELIS is also contraindicated in coadministration with potent CYP3A4/5 inducers, where significantly reduced VICTRELIS plasma concentrations may be associated with reduced efficacy

BID = twice a day; RESPOND-2 = Retreatment with HCV Serine Protease Inhibitor Boceprevir and PR-2; RNA = ribonucleic acid; TID = 3 times a day.

^aSustained virologic response (SVR) was defined as undetectable HCV-RNA from serum by a sensitive polymerase chain reaction (PCR) assay 24 weeks following the discontinuation of therapy. This is generally considered a "virologic cure," as the rate of late relapse (beyond 24 weeks) is <1%^{3,4}



SELECTED SAFETY INFORMATION

- Drugs that are contraindicated with VICTRELIS include: alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort (hypericum perforatum), lovastatin, simvastatin, drosperinone, *Revatio*[®] (sildenafil) or *Adcirca*[®] (tadalafil) (when used for the treatment of pulmonary arterial hypertension), pimozide, triazolam, and orally administered midazolam
- Anemia and/or Neutropenia–The addition of VICTRELIS to PR is associated with an additional decrease in hemoglobin concentrations compared with PR alone and/or may result in worsening of neutropenia associated with PR therapy alone. Dose reduction or discontinuation of peginterferon alfa and/or ribavirin may be required. Dose reduction of VICTRELIS is not recommended. VICTRELIS must not be administered in the absence of PR
- Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating combination therapy with VICTRELIS. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate
- The most commonly reported adverse reactions (>35%) in clinical trials in adult patients receiving the combination of VICTRELIS with PR were: fatigue, anemia, nausea, headache, and dysgeusia. Of these commonly reported adverse reactions, fatigue, anemia, nausea, and dysgeusia occurred at rates ≥5% above the rates for PR alone in either clinical study. The incidence of these adverse reactions in previously untreated subjects that were treated with combination therapy with VICTRELIS compared with PR alone were: fatigue (58% vs 59%), anemia (50% vs 30%), nausea (46% vs 42%), and dysgeusia (35% vs 16%), respectively. The incidence of these adverse reacted with combination therapy with VICTRELIS compared with PR alone were: fatigue (55% vs 50%), anemia (45% vs 20%), nausea (43% vs 38%), and dysgeusia (44% vs 11%), respectively
- VICTRELIS is a strong inhibitor of CYP3A4/5 and is partly metabolized by CYP3A4/5. The potential for drugdrug interactions must be considered prior to and during therapy

Please see Brief Summary of Prescribing Information on the pages that follow.

References: 1. Bacon BR, Gordon SC, Lawitz E, et al; for HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1207–1217. **2.** Birnkrant D. Direct-acting antivirals: a new era for the treatment of chronic hepatitis C. Slide deck presented at: Antiviral Drugs Advisory Committee Meeting; April 27, 2011; Silver Spring, MD. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ Drugs/AntiviralDrugsAdvisoryCommittee/UCM254076.pdf. Accessed October 5, 2011. **3.** Ghany MG, Strader DB, Thomas DL, et al. AASLD practice guidelines. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335–1374. **4.** Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis*. 2011;52(7):889–900.



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VICTRELIS™ (boceprevir)

CONTRAINDICATIONS

Contraindications to peginterferon alfa and ribavirin also apply to VICTRELIS combination treatment VICTRELIS combination treatment is contraindicated in:

 Pregnant women and men whose female partners are pregnant because of the risks for birth defects and fetal death ociated with ribavirin.

- Coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma
- concentrations are associated with serious and/or life-threatening events, including those in Table 2. Coadministration with potent CYP3A4/5 inducers, where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy, including those in Table 2. Table 2: Drugs that are contraindicated with VICTRELIS

Drug Class	Drugs Within Class that are Contraindicated With VICTRELIS	Clinical Comments	
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	Increased alfuzosin concentrations can result in hypotension.	
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to VICTRELIS	
Antimycobacterial	Rifampin	May lead to loss of virologic response to VICTRELIS.	
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.	
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.	
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response to VICTRELIS.	
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis.	
Oral Contraceptives	Drosperinone	Potential for hyperkalemia.	
PDE5 enzyme Inhibitor	REVATIO® (sildenafil) or ADCIRCA® (tadalafil) when used for the treatment of pulmonary arterial hypertension*	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.	
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.	
Sedative/Hypnotics	Triazolam; orally administered midazolam [†]	Prolonged or increased sedation or respiratory depression.	

* See Drug Interactions, Table 5, for coadministration of sildenafil and tadalafil when dosed for erectile dysfunction ⁺ See Drug Interactions, Table 5 for parenterally administered midazolam.

WARNINGS AND PRECAUTIONS

Pregnancy (Use with Ribavirin and Peginterferon Alfa) Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men mus use at least two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Boutine monthly pregnancy tests must be performed during this time. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS. Two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with VICTRELIS and concomitant ribavirin.

Anomia (Use with Ribevitin and Peginterferon Alfa) Anomia (Use with Ribevitin and Peginterferon Alfa) Anomia has been reported with peginterferon alfa and ribevitin therapy. The addition of VICTREUS to peginterferon alfa and ribevitin is associated with an additional decrease in hemoglobic noncentrations. Complete blood counts should be obtained pretreatment, and at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. If hemoglobin is less than 10 g/dL, a decrease in dosage or interruption of ribavirin is recommended; and if hemoglobin is less than 8.5 g/dL, discontinuation of ribavirin is recommended. Refer to the Package Insert for ribavirin for additional information regarding dosage reduction and/or interruption.

Heter to the Package Insert for havinn for additional information regarding dosage reduction and/or interruption. In clinical trials with VICTRELIS, the proportion of subjects who experienced hemoglobin values less than 10 g/dL and less than 8.5 g/dL was higher in subjects treated with the combination of VICTRELIS with PegIntron*/REBETOL® than in those treated with PegIntron/REBETOL alone (see Table 4). With the interventions used for anemia management in the clinical trials, the average additional decrease of hemoglobin was approximately 1 g/dL. Certain adverse reactions consistent with symptoms of anemia, such as dyspnea, exertional dyspnea, diziness and syncope were reported more frequently in subjects who received the combination of VICTRELIS with PegIntron/REBETOL than in those treated with PegIntron/REBETOL alone. In clinical trials with VICTRELIS, dose modifications (generally of PegIntron/REBETOL) (26%) compared to PegIntron/REBETOL (13%). The proportion of subjects who direction of VICTRELIS with PegIntron/REBETOL (26%) compared to PegIntron/REBETOL (13%). The proportion of subjects who discontinued study drug due to anemia was 1% in subjects treated with the combination of VICTRELIS with PegIntron/REBETOL and 1% in subjects who received PegIntron/REBETOL. The use of erythropoiesis stimulating agents was prevented for management of a nemia, at the investigator's discretion, with or without ribavin dose reduction in the Phase 2 and 3 clinical trials. The proportion of subjects who received an erythropoiesis stimulating agent was 43% in the VICTRELIS containing arms compared to 24% in the PegIntron/REBETOL arms. The proportion of subjects who received a the torner be an an an and the second of a second of the subjects in the VICTRELIS-containing arms compared to less than 1% in subjects who received PegIntron/REBETOL alone.

stoject with received regiments (ICC) close and the explored state of the explored states and have also been reported with peginterferon alfa use in hepatitis C patients. Thromboembolic events have reported in clinical trials with VICTRELIS among subjects receiving the combination of VICTRELIS with PegIntron/REBETOL, and among those receiving PegIntron/REBETOL alone, regardless of erythropoiesis stimulating agent use. No definite causality assessment or benefit risk assessment can be made for these events due to the presence of confounding factors and lack of randomization of ervthropoiesis stimulating agent use.

erythropoiesis stimulating agent use. Neutropenia (Use with Ribavirin and Peginterferon Alfa) In Phase 2 and 3 clinical trials, seven percent of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL had neutrophil counts of less than 0.5 x 10⁹/L compared to 4% of subjects receiving PegIntron/REBETOL alone (see Table 4). Three subjects experienced severe or life-threating infections associated with neutropenia, and two subjects experienced life-threatening neutropenia while receiving the combination of VICTRELIS with PegIntron/REBETOL combination therapy. Complete blood cell differential counts must be conducted in all patients prior to initiating VICTRELIS combination therapy. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time senter as oflicable associated. Decrements in contrabil counts must neutrophile neurotecharge and recentrationation of the conduction of discovery and the ordination of the one diversion or differentiation of the contrability on contrability counts and the ordination of differentiation of the conduction or differentiation of the contrability on contrability counts and the one differentiation and the construction of the contrability on the one diversion or differentiation of the construction of the contrability on the one differentiation of differentiation of the construction of the contrability on the one differentiation of the construction of t points, as clinically appropriate. Decreases in neutrophil counts may require dose reduction or discontinuation of peginterferon alfa and ribavirin.

Refer to Package Inserts for peginterferon alfa and ribavirin for additional information regarding dose reduction or discontinuation for peginterferon alfa and ribavirin.

Drug Interactions

See Table 2 for a listing of drugs that are contraindicated for use with VICTRELIS due to potentially life-threatening adverse events, significant drug interactions or loss of virologic activity. Please refer to Table 5 for established and other potentially significant drug interactions.

Laboratory Tests HCV-RNA levels should be monitored at Treatment Weeks 4, 8, 12, and 24, at the end of treatment, during treatment Flow-up, and for other time points as clinically indicated. Use of a sensitive real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV-RNA levels during treatment is recommended. The assay should have a lower limit of HCV-RNA quantification of equal to or less than 25 IU/mL, and a limit of HCV-RNA detection of approximately 10-15 III/III. For the purposes of assessing Response-Guided Therapy milestones, a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result. Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating VICTRELIS combination therapy. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored

closely at other time points, as clinically appropriate. Refer to the Package Inserts for peginterferon alfa and ribavirin, including pregnancy testing requirements.

ADVERSE REACTIONS

See peginterferon alfa and ribavirin Package Inserts for description of adverse reactions associated with their use

Step per primetrie for and any most of the standard standar VICTRELIS cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice

The following serious and otherwise important adverse drug reactions (ADRs) are discussed in detail in another section of the labeling: Anemia and neutropenia.

The most commonly reported adverse reactions (>35% of subjects regardless of investigator's causality assessment) in adult subjects were fatigue, anemia, nausea, headache, and dysgeusia when VICTRELIS was used in combination with PegIntron and REBETOL

and http://www.combination of VICTRELIS 800 mg three times daily with PegIntron/REBETOL was assessed in 2095 subjects with chronic hepatitis C in one Phase 2, open-label trial and two Phase 3, randomized, double-blind, placebo-controlled clinical trials. SPRINT-1 (subjects who were previously untreated) evaluated the use of VICTRELIS in combination with PegIntron/ REBETOL with or without a four-week lead-in period with PegIntron/REBETOL compared to PegIntron/REBETOL and the set of VICTRELS 800 mg three times daily in combination with PegIntron/REBETOL compared to PegIntron/REBETOL and the use of VICTRELS 800 mg three times daily in combination with PegIntron/REBETOL with a four-week lead-in period with PegIntron/ REEFOL compared to PegIntron/REBETOL alone. The population studied had a mean age of 49 years (3% of subjects were >65 years of age), 39% were female, 82% were white and 15% were black.

Years or age, 33% were remains, 62% were write and 15% were black. During the four week lead-in period with PegIntron/REBETOL in the VICTRELIS-containing arms, 28/1263 (2%) subjects experienced adverse reactions leading to discontinuation of treatment. During the entire course of treatment, the proportion of subjects who discontinued treatment due to adverse reactions was 13% for subjects receiving the combination of VICTRELIS subjects with discloring the darget rought of the standard was 13% for subjects receiving the command of the receivance with Pegintron/REBFTOL and 12% for subjects receiving Pegintron/REBFTOL alone. Events resulting in discontinuation were similar to those seen in previous studies with Pegintron/REBFTOL. Only anemia and fatigue were reported as events that led to discontinuation in >1% of subjects in any arm. Adverse reactions that led to dose modifications of any drug (primarily Pegintron and REBFTOL) occurred in 39% of subjects

receiving the combination of VICTRELIS with PegIntron/REBETOL compared to 24% of subjects receiving PegIntron/REBETOL alone. The most common reason for dose reduction was anemia, which occurred more frequently in subjects receiving the combination of VICTRELIS with PegIntron/REBETOL than in subjects receiving PegIntron/REBETOL alone.

Serious adverse events were reported in 11% of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL and in 8% of subjects receiving PegIntron/REBETOL. Adverse events (regardless of investigator's causality assessment) reported in greater than or equal to 10% of subjects

Audesse events (regariliess of infrestigator's classifier) reported in greater than or equal to by or subjects receiving the combination of VICTRELIS with Peglintrov/REBETOL and reported at a rate of greater than or equal to 5% than Peglintron/REBETOL alone in SPRINT-1, SPRINT-2, and RESPOND-2 are presented in Table 3. Table 3. Adverse Events Reported in ≥10% of Subjects Receiving the Combination of VICTRELIS with Peglintron/REBETOL and Reported at a Rate of ≥5% than Peglintron/REBETOL alone

Adverse Events	Previously Untreated (SPRINT-1 & SPRINT-2) Percentage of Subjects Reporting Adverse Events		Previous Treatment Failures (RESPOND-2)	
			Percentage of Subjects Reporting Adverse Events	
Body System Organ Class	VICTRELIS + PegIntron + REBETOL (n=1225)	PegIntron + REBETOL (n=467)	VICTRELIS + PegIntron + REBETOL (n=323)	PegIntron + REBETOL (n=80)
Median Exposure (days)	197	216	253	104
Blood and Lymphatic	System Disorders			
Anemia	50	30	45	20
Neutropenia	25	19	14	10
Gastrointestinal Diso	rders			
Nausea	46	42	43	38
Dysgeusia	35	16	44	11
Diarrhea	25	22	24	16
Vomiting	20	13	15	8
Dry Mouth	11	10	15	9
General Disorders an	d Administration Site	Conditions		
Fatigue	58	59	55	50
Chills	34	29	33	30
Asthenia	15	18	21	16
Metabolism and Nutr	ition Disorders		-	
Decreased Appetite	25	24	26	16
Musculoskeletal and	Connective Tissue Di	sorders		
Arthralgia	19	19	23	16
Nervous System Diso	rders			
Dizziness	19	16	16	10
Psychiatric Disorders	3		-	
Insomnia	34	34	30	24
Irritability	22	23	21	13
Respiratory, Thoracic	, and Mediastinal Dis	orders	_	
Dyspnea Exertional	8	8	11	5
Skin and Subcutaneo	us Tissue Disorders		_	
Alopecia	27	27	22	16
Dry Skin	18	18	22	9
Rash	17	19	16	6

Other Important Adverse Reactions Reported in Clinical Trials

Among subjects (previously untreated subjects or those who failed previous therapy) who received VICTRELIS in combination with peginterferon alfa and ribavirin, the following adverse drug reactions were reported. These events are notable because of their seriousness, severity, or increased frequency in subjects who received VICTRELIS in combination with peginterferon alfa and ribavirin compared with subjects who received only peginterferon alfa and ribavirin.

Gastrointestinal Disorders Dysgeusia (alteration of taste) was an adverse event reported at an increased frequency in subjects receiving VICTRELIS in Combination with peginterferon alfa and ribavirin compared with subjects receiving peginterferon alfa and ribavirin alone (Table 3). Adverse events such as dry mouth, nausea, vomiting and diarrhea were also reported at an increased frequency in subjects receiving VICTRELIS in combination with peginterferon alfa and ribavirin.

Laboratory Value:

Changes in selected hematological parameters during treatment of adult subjects with the combination of VICTRELIS with PegIntron and REBETOL are described in Table 4.

H<u>emoglobin</u> Decreases in hemoglobin may require a decrease in dosage/interruption or discontinuation of ribavirin

Neutrophils and Platelets The proportion of subjects with decreased neutrophil and platelet counts was higher in the VICTRELIS-containing arms compared to subjects receiving PegIntron/REBETOL alone. Three percent of subjects receiving the combination of VICTRELIS with Peginton/REBETOL had platelet counts of less than 50 x 10⁴/L compared to 1% of subjects receiving Pegintron/ REBETOL alone. Decreases in neutrophils or platelets may require a decrease in dosage or interruption of peginterferon alfa, or discontinuation of therapy.

Table 4: Selected Hematological Parameters

	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)				
	Percentage of Subjects Reporting Selected Hematological Parameters		Percentage of Subjects Reporting Selected Hematological Parameters				
Hematological Parameters	VICTRELIS + PegIntron + REBETOL (n=1225)	PegIntron + REBETOL (n=467)	VICTRELIS + PegIntron + REBETOL (n=323)	PegIntron + REBETOL (n=80)			
Hemoglobin (g/dL)							
<10	49	29	49	25			
<8.5	6	3	10	1			
Neutrophils (x 10	Neutrophils (x 10 ⁹ /L)						
<0.75	31	18	26	13			
<0.5	8	4	7	4			
Platelets (x 10 ⁹ /L)							
<50	3	1	4	0			
<25	<1	0	0	0			

DRUG INTERACTIONS

See also Contraindications and Warnings and Precautions. Potential for VICTRELIS to Affect Other Drugs

Boceprevir is a strong inhibitor of CYP3A4/5. Drugs metabolized primarily by CYP3A4/5 may have increased exposure when administered with VICTRELIS, which could increase or prolong their therapeutic and adverse effects. Boceprevir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C6, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 *in vitro*. In addition, boceprevir does not

Induce CYP1A2, CYP2B6, CYP2C9, CYP2C9, CYP2C9 or CYP3A4/5 *in vitro*. Boceprevir is a potential inhibitor of p-glycoprotein (P-gp) based on in vitro studies. The potential for a drug interaction with sensitive substrates of p-glycoprotein (e.g., digoxin) has not been evaluated in a clinical trial.

Potential for Other Drugs to Affect VICTRELIS

Boceprevir is primarily metabolized by aldo-ketoreductase (AKR). In drug interaction trials conducted with AKR inhibitors diffunisal and ibuprofer, boceprevir exposure did not increase to a clinically significant extent. VICTRELIS may be coadministered with AKR inhibitors.

Coordinate events with Arthmittees. Boceprevir is partly metabolized by CYP3A4/5. It is also a substrate for p-glycoprotein. Coadministration of VICTRELIS with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to boceprevir. Established and Other Potential Significant Drug Interactions

Table 5 provides recommendations based on established or potentially clinically significant drug interactions. VICTRELIS is contraindicated with drugs that are potent inducers of CYP3A4/5 and drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Table 5: Established and Other Potentially Significant Drug Interactions

	Concomitant Drug Class: Drug Name	Effect on Concentration of Boceprevir or Concomitant Drug	Recommendations			
Antiarrhythmics: amiodarone, bepridil, flecainide, propafenone, quinidine digoxin t digoxin		1 antiarrhythmics 1 digoxin	Coadministration with VICTRELIS has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with VICTRELIS. Digoxin concentrations may be increased with VICTRELIS. Use the lowest dose initially with careful tirration and monitoring of serum digoxin concentrations.			
	Anticoagulant: warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be altered when coadministered with VICTRELIS. Monitor INR closely.			
	Antidepressants: trazadone, desipramine	↑ trazadone ↑ desipramine	Plasma concentrations of trazadone and desipramine may increase when administered with VICTRELIS, resulting in adverse events such as dizziness, hypotension and syncope. Use with caution and consider a lower dose of trazadone or desipramine.			
	Antifungals: ketoconazole, itraconazole, posaconazole, voriconazole	boceprevir* tiraconazole ketoconazole posaconazole voriconazole	Plasma concentrations of ketoconazole, itraconazole, voriconazole or posaconazole may be increased with VICTRELIS. When coadministration is required, doses of ketoconazole and itraconazole should not exceed 200 mg/day.			
	Anti-gout: colchicine	1 colchicine	Significant increases in colchicine levels are expected; fatal colchicine toxicity has been reported with other strong CYP3A4 inhibitors. Patients with renal or hepatic impairment should not be given colchicine with V(CTRELIS); 0.6 mg (I tablet) × 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prophysiax is of gout flares (giving treatment with VICTRELIS); If the original regimen was 0.6 mg cnce a day, reduce the dose to 0.3 mg cnce a very other day. The original regimen was 0.6 mg cnce a day, reduce the dose to 0.3 mg cnce a very other day. Treatment of familial Mediterranean fever (FMF) (during treatment with VICTRELIS); Maximum daily dose of 0.6 mg (maybe given as 0.3 mg twice a day).			
	Anti-infective: clarithromycin	1 clarithromycin	Concentrations of clarithromycin may be increased with VICTRELIS; however, no dosage adjustment is necessary for patients with normal renal function.			
	Antimycobacterial: rifabutin	↓ boceprevir ↑ rifabutin	Increases in rifabutin exposure are anticipated, while exposure of boceprevir may be decreased. Doses have not been established for the 2 drugs when used in combination. Concomitant use is not recommended.			
	Calcium Channel Blockers, dihydropyridine: felodipine, nifedipine, nicardipine	t dihydropyridine calcium channel blockers	Plasma concentrations of dihydropyridine calcium channel blockers may increase when administered with VICTRELIS. Caution is warranted and clinical monitoring is recommended.			
	Corticosteroid, systemic: dexamethasone	↓ boceprevir	Coadministration of VICTRELIS with CYP3A4/5 inducers may decrease plasma concentrations of boceprevir, which may result in loss of therapeutic effect. Therefore, this combination should be avoided if possible and used with caution if necessary.			
	Corticosteroid, inhaled: budesonide, fluticasone	↑ budesonide ↑ fluticasone	Concomitant use of inhaled budesonide or fluticasone with VICTRELIS may result in increased plasma concentrations of budesonide or fluticasone, resulting in significantly reduced serum cortisol concentrations. Avoid coadministration if possible, particularly for extended durations.			
	Endothelin Receptor Antagonist: bosentan	↑ bosentan	Concentrations of bosentan may be increased when coadministered with VICTRELIS. Use with caution and monitor closely.			
	HIV Non-Nucleoside Reverse Transcriptase	↓ boceprevir*	Plasma trough concentrations of boceprevir were decreased when VICTRELIS was coadministered with efavirenz, which may result in loss of the accountio effort. A weid combination			

Concentration Concomitant Drug of Boceprevir or **Concomitant Drug Class: Drug Name** Recommendations HIV Protease Inhibitors ↓ boceprevir* Boceprevir concentrations decreased with ritonavir: the effect of ritonavir 1 or 1 HIV protease ritonavir-boosted HIV protease inhibitors on boceprevir exposure inhibitors is unknown. The effect of VICTRELIS on HIV protease inhibitor oncentrations is unknown Titrate atorvastatin dose carefully and do not exceed maximum daily dose of 20 mg during coadministration with VICTRELIS HMG-CoA Reductase 1 atorvastatin Inhibitors: atorvastatin Plasma concentrations of cvclosporine, sirolimus and tacrolimus are expected Immunosuppressants: 1 immunosuppressants cyclosporine, sirolimus to be increased significantly during coadministration with VICTRELIS. Close monitoring of immunosuppressant blood levels is recommended. tacrolimus Inhaled beta-agonist: ↑ salmeterol Concurrent use of inhaled salmeterol and VICTBELIS is not recommended salmeterol due to the risk of cardiovascular events associated with salmeterol Narcotic Analgesic/ ↑ or ↓ methadone Plasma concentrations of methadone or buprenorphine may increase Opioid Dependence: ↑ or ↓ buprenorphine or decrease when coadministered with VICTRELIS. However, the combination has not been studied. Clinical monitoring is recommended methadone, buprenorphine as the dose of methadone or buprenorphine may need to be altered during concomitant treatment with VICTRELIS. Oral hormonal The effect of boceprevir on other progestins is unknown; however, increases in exposure are anticipated. Concentrations of ethinyl estradiol decreased in the presence of 1 drospirenone contraceptives ↓ ethinyl estradiol drospirenone/ethinyl boceprevir. Systemic hormonal contraceptives should not be relied upon as an effective method of contraception in women during treatment . estradiol with VICTRELIS. Two alternative effective methods of contraception should be used during combination treatment with ribavirin, and may include intrauterine devices and barrier methods. Increases in PDE5 inhibitor concentrations are expected, and may result in an increase in adverse events, including hypotension, syncope, visual PDE5 inhibitors 1 sildenafil sildenafil, tadalafil, vardenafil tadalafi 1 vardenafil disturbances, and priapism Use of REVATIO® (sildenafil) or ADCIRCA® (tadalafil) for the treatment of pulmonary arterial hypertension (PAH) is contraindicated with VICTRELIS. participation of the second se Sildenafil: 25 mg every 48 hours Tadalafil: 10 mg every 72 hours Vardenafil: 2.5 mg every 24 hours Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during coadministration of VICTRELIS. A Sedative/hypnotics: 1 midazolarr alprazolam; 1 alprazolam IV midazolarr lower dose of IV midazolam or alprazolam should be considered.

Table 5: Established and Other Potentially Significant Drug Interactions (continued)

Effect on

* These combinations have been studied

USE IN SPECIFIC POPULATIONS

Pregnancy VICTRELIS must be administered in combination with peginterferon alfa and ribavirin.

Pregnancy Category X: Use with Ribavirin and Peginterferon Alfa Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans. Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 6 months after treatment. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS. Therefore, two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with VICTRELIS and concomitant ribavirin.

In case of exposure during pregnancy, a Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214. Pregnancy Category B: VICTRELIS

VICTRELIS must not be used as a monotherapy. There are no adequate and well-controlled studies with VICTRELIS in pregnant

No effects on fetal development have been observed in rats and rabbits at boceprevir AUC exposures approximately 11.8- and 2.0-fold higher, respectively, than those in humans at the recommended dose of 800 mg three times daily Nursing Mothers

It is not known whether VICTRELIS is excreted into human breast milk. Levels of boceprevir and/or metabolites in the milk of lactating rats were slightly higher than levels observed in maternal blood. Peak blood concentrations of boceprevir and/ or metabolities in nursing purpose were less than 1% of those of maternal block. Teachood concentrations Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with VICTRELIS, taking into account the importance of the therapy to the mother.

Pediatric Use

The safety, efficacy, and pharmacokinetic profile of VICTRELIS in pediatric patients have not been studied. Geriatric Use

Clinical studies of VICTRELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of VICTRELIS in geriatric patients due to the greater frequency of decreased hepatic function, concomitant diseases and other rug therapy.

Renal Impairment

No dosage adjustment of VICTRELIS is required for patients with any degree of renal impairment.

Hepatic Impairment No dose adjustment of VICTRELIS is required for patients with mild, moderate or severe hepatic impairment. Safety and efficacy of VICTRELIS have not been studied in patients with decompensated cirrhosis. See Package Inserts for peginterferon alfa for contraindication in hepatic decompensation.

Human Immunodeficiency Virus (HIV) Co-Infection The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic

hepatitis C genotype 1 infection have not been established in patients co-infected with HIV and HCV. Hepatitis B Virus (HBV) Co-Infection

The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in patients co-infected with HBV and HCV have not been studied. **Organ Transplantation** The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic

hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied.



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Safety of Telaprevir or Boceprevir in Combination with Peginterferon α/Ribavirin in Cirrhotic Nonresponders. First Results of the French Early Access Program (ANRS CO20-CUPIC)

Triple therapy with a hepatitis C virus (HCV) NS3/4A protease inhibitor such as telaprevir or boceprevir plus peginterferon α -2a and ribavirin can improve sustained virologic response (SVR) rates in patients infected with HCV. However, few cirrhotic patients were included in the studies that first evaluated these therapies, such as REAL-IZE (telaprevir) and RESPOND-2 (boceprevir).^{1,2} Therefore, Christophe Hézode and associates from the ANRS-a French national agency for research on AIDS and viral hepatitis-conducted another study to determine the safety and efficacy of telaprevir or boceprevir plus peginterferon α -2a and ribavirin in HCVinfected patients with cirrhosis.3 Hézode presented the interim safety and tolerability results of this study at the 2012 European Association for the Study of the Liver (EASL) Annual Meeting, which was held April 18-22 in Barcelona, Spain.

This study included patients from the CUPIC cohort who had compensated, Child-Pugh class A cirrhosis, genotype 1 HCV infection, and a history of relapse or partial response (HCV RNA decline >2 log₁₀ at Week 12 but failure to achieve undetectable HCV RNA levels) when previously treated with peginterferon and ribavirin. Patients received 1 of 2 treatments: 12 weeks of telaprevir, peginterferon, and ribavirin followed by 36 weeks of peginterferon and ribavirin; or 4 weeks of peginterferon and ribavirin followed by 44 weeks of boceprevir, peginterferon, and ribavirin. Hézode noted that the patients were not randomized into treatment

groups; therefore, this study cannot provide a direct comparison between telaprevir and boceprevir.

The investigators analyzed safety data from patients who had received at least 16 weeks of antiviral treatment (n=455). The female-to-male ratio was 0.4, and the mean patient age was 57 years. The majority of patients were infected with genotype 1b HCV, and portal hypertension was present in 15% of the patients. Compared to the cirrhotic patients included in the REALIZE study, the patients in this study's telaprevir treatment group (n=296) were older and had lower mean hemoglobin and platelet levels; approximately one third of these patients met at least 1 of the exclusion criteria for the REALIZE study. Similarly, the patients in this study's boceprevir treatment group (n=159) differed from the cirrhotic patients included in the RESPOND-2 study, with 26% of these patients meeting at least 1 of the exclusion criteria for the RESPOND-2 study.

There was a high rate of serious adverse events in both the telaprevir and boceprevir treatment groups (51% and 40%, respectively). Discontinuation due to adverse events occurred in 14% of the telaprevir group and 7% of the boceprevir group. Anemia (hemoglobin level $\leq 10 \text{ g/dL}$) was observed in approximately 30% of patients; interventions included administration of erythropoietin (in approximately two thirds of the patients in each treatment group) and blood transfusions (in 15% and 11% of the telaprevir and boceprevir groups, respectively). Grade 3-4 adverse events included neutropenia

(12% and 10% of the telaprevir and boceprevir treatment groups, respectively), thrombocytopenia (22% and 7%), rash (7% and 1%), and severe infection (9% and 2.5%). Hepatic decompensation occurred in 4.4% of the patients in each treatment group. Hézode noted that the occurrences of severe infection and hepatic decompensation were likely due to interferon rather than the protease inhibitor. Additional adverse events occurred in 53% of the telaprevir group and 32% of the boceprevir group. Six patients in the telaprevir group died from sepsis or hepatic decompensation, and 2 patients in the boceprevir group died from sepsis. While the study design did not allow for direct comparisons between telaprevir and boceprevir, there appears to be a trend towards fewer adverse events with boceprevir.

Hézode also presented some preliminary efficacy data from the CUPIC study. In the telaprevir treatment group, the rapid virologic response (RVR) rate was 53%. At Weeks 12 and 16, undetectable HCV RNA levels were achieved by 86% of patients who received telaprevir-based triple therapy. In the boceprevir treatment group, undetectable HCV RNA levels were achieved by 37% of patients at Week 8 and 71% of patients at Week 16.

Hézode concluded that when telaprevir and boceprevir were administered with peginterferon α -2a and ribavirin as part of a triple therapy regimen, both protease inhibitors had poor safety profiles in genotype 1 HCV–infected patients with compensated cirrhosis. The rate of serious adverse events in this population was 40–51%, compared to rates of

ABSTRACT SUMMARY In Vitro Characterization of the Pan-Genotype Activity of the HCV NS3/4A Protease Inhibitors Boceprevir and Telaprevir

The peptidyl NS3/4A protease inhibitors boceprevir and telaprevir are approved for the treatment of genotype 1 HCV when used in combination with peginterferon and ribavirin. However, evidence suggests that these protease inhibitors may also be useful for the treatment of other HCV genotypes. Telaprevir has been shown to reduce HCV RNA levels in patients infected with genotype 2 HCV but not in those with genotype 3 HCV.¹ Boceprevir has been associated with a reduction in HCV RNA levels in HCV-infected patients with either genotype 2 or 3.²

At the 2012 EASL Annual Meeting, John Howe and coauthors presented data on the in vitro activity of boceprevir and telaprevir against the 6 major genotypes of HCV.³ To measure the inhibitory activity of these drugs, recombinant his-tagged NS3/4A proteases were expressed and purified for use in a kinetic chromogenic assay. Boceprevir and telaprevir both demonstrated activity against genotypes 1 through 6 in this assay.

A replicon assay was then performed to measure the cell-based activity of boceprevir and telaprevir against all 6 HCV genotypes. Replicon cell lines (genotype 1a, 1b, 2a, 2b, 3a, 5a) were treated with boceprevir or telaprevir for 3 days. HCV RNA levels were measured using a real-time polymerase chain reaction assay (Taqman) to determine the potency of the drugs. Both boceprevir and telaprevir were found to be active against the assayed genotypes.

Finally, in a cell-based NS3/4A phenotype assay, genotype 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a NS3/4A sequences were cloned from patient isolates and inserted into an expression vector. The expression vectors were coexpressed in cells with a modified secreted alkaline phosphatase (SEAP) reporter plasmid that contained a NS3/4A cleavage site. Measurement of SEAP activity revealed boceprevir and telaprevir potency. With boceprevir, there was a 2.2-fold shift for genotype 3a compared to genotype 1a and a 3.2-fold shift for genotype 4a compared to genotype 1a. With telaprevir, there was an 8-fold shift for genotype 3a and a 5.9-fold shift for genotype 4a, both compared to genotype 1a. Structural modeling and sequence alignment determined that the nonconserved NS3 amino acids R123T, D168Q, and I132L might play an important role in boceprevir and telaprevir interactions with genotype 3 HCV; this hypothesis is currently under investigation.

The authors concluded that use of boceprevir for the treatment of genotypes 3 and 4 and use of telaprevir for the treatment of genotypes 2, 5, and 6 should be further evaluated in the clinical setting.

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2. Silva M, Kasserra C, Gupta S, et al. Antiviral efficacy of boceprevir monotherapy in treatmentnaïve subjects with chronic hepatitis C genotype 2/3. *Hepatology International*. 2011;5:259.

3. Howe JA, Graham D, McMonagle P, et al. In vitro characterization of the pan-genotype activity of the HCV NS3/4A protease inhibitors boceprevir and telaprevir. Presented at the 47th Annual Meeting of the European Association for the Study of the Liver; April 18–22, 2012; Barcelona, Spain. Abstract #884.

9% and 14% in the REALIZE and RESPOND-2 studies, respectively. However, the initial efficacy data suggest that triple therapy can achieve good on-treatment virologic responses in cirrhotic patients. The investigators concluded that triple therapy should be used with caution and close monitoring in patients with cirrhosis and genotype 1 HCV infection.

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3. Hézode C, Dorival C, Zoulim F, et al; ANRS CO20-CUPIC Study Group. Safety of telaprevir or boceprevir in combination with peginterferon α/ribavirin in cirrhotic nonresponders. First results of the French early access program (ANRS CO20-CUPIC). Presented at the 47th Annual Meeting of the European Association for the Study of the Liver; April 18–22, 2012; Barcelona, Spain. Abstract #8.

Sustained Virologic Response (SVR) in Prior Peginterferon/ Ribavirin (PR) Treatment Failures After Re-treatment with Boceprevir (BOC) + PR: The PROVIDE Study Interim Results

ddition of boceprevir to peginterferon and ribavirin significantly improves SVR rates in both treatment-naïve and previously treated patients. The PROVIDE study was conducted to determine SVR rates among prior null responders, prior partial nonresponders, and prior relapsers when these patients were re-treated with triple therapy consisting of boceprevir, peginterferon, and ribavirin. Jean-Pierre Bronowicki presented interim efficacy and safety data from the PROVIDE study at the 2012 EASL Annual Meeting.¹

The PROVIDE study enrolled patients from the control arms of phase II and phase III clinical trials of boceprevir; these patients had all received at least 12 weeks of peginterferon and ribavirin but failed to achieve SVR due to futility, virologic breakthrough, or relapse. As part of the PROVIDE study, patients received 4 weeks of lead-in therapy with peginterferon and ribavirin if it had been more than 2 weeks since their last treatment. Patients then received boceprevir (800 mg three times daily), peginterferon (1.5 µg/kg/week), and weight-based ribavirin (600-1,400 mg/day) for up to 44 weeks. Treatment was stopped due to futility if patients had a detectable HCV RNA level at 12 weeks. The primary endpoint of the analysis was undetectable HCV RNA levels 24 weeks after the end of treatment (SVR24).

The study enrolled 168 patients from the control arms of the SPRINT-1, SPRINT-2, RESPOND-2, and boceprevir/Pegasys trials; 51% of patients were partial responders, 31% were null responders (<2 log₁₀ decline in HCV RNA level at Treatment Week 12), and 15% were relapsers. The majority of patients were white (84%) and male (67%), and the mean patient age was 52 years. A high viral load (>800,000 IU/mL) was present in 77% of patients, and 61% of patients were infected with genotype 1a HCV. The proportion of patients with severe fibrosis (Metavir score of F3 or F4) ranged from 8% among prior relapsers to 22% among prior partial responders.

Four patients discontinued therapy during the lead-in phase; of the 164 patients who received triple therapy, 94 patients completed treatment, 53 discontinued treatment, and 17 patients were on-therapy at the time of this analysis. Reasons for discontinuation included adverse events (n=11), treatment failure (n=32), and nonmedical reasons (n=10). Thus, 138 patients were included in the interim analysis presented by Bronowicki.

After the lead-in phase, 78% of prior null responders and 24% of prior partial responders/relapsers had a less-than-1 log₁₀ decline in HCV RNA level; among these patients, SVR rates were 36% in prior null responders and 64% in prior partial responders. Among patients with at least a 1 log₁₀ decline in HCV RNA level, the overall SVR rate was 68%: 55% in prior null responders, 72% in prior partial responders, and 56% in relapsers. The overall SVR rate at the end of the follow-up period was 59% (81 of 138 patients): 40% in prior null responders, 68% in prior partial responders, and 56% in relapsers. Bronowicki noted that few relapsers were included in this analysis; while 26 relapsers were enrolled in the study, only 9 of these patients were included in the interim analysis. A multivariate analysis found that prior nonresponder status, baseline platelet levels, gender, and high viral load were independent predictive factors for SVR.

Serious adverse events were observed in 10% of patients. No life-threatening adverse events or deaths occurred during the study, but 7% of patients discontinued the study drug due to adverse events. The most common adverse event was anemia, which occurred in 48% of patients; severe anemia (hemoglobin level <8.5 g/dL) occurred in 11% of patients, with 1 patient discontinuing the study drug for this reason. Forty percent of patients were treated with erythropoietin for management of anemia, and 2% of patients required blood transfusions. Other common adverse events included fatigue (47%), dysgeusia (34%), nausea (30%), and neutropenia (22%). Bronowicki noted that this safety profile is similar to the safety profile observed in other studies of triple therapy with boceprevir, peginterferon, and ribavirin.

In conclusion, Bronowicki stated that triple therapy with boceprevir, peginterferon, and ribavirin achieved high SVR rates among patients in whom prior therapy with peginterferon and ribavirin alone had led to null response, partial response, or relapse.

Reference

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Futility Rules in Telaprevir Combination Treatment

or patients treated with directacting antiviral drugs such as telaprevir, the application of futility rules limits the emergence or selective expansion of drug-resistant HCV variants and avoids prolonged exposure to side effects in patients who are unlikely to respond to therapy. According to the stopping rules used in phase III clinical trials of telaprevir, this drug was discontinued if a treatment-naïve patient's HCV RNA level was greater than 1,000 IU/mL at Week 4 or if a treatment-experienced patient's HCV RNA level was greater than 100 IU/mL at Week 4, 6, or 8.1-3

In addition, all study drugs were discontinued if the patient had a less-than-2 \log_{10} decrease in HCV RNA level at Week 12 or if HCV RNA was detectable at Week 24. To ensure that these futility rules are appropriate for clinical use, an international group of investigators performed retrospective analyses of the major phase III studies of telaprevir. Ira M. Jacobson presented results of this analysis at the 2012 EASL Annual Meeting.⁴

This retrospective analysis included data from 2 phase III trials of treatmentnaïve genotype 1 HCV-infected patients (ADVANCE and ILLUMINATE) and a phase III trial of prior relapsers, partial responders, and nonresponders (REAL-IZE).1-3 The analysis was restricted to patients from the ADVANCE and ILLU-MINATE studies who received 12 weeks of telaprevir, peginterferon, and ribavirin followed by 12 or 36 weeks of peginterferon and ribavirin and patients from the REALIZE study who received 12 weeks of telaprevir, peginterferon, and ribavirin followed by 36 weeks of peginterferon and ribavirin. On-treatment HCV RNA levels were measured at Weeks 4 and 12 for the treatment-naïve patients (ADVANCE and ILLUMINATE) and at Weeks 4, 6, 8, and 12 for treatment

ABSTRACT SUMMARY 100% SVR in *IL-28B* CC Patients Treated with 12 Weeks of Telaprevir, Peginterferon, and Ribavirin in the PROVE2 Trial

In the ADVANCE trial, 90% of patients with genotype 1 HCV infection and the interleukin (IL)-28B CC genotype achieved SVR when treated with telaprevir, peginterferon, and ribavirin. To investigate SVR rates in patients with *IL-28B* genotype CC versus non-CC, Bronowicki and associates performed a retrospective analysis of data from the PROVE2 study; their results were presented at the 2012 EASL Annual Meeting.¹

The PROVE2 study enrolled noncirrhotic, treatment-naïve patients who were infected with genotype 1 HCV. In this trial, patients were assigned to 1 of 4 treatment regimens: telaprevir, peginterferon α -2a, and ribavirin for 12 weeks; telaprevir, peginterferon α -2a, and ribavirin for 12 weeks followed by peginterferon α -2a and ribavirin for an additional 12 weeks; telaprevir and peginterferon α -2a for 12 weeks; or peginterferon α -2a and ribavirin for 48 weeks (control group).

Samples from treatment-naïve patients with genotype 1 HCV infection were analyzed for the presence of the IL-28B CC genotype at polymorphic site rs12979860. Of the 156 patients who consented to genetic testing, data were available for 141 patients. The mean age of the patients was 44.5 years, the mean body mass index was 23.7 kg/m², and 64% were male. Patients had a mean baseline viral load of 6.5 log₁₀ IU/mL, and 52% of patients had genotype 1b HCV infection. In terms of IL-28B genotype, 43 patients (30%) had genotype CC, 83 patients (59%) had genotype CT, and 15 patients (11%) had genotype TT.

All of the patients with *IL-28B* genotype CC who received telaprevir, peginterferon, and ribavirin for 12 weeks achieved SVR (n=12). SVR was also achieved in the majority of patients with *IL-28B* genotype CC who received other treatment regimens: 94% (15/16) of patients who were treated with telaprevir, peginterferon,

and ribavirin for 12 weeks followed by peginterferon and ribavirin for an additional 12 weeks; 75% (3/4) of patients treated with telaprevir and peginterferon for 12 weeks; and 64% (7/11) of patients in the control group. The investigators concluded that 12 weeks of treatment with telaprevir, peginterferon α -2a, and ribavirin was a successful therapy for treatment-naïve, noncirrhotic, white patients with genotype 1 HCV and IL-28B genotype CC. The CONCISE trial is currently being conducted to investigate SVR rates in IL-28B genotype CC patients treated with telaprevir, peginterferon α -2a, and ribavirin for 12 or 24 weeks.

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At Week 4, a total of 25 patients had HCV RNA levels greater than 1,000 IU/mL: 1.7% (14/844) of treatment-naïve patients, 0.7% (1/138) of prior relapsers, 0% (0/46) of prior partial responders, and 14% (10/70) of prior null responders. None of these patients subsequently achieved SVR. Twenty-three of these 25 patients reached their lowest HCV RNA levels around Week 2, after which HCV RNA levels increased by Week 4. This pattern was observed in both treatment-naïve and treatment-experienced patients. At least 1 resistance variant was present in 23 of the 25 patients. Twelve treatmentnaïve patients and 8 treatment-experienced patients had the V36M+R115K variant, 1 treatment-naïve patient had

the A156S/T/V variant, and 2 treatmentexperienced patients had the R155K variant. Jacobson underscored the fact that most patients who had an HCV RNA level above 1,000 IU/mL at Week 4 were already experiencing viral rebound and harboring viral variants.

A second subset of patients had HCV RNA levels between 100 IU/mL and 1,000 IU/mL at Week 4: 1.9% (16/844) of treatment-naïve patients, 0% (0/138) of prior relapsers, 2.2% (1/46) of prior partial responders, and 8.6% (6/70) of prior null responders. Of these 23 patients, 5 (22%) achieved SVR; 4 of these patients were treatmentnaïve and 1 patient was treatmentexperienced. Thus, Jacobson noted that there was a low but persistent chance for SVR in both treatment-naïve and treatment-experienced patients who had HCV RNA levels between 100 IU/mL and 1,000 IU/mL at Week 4.

At Week 12, HCV RNA levels over 1,000 IU/mL were detected in 1.5% (9/605) of treatment-naïve patients, 0.8% (1/119) of prior relapsers, 0% (0/39) of prior partial responders, and 3.9% (2/51) of prior null responders. None of these patients achieved SVR. HCV RNA levels between 100 IU/mL and 1,000 IU/mL were detected in 1.2% (7/605) of treatment-naïve patients and 12% (6/51) of prior null responders at Week 12; 2 of the 7 treatment-naïve patients achieved SVR, but none of the treatment-experienced patients achieved SVR. At Week 24, 32 (3.5%) treatmentnaïve patients and 12 (17%) treatmentexperienced patients had detectable HCV RNA levels; none of these patients achieved subsequent SVR.

In summary, none of the patients in this retrospective analysis achieved SVR if their HCV RNA levels were above 1,000 IU/mL at Week 4 or

ABSTRACT SUMMARY Burden of Illness in Treatment-Naïve Hepatitis C (HCV) Patients in the US

At the 2012 EASL Annual Meeting, Antoine El Khoury and colleagues presented the results of a study that examined work productivity, daily activities, healthcare resource use, economic costs, and health-related quality of life among treatment-naïve, HCV-infected patients in the United States.1 Patient data were collected using the 2010 US National Health and Wellness Survey. The analysis was restricted to patients who reported physician-diagnosed HCV infection, no HIV/AIDS or hepatitis B co-infection, and no prior or current treatment for HCV infection (n=306). The HCV-infected group was compared to an unmatched control group (n=73,586) and to a matched control aroup (n=306).

The Work Productivity and Activity Impairment questionnaire was used to assess impairment in work and nonwork activities. This questionnaire revealed that activity impairment was significantly greater in untreated HCV-infected patients (42.2%) than in matched controls (27.3%; P<.001). Impairment at work was assessed among employed HCVinfected patients (n=121) and matched controls (n=141) in terms of absenteeism (the percentage of work time missed due to the patient's health in the past 7 days), presenteeism (the percentage of impairment at work due to the patient's health in the past 7 days), and overall work impairment (combination of absenteeism and presenteeism). There was no significant difference in absenteeism between untreated HCV-infected patients and matched controls (5.0% vs 2.8%; P=.089); however, untreated HCV-infected patients had increased rates of presenteeism (23.2% vs 13.1%; P<.001) and overall work impairment (26.2% vs 14.9%; P<.001). A cost analysis showed that estimated average indirect costs were higher in the untreated HCVinfected group, although this difference was only significant for indirect costs related to presenteeism (P<.001).

In terms of healthcare resource utilization, untreated HCV patients had significantly more physician visits annually than matched controls (12.2 vs 8.2; P<.001), as well as more emergency room visits (0.76 vs 0.54; P=.023); however, there was no significant difference in hospitalizations (0.42 vs 0.25; P=.071). Associated direct costs were all higher among untreated Additionally, HCV-infected patients. health-related quality of life in untreated HCV-infected patients was poorer than in matched controls as shown by a lower mean Mental Component Summary score (43.7 vs 48.6; P<.001), a lower mean Physical Component Summary score (40.2 vs 44.9; P<.001), and a lower Health Utility score (0.65 vs 0.73; P<.001).

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therapy if detectable virus is present at Week 24. Jacobson added that this analysis should increase practicing clinicians' confidence that these stopping rules are appropriate for their patients.

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ABSTRACT SUMMARY A Randomized Trial Comparing Ribavirin Dose Reduction Versus Erythropoietin for Anemia Management in Previously Untreated Patients with Chronic Hepatitis C Receiving Boceprevir Plus Peginterferon/Ribavirin

The addition of an HCV protease inhibitor to peginterferon and ribavirin therapy can increase the risk for anemia. Management strategies for combating anemia include ribavirin dose reduction and administration of erythropoietin. At the 2012 EASL Annual Meeting, Fred Poordad and colleagues presented the results of a study that sought to determine the efficacy, safety, and tolerability of erythropoietin administration versus ribavirin dose reduction for the treatment of anemia in patients receiving boceprevir, peginterferon, and ribavirin.¹

Treatment-naïve patients with chronic, genotype 1 HCV infection were enrolled in this study. Participants were at least 18 years of age, showed no evidence of hepatocellular carcinoma (HCC) or co-infection, and had normal baseline hemoglobin levels (12–15 g/dL for female patients; 13–15 g/dL for male patients). Patients received 4 weeks of lead-in therapy with peginterferon (1.5 µg/kg/week) and ribavirin (600–1,400 mg/day) followed by boceprevir (800 mg three times daily) plus peginterferon and ribavirin for a total treatment duration of either 28 or 48 weeks.

Hemoglobin levels at or below 10 g/dL after the 4-week lead-in period occurred in 73% (500/687) of patients; these patients were randomly assigned to either a 200–400 mg/day reduction in ribavirin dose (n=249) or 40,000 IU/week erythropoietin (n=251). If hemoglobin levels dropped to 8.5 g/dL or lower, secondary intervention was allowed. If hemoglobin levels dropped to 7.5 g/dL or lower, the patient was discontinued from the study.

Comparison of the ribavirin dosereduction arm and the erythropoietin arm revealed no differences in end-oftreatment virologic response rates (82% in both groups), relapse rates (10% in both groups), or SVR rates (71% in both groups). A multivariate logistic regression analysis that assessed race, gender, body weight, fibrosis score, and *IL-28B*

genotype found similar SVR rates in the ribavirin dose-reduction arm and the erythropoietin arm regardless of subgroup. Statistical analyses also revealed that the probability of achieving SVR was similar for patients managed with ribavirin dose reduction and those given erythropoietin (P=.769), and SVR was not associated with the degree of hemoglobin decline among patients who developed anemia. Finally, the rates of serious adverse events and study discontinuations were similar for patients who were managed with ribavirin dose reduction and those who received erythropoietin.

Reference

1. Poordad FF, Lawitz EJ, Reddy KR, et al. A randomized trial comparing ribavirin dose reduction versus erythropoietin for anemia management in previously untreated patients with chronic hepatitis C receiving boceprevir plus peginterferon/ribavirin. Presented at the 47th Annual Meeting of the European Association for the Study of the Liver; April 18–22, 2012; Barcelona, Spain. Abstract #1419.

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Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients: End-of-Treatment (Week 48) Interim Results

ne third of all HCV-infected patients are co-infected with HIV, but few studies have examined the safety and efficacy of protease inhibitors in this population. Thus, a double-blind, phase II trial was conducted to determine the efficacy and safety of triple therapy with boceprevir, peginterferon, and ribavirin in patients who were co-infected with genotype 1 HCV and HIV (<50 copies/mL).

After a 4-week lead-in period during which patients received peginterferon α -2b (1.5 µg/kg/week) and weight-based ribavirin (600–1,400 mg/day), patients were randomized (2:1) to receive either boceprevir (800 mg three times daily) or placebo plus peginterferon and ribavirin for an additional 44 weeks. All patients were on combination antiretroviral therapy, but zidovudine, didanosine, stavudine, efavirenz, etravirine, and nevirapine were not permitted, and patients had not received previous treatment for HCV. The primary efficacy endpoint for this study was SVR24. Josep Mallolas presented interim results of this ongoing study at the 2012 EASL Annual Meeting.¹

Most of the enrolled patients were noncirrhotic (95%), white (82%), and male (69%); patients had a median age of 43 years; 88% of patients had high baseline HCV RNA levels; and 65% of patients were infected with genotype 1a HCV. Overall, patients' HIV infection was well controlled; patients had median CD4+ T-cell counts of at least 200 cells/mm³ and stable undetectable HIV viral loads. The full 48-week treatment regimen was completed by 61% of the patients assigned to boceprevir plus peginterferon and ribavirin (boceprevir group) and by 32% of patients treated with peginterferon and ribavirin alone (control group). Mallolas noted that the high rate of discontinuation in the control group was primarily due to virologic treatment failure (41%), whereas discontinuation in the boceprevir group was largely due to adverse events (20%).

Undetectable HCV RNA levels were observed in 42.2% of patients in the boceprevir group and 14.7% of patients in the control group by Treatment Week 8. By the end of treatment, undetectable HCV RNA levels were observed in 63.9% of patients in

ABSTRACT SUMMARY Development and Validation of Prediction Models for Risk of Hepatocellular Carcinoma Among Hepatitis C Virus–Infected Patients

At the 2012 EASL Annual Meeting, Mei-Hsuan Lee and colleagues presented the results of a study that sought to develop and validate a tool for estimating the risk of HCC among patients infected with HCV.1 Two cohorts of patients were used for the study: (1) a model development cohort of 975 anti-HCV seropositive patients and (2) the external validation cohort of 562 anti-HCV seropositive patients. The investigators developed 3 models for predicting the 5-year risk of HCC. Model 1 included age, alanine aminotransferase (ALT) level, the ratio of aspartate aminotransferase to ALT (AAR), and the presence of cirrhosis. Model 2 included age, ALT, AAR, cirrhosis, and serum HCV RNA level. Model 3

included age, ALT, AAR, cirrhosis, serum HCV RNA level, and HCV genotype. To estimate regression coefficients for each HCC risk factor in the model development cohort, the investigators used Cox proportional hazards models. The coefficient was then converted to a risk score that was applied to patients in the validation cohort.

There were varying total risk scores for each of the 3 models; overall, patients were at an increased risk for HCC if they had higher total risk scores. The total risk score for each patient in the validation cohort was calculated by using the scoring system; patients were then categorized as having a low, medium, or high risk for HCC. For model 1, the cumulative risks for these 3 groups were 3%, 14%, and 27%, respectively. For model 2, the cumulative risks were 5%, 13%, and 19%, respectively. For model 3, the cumulative risks were 6%, 13%, and 23%, respectively. The performance of each model was evaluated by the area under the receiver operating curve (AUROC). For all 3 models, the AUROCs in the validation cohort ranged from 0.71 to 0.75.

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ABSTRACT SUMMARY High Sustained Virologic Response Rates with Response-Guided Danoprevir Plus Peginterferon α -2A (40KD) and Ribavirin in Treatment-Naïve, HCV Genotype 1 Patients: ATLAS Study Final Results

The ATLAS study was a multicenter, phase II trial that evaluated the safety, efficacy, and tolerability of responseguided treatment with danoprevir (a second-generation HCV protease inhibitor), peginterferon α -2a, and ribavirin in treatment-naïve patients with chronic, genotype 1 HCV infection. Patients were randomized to receive 1 of 3 doses of danoprevir (300 mg every 8 hours, 600 mg every 12 hours, or 900 mg every 12 hours) or placebo plus peginterferon (180 µg/week) and ribavirin (1,000-1,200 mg/day) for 12 weeks. Response-guided peginterferon and ribavirin therapy was continued for a total treatment duration of 24 weeks in those patients who achieved extended RVR (HCV RNA level <15 IU/mL); patients who did not achieve extended RVR continued therapy for a total treatment duration of 48 weeks. Due to reversible grade 4 elevations in ALT levels, treatment with 900 mg danoprevir was terminated early.

At the 2012 EASL Annual Meeting, Patrick Marcellin and coauthors presented the final efficacy and safety data from the ATLAS study.¹ During the first 24 weeks of treatment with danoprevir, peginterferon, and ribavirin, patients showed a rapid and sustained reduction in serum HCV RNA levels. Extended RVR was achieved in 65% of patients treated with 300 mg danoprevir, 79% of patients treated with 600 mg danoprevir, and 18% of patients treated with 900 mg danoprevir; 87-96% of these patients achieved SVR. Rates of SVR24 were higher in patients treated with danoprevir compared to placebo (68-85% vs 42%, respectively). The highest SVR rate (100% across all treatment arms) was achieved in patients with the IL-28B CC genotype and HCV genotype 1b (n=16). Among patients who achieved end-of-treatment virologic response, relapse occurred in 38% of patients in the placebo group compared to 18%, 8%, and 11% of patients in the 300 mg, 600 mg, and 900 mg danoprevir-treatment groups, respectively.

Viral resistance-related breakthrough or partial response occurred in 4% (8/194) of patients; all of these patients were receiving danoprevir as part of their treatment regimen. All of these patients were infected with HCV genotype 1a and harbored the R155K variant, and none of these patients showed evidence of danoprevir resistance mutations at baseline. Of the danoprevir-treated patients with undetectable HCV RNA levels at the end of treatment, viral relapse occurred in 12% (21/172); 9 of these patients harbored the R155K variant and were infected with HCV genotype 1a.

The safety profile of danoprevir plus peginterferon and ribavirin was comparable to that of peginterferon and ribavirin alone, with the exception of reversible grade 4 elevations in ALT levels (4/194 patients in the danoprevir arms). The most common adverse events were fatigue, headache, nausea, insomnia, myalgia, and chills. Nineteen patients withdrew from the study due to adverse events; these patients included 23% of the placebo group and 12% of the 900 mg danoprevir arm.

Reference

1. Marcellin P, Cooper C, Balart LA, et al. High sustained virologic response rates with responseguided danoprevir plus peginterferon alfa-2A (40KD) and ribavirin in treatment-naive, HCV genotype 1 patients: ATLAS study final results. Presented at the 47th Annual Meeting of the European Association for the Study of the Liver; April 18–22, 2012; Barcelona, Spain. Abstract #1192.

the boceprevir group and 29.4% of patients in the control group. At the time of this interim analysis, SVR24 had not yet been reached; however, 62.5% of the boceprevir group and 26% of the control group had achieved SVR12.

Recent findings suggest that concomitant use of boceprevir and ritonavir-boosted HIV protease inhibitor therapy may cause significant drug-drug interactions, thereby reducing the effective levels of these drugs.² In this study, HCV therapy appeared to remain effective—as shown by high rates of SVR12 (approximately 67%)-regardless of the specific HIV protease inhibitor used (primarily atazanavir, lopinavir, or darunavir). In addition, rates of HIV breakthrough were similar in the boceprevir and control groups; HIV virologic failure (defined as >50 copies/mL at 2 consecutive visits) occurred in 2 patients in the boceprevir group and in 3 patients in the control group by Treatment Week 48. One additional patient in each group showed HIV breakthrough during the first 12 weeks post-treatment. While pharmacokinetic analysis of the HIV protease inhibitors was not performed in this study, Mallolas noted that no clinically evident drug-drug interactions between boceprevir and ritonavir-boosted HIV protease inhibitors were observed.

All of the patients in the control group and 98% of patients in the boceprevir group experienced at least 1 adverse event during the study. The incidences of serious adverse events were similar in both groups (17–21%). Patients in the boceprevir group were more likely to experience decreased appetite, pyrexia, dysgeusia, vomiting, asthenia, anemia, and neutropenia. Also, more patients in

ABSTRACT SUMMARY Low Vitamin D Serum Levels Are Associated with Liver Fibrosis and Impaired Virologic Response to Antiviral Therapy with PEG IFN+RBV in HIV/HCV Co-Infected Patients

Patients who are co-infected with HIV and HCV often exhibit low levels of 25-hydroxy vitamin D [25(OH)D], which has been associated with liver fibrosis. At the 2012 EASL Annual Meeting, Mattias Mandorfer and coworkers presented the results of a study that sought to determine whether 25(OH)D levels were associated with virologic response to peginterferon α -2a/2b plus ribavirin in HIV/HCV co-infected patients.¹

Epidemiologic data, infection parameters, and liver biopsies were analyzed from 93 patients with HIV/HCV co-infection. Patients were grouped according to their 25(OH)D levels: 16 patients (17%) had normal 25(OH)D levels (>30 ng/mL); 53 patients (57%) had 25(OH)D insufficiency (10-30 ng/mL); and 24 patients (26%) had 25(OH)D deficiency (<10 ng/mL). The proportion of patients with advanced liver fibrosis (Metavir score F3 or F4) was significantly higher in the group with 25(OH)D deficiency (63%) and the group with

the boceprevir group discontinued treatment due to adverse events (20% in the boceprevir group vs 9% in the control group). Discontinuation of treatment due to anemia was very low in each group (2–3%), but erythropoietin administration occurred more frequently in the boceprevir group.

Given these interim results, Mallolas concluded that patients co-infected with HCV and HIV achieved higher rates of HCV response when treated 25(OH)D insufficiency (40%) compared to the group with normal 25(OH)D levels (13%). Low levels of 25(OH)D were also associated with a higher rate of liver fibrosis progression; the group with normal 25(OH)D levels progressed at a rate of 0.108 U/yr compared to a rate of 0.182 U/yr for the group with 25(OH)D insufficiency and 0.191 U/yr for the group with 25(OH)D deficiency (*P*=.001).

Information regarding virologic response was available for 65 patients who were receiving chronic HCV therapy with peginterferon plus ribavirin. Significantly more patients in the group with normal 25(OH)D levels versus the 25(OH)D deficiency group achieved cEVR (92% vs 47%; P=.016) and SVR (85% vs 40%; P=.024). Of the patients with 3-4 risk factors for treatment failure at baseline (HCV genotype 1 or 4, high HCV RNA viral load, advanced liver fibrosis, and IL-28B rs12979860 non-C/C single nucleotide polymorphism), patients with 25(OH)D deficiency had lower SVR rates than patients with normal 25(OH)D levels (0% vs 52%; P=.012). Of the patients with 0–2 risk factors for treatment failure at baseline, SVR rates were comparable between the group with 25(OH)D deficiency and the group with normal 25(OH)D levels.

The authors concluded that low levels of 25(OH)D were associated with advanced liver fibrosis, progression of fibrosis, and impaired virologic response to peginterferon plus ribavirin therapy. Based on these data and the findings of other studies, vitamin D supplementation may improve virologic response rates and attenuate liver fibrosis in patients co-infected with HIV/HCV.

Reference

1. Mandorfer M, Reiberger T, Payer BA, et al. Low vitamin D serum levels are associated with liver fibrosis and impaired virologic response to antiviral therapy with PEG IFN+RBV in HIV/HCV coinfected patients. Presented at the 47th Annual Meeting of the European Association for the Study of the Liver; April 18–22, 2012; Barcelona, Spain. Abstract #907.

with boceprevir-based triple therapy versus treatment with peginterferon and ribavirin alone. In addition, the preliminary safety profile of boceprevir-based triple therapy in HCV/HIV co-infected patients was comparable to the safety profile observed in HCVmonoinfected patients. Importantly, rates of viral breakthrough in HCV/ HIV co-infected patients who were treated with boceprevir were not higher than rates of viral breakthrough in the control group.

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Commentary

Jean-Pierre Bronowicki, MD, PhD

➡he 47th Annual Meeting of EASL was held in Barcelona, Spain in April 2012. Again this year, treatment of HCV infection was a major topic of the congress. The main highlights were the many abstracts that reported the first efficacy and safety results of combination therapy involving different directacting antiviral (DAA) agents with or without ribavirin and with or without peginterferon. Some results look very promising. However, these results are very preliminary and should be confirmed in a greater number of patients and in patients with more advanced liver disease. Several studies whose results may have a direct impact on current clinical practice were selected for inclusion in this supplement.

Relatively few cirrhotic patients were included in the phase III studies that assessed the efficacy and tolerance of telaprevir and boceprevir. It was shown that cirrhosis negatively impacts the probability of achieving SVR; however, no safety data on triple therapy are available in cirrhotic patients. Christophe Hézode and colleagues (abstract #8) reported the interim safety and efficacy analysis of the CUPIC study, which is a multicenter, observational French study. Patients included in CUPIC were all cirrhotic patients who failed to respond to prior treatment with peginterferon and ribavirin and who were treated with triple therapy including boceprevir or telaprevir as part of the French early access program, which was started in January 2011. A total of 455 patients who received at least 16 weeks of antiviral treatment were included in the analysis. All patients had Child-Pugh class A cirrhosis, but comparing these patients with the cirrhotic patients included in the pivotal studies (such as REALIZE and RESPOND-2) showed that the mean age was greater and the mean platelet count was lower in the CUPIC population. Moreover, 15% of patients had esophageal varices, and some had a history of liver decompensation. The major conclusion of this work is that the safety profile of DAAs among compensated cirrhotic patients was poor but compatible with their use in real-world practice. The rates of serious adverse events and discontinuations due to adverse events were higher compared to the pivotal studies. Indeed, despite widespread use of erythropoietin (56-66%), severe anemia (hemoglobin level <8 g/dL) occurred in 10% of patients, and 10-15% of patients received blood transfusions. Moreover, 8 deaths were reported, mainly due to infection. In terms of efficacy, the early virologic response looks relatively good. These results should be compared to the tolerance of dual therapy with peginterferon and ribavirin in cirrhotic patients. In a retrospective analysis of 68 treated HCV cirrhotic patients, Dultz and coauthors (abstract #1105) showed that the risk of hepatic decompensation was 83% in patients with a Model for End-Stage Liver Disease score above 13 and 59% in patients with a platelet count below 120,000. Therefore, it is important to define the subgroup of cirrhotic patients who are at risk of serious or life-threatening adverse events while on antiviral therapy. In the meantime, patients with cirrhosis should be treated cautiously and should be carefully monitored during treatment, maybe exclusively at expert centers.

The *IL-28B* genotype is the strongest predictor of SVR to peginterferon and ribavirin therapy. The impact of *IL-28B* seems to be less pronounced

in the case of triple therapy. However, 80-90% of genotype 1 patients with IL-28B genotype CC who received triple therapy based on boceprevir or telaprevir achieved SVR. Moreover, 80-90% of patients were eligible for a shortened duration of therapy (24-28 weeks). The PROVE2 study was a phase II study assessing the efficacy of telaprevir in noncirrhotic, European, treatment-naïve patients infected with HCV genotype 1. In 1 arm, patients were treated with only 12 weeks of triple therapy. In this arm, the SVR rate was 60%. The aim of the study conducted by my colleagues and I (abstract #1094) was to evaluate the SVR rates in IL-28B genotype CC and non-CC French patients who received 12 weeks of telaprevir in combination with peginterferon and ribavirin. The SVR rate was 100% in the 12 genotype CC patients, 44% in the 27 genotype CT patients, and 20% in the 5 genotype TT patients. These results suggest that a very short treatment duration may be sufficient to cure IL-28B genotype CC, white, noncirrhotic, treatment-naïve patients infected with genotype 1 HCV. The same results were observed in the Austrian patients who were included in PROVE2 and also in 3 French patients treated in real-world practice (data not included in abstract). A randomized multicenter clinical trial, CONCISE, is ongoing in the United States and Europe with the aim of determining the SVR rate in IL-28B genotype CC patients who are treated with triple therapy for a total of 12 weeks compared to those treated for 24 weeks. Because of the cost of protease inhibitor therapy, some countries recommend that genotype CC, treatment-naïve patients receive only peginterferon and ribavirin without a protease inhibitor. This strategy may be reconsidered if a very short treatment duration of triple therapy may be applied to these patients, because it is probable that the overall cost (direct plus indirect costs) of this strategy may be less. At this time, this strategy should be reserved for white patients without cirrhosis who are not overweight. Therefore, it is unclear whether it can be fully applicable to the general American population.

Triple therapy including telaprevir or boceprevir significantly increases the incidence of anemia (hemoglobin level <10 g/dL). The management of anemia may have an impact on SVR rates and the overall cost of the treatment. Indeed, ribavirin dose reduction may negatively impact SVR rates, whereas the use of erythropoietin will significantly increase the cost of treatment. In this randomized controlled trial, Poordad and colleagues (abstract #1419) compared the impact of anemia management strategy on the SVR rate. More than 680 genotype 1, treatment-naïve patients were treated with boceprevir-based triple therapy. In cases of anemia (hemoglobin level <10 g/dL), patients were randomized either to erythropoietin or ribavirin dose reduction as the primary anemia management strategy. The main objective was to compare SVR rates in the 2 arms. The end-of-treatment response and SVR rates were strictly similar in

the 2 arms: 82% and 71%, respectively. The efficacy of erythropoietin seems to be weak in this case. Indeed, a second anemia management strategy (erythropoietin or ribavirin dose reduction) was necessary in 38% of the patients who received erythropoietin first, compared to only 18% of patients in whom anemia was first managed by ribavirin dose reduction. In this trial, the recommendation was to reduce the dose of ribavirin by 200-400 mg/day. In a post-hoc analysis of the telaprevir phase III studies, Sulkowski and coauthors (abstract #1162) assessed the efficacy of outcomes based on ribavirin dose reduction. There was no clear negative impact of ribavirin dose reduction on SVR rates even in patients who received a daily ribavirin dose less than or equal to 600 mg. SVR rates were 71% in patients with no ribavrin dose reduction, 77% in patients in whom ribavirin was reduced to 800-1,000 mg/day, and 68% in patients in whom ribavirin was reduced to 600 mg/day or lower. However, the SVR rate seems to be slightly lower (10–15% difference) in patients in whom ribavrin dose reduction occurred within the 4 first weeks of treatment. These 2 studies strongly suggest that anemia can be managed by ribavrin dose reduction without a real negative impact on SVR. Erythropoietin should be

reserved as a second-line intervention. Finally, studies presented at EASL addressed HIV/HCV co-infected patients, a group of patients who are difficult to cure. Therefore, there is an urgent need for new therapeutic strategies in this population. Mallolas and colleagues (abstract #50) reported the interim results of a randomized controlled trial in HIV/HCV co-infected treatment-naïve patients. The efficacy and tolerance of boceprevir triple therapy were assessed. Triple therapy increased rates of SVR12 (63% vs 26%). The safety profile seems comparable to that reported in monoinfected patients. HIV breakthroughs were observed in 3 of 64 patients in the boceprevir group and 4 of 34 patients in the control group. A drug interaction study showed that taking boceprevir with ritonavir in combination with atazanavir or darunavir, or with lopinavir/ritonavir, reduced the blood levels of the HIV medicines and boceprevir. The US Food and Drug Administration updated the label for boceprevir to include information about these drug interactions. Based on outcomes in clinical trials, however, some experts think these drugs can be used together safely if HIV and HCV viral loads are carefully monitored. Further studies are needed to reconcile these conflicting findings.





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