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MEETING REPORT

NEW DRUGS FOR HIV AND HEPATITIS C VIRUS INFECTIONS

A REPORT FROM CROI 2011

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SUMMARY

Presentations on new therapies for hepatitis C virus (HCV) generated the most excitement at CROI 2011. Two new, orally available, direct-acting antivirals, boceprevir and telaprevir, promise to usher in a new era of combination therapy for chronic HCV infection. The antiretroviral drug development pipeline continues to expand, albeit at a slower pace than in recent years.

INTRODUCTION

The 18th Conference on Retroviruses and Opportunistic Infections (CROI 2011) took place on February 27-March 2, 2011, in Boston, Massachusetts. As in previous years, CROI brought together basic scientists and clinicians to discuss the current status of and advances in various aspects of HIV medicine. This article focuses on presentations at the conference that deal with new drug development. The author is solely responsible for the selection of topics and presentations to be included in this report. This report is not an endorsed activity of CROI itself.

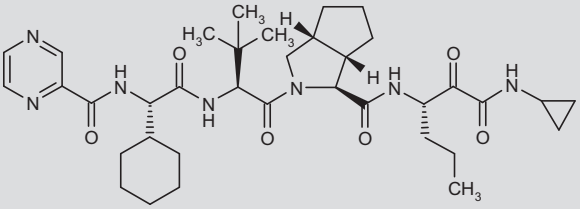
NEW DRUGS FOR HEPATITIS C VIRUS (HCV)

Until now, the standard of care for the treatment of chronic HCV infection has been the combination of pegylated interferon (peginterferon) and ribavirin. This current standard of care has a number of shortcomings, including the requirement for parenteral administration of peginterferon, toxicities of both drugs, as well as the inability of a significant proportion of patients with chronic HCV (especially those with genotype 1 HCV) to achieve a sustained virological response with these regimens. Several new drug candidates are in development; two of these drugs, telaprevir and boceprevir, have recently been approved by the U.S. Food and Drug Administration (FDA).

Telaprevir

The HCV virus utilizes two key enzymes, NS3 protease and NS5B polymerase, for post-translational processing and replication. NS3 protease has two substrate binding sites, NS4A and NS2/NS3. Telaprevir is a selective inhibitor of HCV NS3-NS4A protease.

Pooled analysis of ADVANCE and ILLUMINATE, two pivotal phase III clinical trials of telaprevir in patients with genotype 1 HCV monoinfection, were presented at CROI 2011 (1). ADVANCE was a randomized, placebo-controlled phase III clinical trial that evaluated the efficacy and safety of telaprevir in combination with peginterferon and ribavirin in chronic HCV genotype 1-infected treatment-naive



Telaprevir

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Table I. *Pooled analysis of ADVANCE and ILLUMINATE: virological response.*

	Telaprevir/peginterferon/ribavirin	Peginterferon/ribavirin
Rapid virological response (RVR) (%)	70	9
Extended rapid virological response (eRVR) (%)	63	8
Sustained virological response (SVR) (%)	73	44
Virological failure (%)	7	32
Relapse (%)	8	28

RVR, undetectable HCV RNA at week 4 of treatment; eRVR, undetectable HCV RNA at weeks 4 and 12 of treatment; SVR, undetectable HCV RNA 24 weeks after the last dose; relapse, undetectable HCV RNA at the end of treatment followed by detectable HCV RNA after the end of treatment.

patients. ILLUMINATE was an open-label, randomized phase III clinical trial that evaluated the efficacy and safety of 24 weeks of telaprevir-based treatment versus 48 weeks in chronic HCV genotype 1-infected treatment-naive patients who achieved extended rapid virological response (undetectable HCV RNA at weeks 4 and 12). The pooled analysis included 903 patients treated with telaprevir/peginterferon/ribavirin and 361 patients treated with the traditional peginterferon/ribavirin regimen. Baseline characteristics for the telaprevir/peginterferon/ribavirin group included 83% Caucasian and 11% black patients, median age of 50 years, baseline HCV RNA > 800,000 copies/mL in 80% and 25% with bridging fibrosis or cirrhosis. The dose of telaprevir used was 750 mg every 8 hours for 12 weeks. Virological responses at various time points during the study are presented in Table I. Substantially more patients receiving telaprevir/peginterferon/ribavirin achieved virological undetectability at all time points than patients receiving peginterferon/ribavirin only. The most common adverse events reported in patients receiving telaprevir/peginterferon/ribavirin were pruritus, nausea, anemia and rash. During the 12 weeks when telaprevir was administered, 7% and 4%, respectively, of telaprevir/peginterferon/ribavirin and peginterferon/ribavirin patients discontinued all study drugs.

Interim analysis of a double-blind phase IIa study of the efficacy, safety and viral kinetics of telaprevir in 60 patients coinfected with HIV and HCV was also reported (2). Participants were categorized in three groups based on their antiretroviral treatment regimen: A, patients not receiving antiretroviral therapy; B, patients receiving tenofovir/emtricitabine plus efavirenz; C, patients receiving tenofovir/emtricitabine plus ritonavir-boosted atazanavir. Patients in each category were randomized to receive either telaprevir/peginterferon/ribavirin or peginterferon/ribavirin. The doses used were telaprevir 750 mg every 8 hours + peginterferon alfa-2a 180 mg/week + ribavirin 800 mg/day for 12 weeks, followed by 36 weeks of peginterferon alfa-2a + ribavirin for the telaprevir/peginterferon/ribavirin groups, and placebo + peginterferon alfa-2a/ribavirin for 48 weeks for the peginterferon/ribavirin groups. Where the antiretroviral regimen included efavirenz, the dose of telaprevir was increased to 1125 mg every 8 hours. Baseline characteristics included 88% male, 69% white, mean age of 46 years, genotype 1a in 68%, baseline HCV RNA > 800,000 copies/mL in 83% and advanced fibrosis in 10%. All study participants on antiretroviral therapy had HIV RNA < 50 copies/mL. Median CD4 cell count was above 400 cells/mm^3 for all groups. Interim virological responses are detailed in Table II. Substantially more patients in the telaprevir/peginterferon/ribavirin group achieved undetectable HCV RNA at weeks 4 and 12 compared to patients receiving peginterferon/ribavirin only.

Pharmacokinetic properties of telaprevir are important considerations, as the compound is a substrate as well as an inhibitor of cytochrome P450 CYP3A, and thus has potential for a significant interaction with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The effect of low-dose ritonavir on the pharmacokinetics of telaprevir was evaluated in an open-label,

Table II. *Interim virological responses in phase IIa study of telaprevir/peginterferon/ribavirin in HIV/HCV-coinfected patients.*

	Group A		Group B		Group C		Total	
	TVR/PR (n = 7)	PR (n = 6)	TVR/PR (n = 16)	PR (n = 8)	TVR/PR (n = 14)	PR (n = 8)	TVR/PR (n = 37)	PR (n = 22)
Undetectable HCV RNA at week 4 (%)	71	0	75	12	64	0	70	5
Undetectable HCV RNA at week 12 (%)	71	17	75	12	57	12	68	14
Undetectable HCV RNA at weeks 4 and 12 (%)	43	0	62	0	43	0	49	0

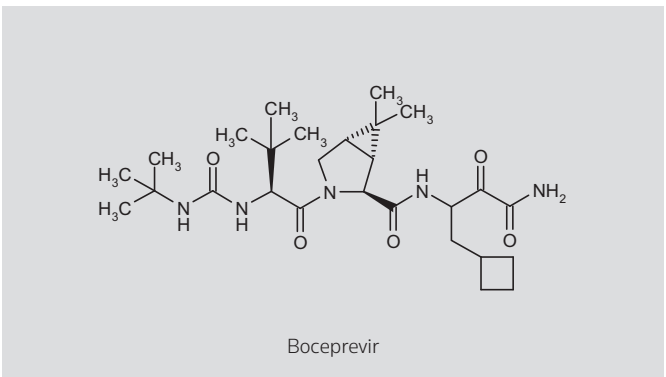
TVR, telaprevir; PR, peginterferon/ribavirin.

randomized, parallel-group study of 3 groups of 6 healthy volunteers, each given telaprevir in the fed state with or without ritonavir for 14 days (3). Group A received telaprevir 250 mg every 8 hours with 100 mg of ritonavir every 12 hours; group B received telaprevir 750 mg every 12 hours with 100 mg of ritonavir every 12 hours; and group C received telaprevir 750 mg every 8 hours alone. The plasma pharmacokinetic parameters of telaprevir after the last dose on day 14 in group A or B were compared with corresponding parameters in group C. No significant boosting of telaprevir exposure by ritonavir was observed. Pharmacokinetic parameters were lower for group A than for group B or C.

On May 23, 2011, the U.S. FDA approved telaprevir for the treatment of chronic HCV genotype 1 infection in combination with peginterferon/ribavirin.

Boceprevir

Boceprevir is another HCV NS3 protease inhibitor. SPRINT-2 was a double-blind, randomized phase III study that compared the efficacy and safety of boceprevir in combination with peginterferon/ribavirin to that of peginterferon/ribavirin plus placebo (4). All patients received peginterferon/ribavirin during an initial lead-in period of 4 weeks and were then randomized into 3 groups: group 1 received boceprevir/peginterferon/ribavirin for 24 weeks; group 2 (control) received peginterferon/ribavirin plus placebo for 44 weeks; and group 3 (response-guided therapy) received boceprevir/peginterferon/ribavirin for 24 weeks plus an additional 20 weeks of peginterferon/ribavirin if HCV RNA was detectable during weeks 8-24. The doses used were peginterferon 1.5 μg/kg s.c. weekly, weight-based ribavirin 600-1400 mg/day twice daily and boceprevir 800 mg orally 3 times a day. Participants were stratified based on race (nonblack vs. black). A total of 938 nonblack and 159 black patients were enrolled. Baseline characteristics included HCV RNA > 400,000 IU/mL in 92% of participants and advanced fibrosis in 9% of participants. Results are detailed in Table III. The sustained virological response was significantly higher ($P < 0.0001$ for cohort 1; $P = 0.04$ for cohort 2) in both boceprevir arms compared to control. The sustained virological response for response-guided therapy was comparable to the 44 weeks of boceprevir/peginterferon/ribavirin. Anemia was reported in 29% of controls versus 49% in the boceprevir arms. Discontinuation due to adverse events was similar across the three groups.



Boceprevir

HCV RESPOND-2 was a double-blind, placebo-controlled trial that evaluated the safety and efficacy of boceprevir/peginterferon/ribavirin in the treatment of patients with genotype 1 HCV infection who previously either did not respond to or relapsed following peginterferon/ribavirin therapy (5). All patients received peginterferon/ribavirin during an initial lead-in period of 4 weeks and were then randomized 1:2:2 into 3 groups: group 1 (control) received peginterferon/ribavirin; group 2 (response-guided therapy) received boceprevir/peginterferon/ribavirin for 32 weeks plus an additional 12 weeks of peginterferon/ribavirin if HCV RNA was detectable at week 32; and group 3 received boceprevir/peginterferon/ribavirin for 44 weeks. Patients were discontinued from the study if HCV RNA was detectable at week 8. Baseline characteristics of the 403 patients enrolled include 67% male, 12% black and 12% cirrhotic. Results are detailed in Table IV. Substantially higher virological response rates were observed in the boceprevir/peginterferon/ribavirin group than in the peginterferon/ribavirin group, and more patients in the boceprevir/peginterferon/ribavirin group achieved undetectable HCV RNA at weeks 4 and 12 compared to patients receiving peginterferon/ribavirin in genotype 1 HCV patients who were previous nonresponders and relapsers to peginterferon/ribavirin therapy.

Table III. *Virological response in SPRINT-2.*

	Cohort 1 (nonblack)			Cohort 2 (black)		
	Boceprevir/peginterferon/ribavirin (n = 311)	Response-guided therapy (n = 316)	Control (n = 311)	Boceprevir/peginterereron/ribavirin (n = 55)	Response-guided therapy (n = 52)	Control (n = 52)
Sustained virological response (%)	68	67	40	53	42	23
End-of-therapy response (%)	77	74	57	65	50	29
Relapse (%)	8	9	23	17	12	14

Table IV. *Virological response in HCV RESPOND-2.*

	Group 1 (control; n = 80)	Group 2 (response-guided therapy; n = 162)	Group 3 (BOC/PR; n = 161)
End-of-therapy response (%)	31	70	77
Sustained virological response (SVR) (%)	21	59	67
Relapse (%)	32	15	12
$< 1 \log_{10}$ viral load decline at week 4 (%)	0	33	34
$\geq 1 \log_{10}$ viral load decline at week 4 (%)	26	73	79

SVR, undetectable HCV RNA 24 weeks after the last dose of treatment; relapse, undetectable HCV RNA at the end of treatment followed by detectable HCV RNA after the end of treatment; BOC/PR, boceprevir/peginterferon/ribavirin.

While efficacy trials for boceprevir in HIV/HCV-coinfected patients were not reported at CROI, the results of a phase I pharmacological study investigating the metabolic pathways and drug interactions of boceprevir in healthy volunteers were presented (6). There were no clinically relevant changes in boceprevir exposure when coadministered with peginterferon/tenofovir, but there was a slight reduction in boceprevir AUC, C_{max} and C_{min} (19%, 8% and 44%, respectively) when boceprevir was coadministered with efavirenz. Ritonavir and clarithromycin had minimal effects on steady-state boceprevir exposure.

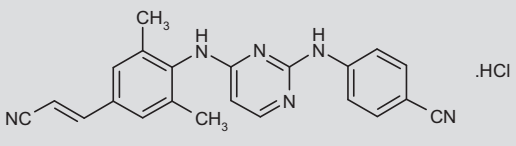
On May 16, 2011, the U.S. FDA approved boceprevir for the treatment of chronic HCV genotype 1 infection in combination with peginterferon/ribavirin.

NEW DRUGS FOR HIV

There were only a limited number of presentations at CROI 2011 on new HIV drugs, in particular drugs in advanced clinical development.

Rilpivirine hydrochloride

Previously known as TMC-278, rilpivirine is a new NNRTI that was approved by the FDA on May 20, 2011, for the treatment of HIV infection. Its safety and efficacy for this indication were evaluated in ECHO and THRIVE, two previously reported, large, randomized, double-blind clinical trials (7). Results from supplemental studies to characterize the drug further were presented.



Rilpivirine hydrochloride

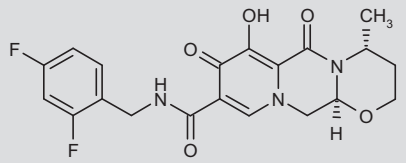
A sub-study of ECHO and THRIVE used pooled data over 48 weeks to compare changes in lipid parameters (in fasted conditions) between rilpivirine and efavirenz (8). Significantly greater increases from baseline, as well as a greater incidence of grade 3/4 abnormalities in total cholesterol, LDL cholesterol and triglycerides, were seen with efavirenz than with rilpivirine. However, HDL cholesterol increased significantly more with efavirenz than with rilpivirine and there was no difference between the two groups in the change in the total cholesterol/HDL ratio, a ratio that is more indicative of atherosclerosis than individual total cholesterol or HDL values. The change from baseline to week 48 in the Framingham Coronary Heart Disease relative 10-year risk score was the same in both groups as well.

A sub-study of the ECHO trial compared serum levels of 25-hydroxyvitamin D (25[OH]D), the precursor form of active vitamin D, proportions of patients with 25(OH)D deficiency and changes in 25(OH)D in patients receiving rilpivirine versus efavirenz over 48 weeks (9). The proportion of patients with severe 25(OH)D deficiency at baseline was similar in both groups (4.8% for rilpivirine vs. 5.2% for efavirenz), but was significantly lower for rilpivirine than for efavirenz at week 48 (4.5% for rilpivirine vs. 9% for efavirenz; $P = 0.032$). Levels of 25(OH)D changed minimally over 48 weeks in patients who received rilpivirine but declined significantly in patients receiving efavirenz.

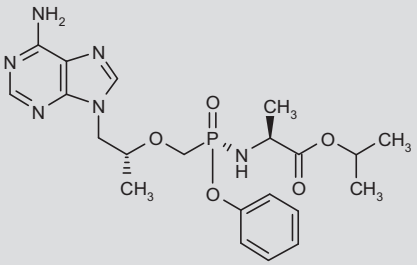
Another sub-study of ECHO and THRIVE also used pooled data over 48 weeks to compare neuropsychiatric adverse events between patients receiving rilpivirine and efavirenz (10). In general, the incidence of neurological and psychiatric serious adverse events was low (rilpivirine 0.3% vs. efavirenz 0.1%); most adverse events in both groups were grade 1 or 2. Differences in the incidence of neurological and psychiatric adverse events were most pronounced in the first 4 weeks of treatment, but were consistently numerically lower with rilpivirine than with efavirenz throughout the study. Neurological (rilpivirine 0.1% vs. efavirenz 0.7%) and psychiatric (rilpivirine 1.5% vs. efavirenz 2.2%) adverse events leading to discontinuation were low.

Dolutegravir

Previously known as S/GSK-1349572, dolutegravir is a new integrase inhibitor that is currently in advanced clinical development. Results of two phase IIb clinical trials of dolutegravir (SPRING-1 and VIKING)



Dolutegravir



GS-7340

have previously been reported (11, 12). The VIKING study investigated the activity of dolutegravir in HIV-infected individuals with raltegravir-resistant HIV who received dolutegravir 50 mg once daily and reported that the presence of the Q148 mutation with two or more additional mutations significantly and adversely affected response to treatment (13). Therefore, another study using dolutegravir 50 mg twice daily in 24 HIV-infected patients failing treatment with genotypic resistance to raltegravir and to ≥ 2 other antiretroviral classes was conducted (13). In the first 11-day, functional monotherapy phase of the study, patients received dolutegravir 50 mg twice daily while continuing their failing regimen. Subsequently, the background regimen was optimized to include at least one fully active antiretroviral drug. The median baseline fold change in susceptibility compared to wild-type was > 128 (0.8- > 128) for raltegravir and 2.7 (0.9-9.5) for dolutegravir. Baseline $CD4^+$ and plasma HIV-1 RNA were (median): 202 cells/mm^3 (19-528) and 4.3 $\log_{10}$ copies/mL (3.3-5.8). At day 11, 13 of 24 (54%) patients achieved plasma HIV-1 RNA < 400 copies/mL and 23 of 24 (96%) had a ≥ 0.7 $\log_{10}$ copies/mL decline in HIV-1 RNA; the mean reduction in plasma HIV-1 RNA was –1.76 copies/mL and the mean reduction in plasma HIV-1 RNA for Q148+ virus was –1.57. Thus, dolutregravir at this higher dose appeared to show activity against raltegravir-resistant virus, even against virus with Q148 combined with additional mutation(s). Twenty-four week assessments are planned.

GS-7340

Tenofovir is a widely used antiretroviral drug, a component of first-line antiretroviral regimens in various guidelines. It is a nucleotide reverse transcriptase inhibitor; unlike other nucleoside analogues, its intracellular activation requires only two phosphorylation steps to yield its active diphosphate form. GS-7340 is an experimental prodrug of tenofovir in early clinical development. Compared to the parent drug, it has demonstrated 500-1,000-fold enhanced activity against HIV-1 in a variety of cells, including T lymphocytes, activated peripheral blood mononuclear cells (PBMCs) and macrophages (14). The rationale behind its development is the consideration that its in vitro potency may translate into greater clinical efficacy, while its predilection for lymphoid cells and the subsequent lower plasma concentrations may result in less toxicity. To investigate this potential, a randomized, double-blind, dose-escalation, 14-day monotherapy study compared GS-7340 (50 or 150 mg) to tenofovir (300 mg) in 30 treatment-naive, HIV-1-infected subjects with HIV-1 RNA ≥ 15,000 copies/mL (mean 4.82 $\log_{10}$ copies/mL) and CD4 count ≥ 200 cells/mm^3 (mean 424 cells/mm^3) (15). At day 14, tenofovir plasma concentrations were lower for GS-7340 50 mg (C_{max} 94% and AUC 88% lower) or GS-7340 150 mg (C_{max} 80% and AUC 58% lower) than tenofovir; tenofovir PBMC concentrations were approximately 30-fold higher with GS-7340 than with tenofovir. There were no clinically significant laboratory abnormalities or serious adverse events in any treatment group. No significant laboratory abnormalities were observed in any arm of the study. Headache was the most common adverse event.

CONCLUSIONS

CROI continues to be a forum for the presentation and discussion of valuable basic science and clinical data. From a clinical and therapeutic standpoint, the development of the oral, direct-acting anti-HCV drugs boceprevir and telaprevir has generated the most excitement. Anti-HCV therapy may be entering a new era of new and more potent combination treatment similar to what occurred with antiretroviral therapy in 1996. Studies of these new drugs in HIV/HCV-coinfected patients are thus far lacking; we look forward to seeing more at the next CROI. As regards antiretroviral therapy, the number of new agents in advanced clinical development is relatively few compared to in recent years. However, a new drug, rilpivirine, was just approved by the FDA, and the armamentarium of antiretroviral drugs for clinical use continues to expand. Newer targets and approaches continue to be explored and the utility of antiretroviral therapy for the prevention of HIV infection has become an active area of interest.

DISCLOSURES

The author states no conflicts of interest.

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