

Clinical Trials Study

Phase 3 trial of first generation protease inhibitor therapy for hepatitis C virus/human immunodeficiency virus coinfection

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Abstract

AIM

To evaluate efficacy/safety of hepatitis C virus (HCV) protease inhibitor boceprevir with pegylated interferon (PEG-IFN) alfa and weight-based ribavirin (RBV) in a phase 3 trial.

METHODS

A prospective, multicenter, phase 3, open-label, single-arm study of PEG-IFN alfa, weight-based RBV, and boceprevir, with a PEG-IFN/RBV lead-in phase was performed. The HCV/human immunodeficiency virus coinfecting study population included treatment naïve (TN) and treatment experienced (TE) patients. Treatment duration ranged from 28 to 48 wk dependent upon response-guided criteria. All patients had HCV Genotype 1 with a viral load > 10000 IU/mL. Compensated cirrhosis was allowed. Sample size was determined to establish superiority to historical (PEG-IFN plus RBV) rates in sustained viral response (SVR).

RESULTS

A total of 257 enrolled participants were analyzed (135 TN and 122 TE). In the TN group, 81.5% were male and 54.1% were black. In the TE group, 76.2% were male and 47.5% were white. Overall SVR12 rates (HCV RNA < lower limit of quantification, target not detected, target not detected) were 35.6% in TN and 30.3% in TE. Response rates at SVR24 were 28% in TN and 10% in TE, and exceeded those in historical controls. The highest rate was observed in TN non-cirrhotic participants (36.8% and the lowest in TE cirrhotics (26.3%). Cirrhotic TN participants had a 27.8% SVR12 rate and 32.1% of TE non-cirrhotics achieved SVR12. Significantly lower response rates were observed among black participants; in the TE, SVR12 was 39.7% in white participants but only 13.2% of black subjects ($P = 0.002$). Among the TN, SVR12 was 42.1% among whites and 27.4% among blacks ($P = 0.09$).

CONCLUSION

The trial met its hypothesis of improved SVR compared to historical controls but overall SVR rates were low. All-oral HCV treatments will mitigate these difficulties.

Key words: Human immunodeficiency virus; Hepatitis C virus; Boceprevir; Pegylated interferon alfa; Ribavirin

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Core tip: Approval of first generation hepatitis C virus (HCV) protease inhibitors has initiated a change in care of HCV infected patients. Phase 2 trials in HCV/human immunodeficiency virus coinfecting patients have suggested improved efficacy and tolerability for regimens that combined pegylated interferon (PEG-IFN) + ribavirin (RBV) with either boceprevir or telaprevir. We evaluated an HCV treatment regimen using a first generation HCV protease inhibitor (boceprevir) with PEG-IFN, and weight-based RBV in a phase 3 treatment trial, including HCV

treatment-naïve and treatment-experienced coinfecting subjects. While sustained viral response rates were low overall they did exceed historical PEG-IFN/RBV rates. Use of new interferon-free direct acting antiviral agents modalities in this population is indicated.

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INTRODUCTION

Hepatitis C virus (HCV) coinfection is a major cause of morbidity and mortality among those with human immunodeficiency virus (HIV) infection^[1-4]. Prior to the emergence of new HCV targeted direct acting antiviral agents (DAAs) in 2011, response to standard therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) was poor, both in terms of efficacy and medication tolerability^[5]. The approvals of first generation serine protease inhibitors of HCV replication initiated a revolution in terms of the care and management of HCV infected patients. Phase 2 trials in HCV/HIV coinfecting patients suggested improved efficacy with moderate drug tolerability for treatment regimens that combined either boceprevir or telaprevir with PEG-IFN + RBV^[6,7]. In an effort to define treatment efficacy with response- and cirrhosis-guided regimens in HCV/HIV coinfecting, we conducted a prospective, multicenter, open-label Phase 3 trial in both HCV treatment naïve and treatment experienced participants with comparison to historical controls in the same clinical trials network.

MATERIALS AND METHODS

The study was performed in the NIH AIDS Clinical Trials Group network (ACTG, National Institutes of Health Registration number NCT01482767) with enrollment of participants at 42 sites across the United States. All participants provided informed consent and the study was conducted with approval of Institutional Review Boards at each site. The study was monitored by an independent, NIH-chartered data safety and monitoring board.

The overall study design is shown in Figure 1. Briefly, treatment naïve (TN) participants (Group A) were treated with PEG-IFN alfa 2b 1.5 µg/kg subcutaneously with weight-based ribavirin (800-1400 mg/d) for 4 wk (lead-in). Then boceprevir 800 mg tid was added to the treatment regimen. Cirrhotic participants received 44 wk of triple therapy. Among non-cirrhotics, the week 8 serum HCV RNA was used to determine total duration of therapy. Those who had undetectable HCV RNA at week

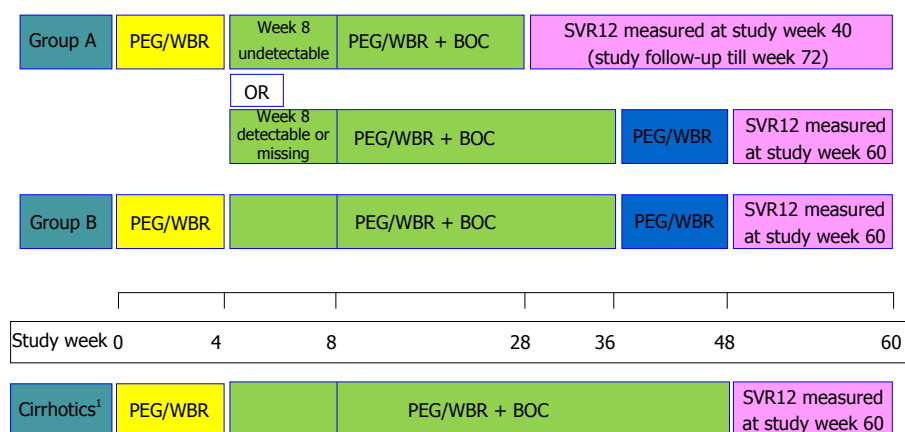


Figure 1 Overall study design. Group A refers to treatment naïve participants while Group B refers to treatment experienced participants. PEG/WBR treatment is pegylated-interferon alpha 2b (PEG-IFN) and weight-based ribavirin (WBR). ¹Cirrhotic participants received 44 wk of triple therapy. SVR12: HCV RNA < LLOQ, target not detected at 12 wk post treatment discontinuation; BOC: Boceprevir; SVR: Sustained viral response; HCV: Hepatitis C virus; LLOQ: Lower limit of quantification.

8 completed therapy at week 28. Those with detectable HCV RNA at week 8 received 32 wk of triple therapy followed by 12 additional weeks of double-drug therapy with PEG-IFN/RBV. Treatment experienced participants (TE) (Group B) also had lead-in followed by 32 wk of triple therapy and 12 wk of PEG-IFN/RBV double therapy if non-cirrhotic, or by 44 wk of triple therapy if cirrhotic. Treatment was to be discontinued due to failure if: (1) HCV RNA ≥ 100 IU/mL at week 12; (2) detectable HCV RNA at week 24; or (3) confirmed HCV RNA > 1000 IU/mL any time after week 12. HCV RNA was determined to be undetectable if below the lower limit of quantification (LLOQ) and target not detected (TND) by Roche COBAS[®] TaqMan[®] HCV Test v2.0.

Key inclusion criteria included HCV genotype 1 with HCV RNA ≥ 10000 IU/mL. All participants underwent either liver biopsy or non-invasive marker (FibroSure[®]) testing to determine whether or not cirrhosis was present. Cirrhotics were confirmed to have stage A Child-Pugh disease. HIV RNA viral load was required to be < 50000 copies/mL for participants not on antiretroviral therapy, or less than 50 copies/mL for those on an approved antiretroviral regimen. A CD4⁺ T-cell count of > 200 cells/mm³ was also required within 42 d of study entry. Approved regimens included efavirenz, raltegravir, lopinavir/ritonavir, atazanavir/ritonavir or darunavir/ritonavir plus a dual nucleoside reverse transcriptase inhibitor backbone that did not include zidovudine or didanosine. Key exclusion criteria were those with mixed HCV genotypes, prior use of HCV protease or polymerase inhibitors or the presence of decompensated liver disease. Also excluded were other known causes of significant liver disease including HBV, HAV, hemochromatosis, or alpha-1 antitrypsin deficiency.

Data were centrally submitted and analyzed using SAS 9.4 (SAS Institute, Cary, NC, United States). The key outcome measure was sustained viral response in each study group and how the estimates compared to those in historical controls from a prior study of PEG-IFN plus RBV therapy (ACTG 5178). The study was powered

to conclude that sustained viral response (SVR) is greater than 28% in TN and 10% in treatment experienced participants, based on A5178 results on HCV genotype 1 participants. The SVR proportions were estimated with two-sided 95% Wilson confidence intervals (CI), and Fisher's exact tests were conducted for comparisons between groups. The analyses included all participants who met the eligibility criteria and initiated the study treatment.

RESULTS

The baseline characteristics of the TN and TE participants as well as the historical controls are shown in Table 1. A total of 257 enrolled participants were analyzed: 135 TN (Group A) and 122 TE (Group B). The study included primarily middle-age males. There was a high representation of black/African-American participants, and this was accompanied by a similarly high percentage of IL28b genotypes carrying the "T" allele. Median CD4 counts were above 600 cell/mm³ in both groups, corresponding to the high rate of active antiretroviral therapy (> 95%). There were more participants with cirrhosis in TE than in TN, in both A5294 and historical controls.

Overall SVR12 (HCV RNA < LLOQ, TND (target not detected) at 12 wk post treatment discontinuation) rates were 35.6% (95%CI: 28.0-43.9%) in TN and 30.3% (95%CI: 22.9%-39.0%) in TE (Table 2). Rates of response exceeded SVR24 in historical controls: 28% in TN and 10% in TE. The highest rate was observed in TN non-cirrhotic participants (36.8%, 95%CI: 28.6%-45.8%) and the lowest in TE cirrhotic participants (26.3%, 95%CI: 15.0%-42.0%). Cirrhotic TN participants had a 27.8% (95%CI: 12.5%-50.9%) SVR12 rate and 32.1% (95%CI: 23.1%-42.7%) of TE non-cirrhotics achieved SVR12. Race was a significant factor in treatment outcome. Indeed, among TE, SVR12 was noted to occur in 39.7% of white participants but in only 13.2% of those identified as black ($P = 0.002$). Among TN, SVR12 was 42.1% among whites and 27.4% among blacks ($P =$

Table 1 Demographic and laboratory characteristics *n* (%)

Characteristic	A5294		Historical controls	
	Treatment naïve (<i>n</i> = 135)	Treatment Exp (<i>n</i> = 122)	Treatment naïve (<i>n</i> = 183)	Treatment Exp (<i>n</i> = 87)
Age (yr)				
Median	51	53	48	48
Q1, Q3	44, 57	49, 57	41, 52	42, 51
Sex				
Male	110 (81.5)	93 (76.2)	151 (82.5)	74 (85.1)
Female	25 (18.5)	29 (23.8)	32 (17.5)	13 (14.9)
IV drug history				
Never	71 (52.6)	70 (57.4)	73 (39.9)	39 (44.8)
Currently	0	0	4 (2.2)	1 (1.1)
Previously	64 (47.4)	52 (42.6)	106 (57.9)	47 (54.0)
Race				
Asian	2 (1.5)	2 (1.6)	1 (0.5)	0
Black or African American	73 (54.1)	53 (43.4)	91 (49.7)	24 (27.6)
White	57 (42.2)	58 (47.5)	79 (43.2)	59 (67.8)
American Indian	0	2 (1.6)	3 (1.6)	1 (1.1)
More than One Race	2 (1.5)	2 (1.6)	5 (2.7)	0
Unknown	1 (0.7)	5 (4.1)	4 (2.2)	3 (3.4)
BMI (kg/m ²)				
Median	26.3	27.5	25.7	26
Q1, Q3	22.6, 29.6	25.0, 31.0	22.9, 29.4	23.6, 30.1
Missing	1	0	0	0
IL28b genotype (RS 12979860)				
c/c	32 (25.2)	31 (27.2)	38 (33.9)	19 (31.1)
c/t	61 (48.0)	39 (34.2)	51 (45.5)	30 (49.2)
t/t	34 (26.8)	44 (38.6)	23 (20.5)	12 (19.7)
Missing	8	8	71	26
CD4 (cells/mm ³)				
Median	646	621.5	495	520
Q1, Q3	462, 818	488.5, 858.5	373, 697	368, 706
Missing	2	2	0	0
HIV RNA quantitation				
Unquantifiable	133 (100.0)	113 (92.6)	129 (70.5)	71 (81.6)
Quantifiable	0	9 (7.4%)	54 (29.5)	16 (18.4)
Missing	2	0	0	0
HCV RNA (log ₁₀ IU/mL)				
Median	6.7	6.9	6.5	6.6
Q1, Q3	6.2, 7.1	6.5, 7.3	6.1, 6.8	6.3, 7.0
Missing	1	0	0	0
Cirrhosis				
Yes	18 (13.3)	38 (31.1)	20 (10.9)	18 (20.7)
No	117 (86.7)	84 (68.9)	163 (89.1)	69 (79.3)
Baseline cART regimen				
No ART	2 (1.5)	6 (4.9)	40 (21.9)	11 (12.6)
EFV + 2 NRTIs	58 (43.0)	51 (41.8)	NA	NA
RAL + 2 NRTIs	47 (34.8)	45 (36.9)	NA	NA
LPV/RTV + 2 NRTIs	4 (3.0)	4 (3.3)	NA	NA
ATV/RTV + 2 NRTIs	18 (13.3)	10 (8.2)	NA	NA
DRV/RTV + 2 NRTIs	6 (4.4)	6 (4.9)	NA	NA

NA: A5178 did not have cART restrictions; Exp: Experienced; Q1, Q3: First quartile (Q1), third quartile (Q3); BMI: Body mass index; rs: Reference sequence for single nucleotide polymorphism; ART: Antiretroviral therapy; EFV: Efavirenz; NRTIs: Nucleoside reverse transcriptase inhibitors; RAL: Raltegravir; LPV: Lopinavir; RTV: Ritonavir; ATV: Atazanavir; DRV: Darunavir; cART: Combination antiretroviral therapy.

0.09). Treatment discontinuation rates were high in all groups and were attributed to a mix of treatment failure per HCV viral load criteria or due to adverse events. Among TN, there was one death unrelated to the study, 42 (31%) treatment failures leading to early discontinuation, and additional 22 (16%) premature treatment discontinuations due to adverse events. In TE, there were 52 treatment failures (43%), additional 16 (13%) premature treatment discontinuations due to adverse events, and no deaths. The most commonly

reported adverse events of grade 3 or higher included hematologic laboratory events (44% in TN and 48% in TE), and general body (chills, fatigue, pain, weight loss; 23% in TN and 22% in TE), gastrointestinal (4% in TN and in 3% TE) and neurologic (7% in TN and 5% in TE) symptoms. HIV breakthrough was rare and only two study participants (both on raltegravir regimen) met predetermined criteria for this event.

Among TN, the highest SVR rates were observed among participants whose cART regimen included rito-

Table 2 Sustained viral response rates

A5294 participants (n = 257)	% SVR12
Treatment naïve (n = 135)	35.6
Non-cirrhotic (n = 117)	36.8
Cirrhotic (n = 18)	27.8
Treatment experienced (n = 122)	30.3
Non-cirrhotic (n = 84)	32.1
Cirrhotic (n = 38)	26.3

navir - boosted atazanavir with a 2 nucleoside/nucleotide backbone. Overall SVR12 rate in this group (n = 18) was 61.1% (95%CI: 38.6%-79.7%) which was significantly higher than SVR12 rates among participants receiving other cART regimens combined (P = 0.018) in a post-hoc analysis. However, we note that this was an exploratory analysis on a small subset not adjusted for baseline co-variables, and this effect was not observed in TE.

DISCUSSION

HCV/HIV coinfection remains a serious medical problem characterized by a high global disease burden (4-5 million) of patients who are at risk for increased fibrotic progression, cirrhosis, and hepatocellular carcinoma^[8]. Coinfected patients also have significant non-hepatic complications including increased cardiovascular risk^[9]. Therefore, HCV cure is a priority in the management of coinfecting HCV/HIV patients. The emergence of new DAAs for HCV has been a rapid and turbulent process which followed years of stagnation in the field. It is not surprising that new therapeutic regimens have been under investigation, even as earlier regimens were entering confirmatory clinical trials. The primary Phase 2 trial for boceprevir/PEG-IFN/RBV was initiated in 2010 and results were reported in July 2013^[6]. Planning for the Phase 3 trial reported in this publication began in 2011, and the study completed in early 2015. During this brief interlude, even more effective, shorter duration regimens were studied and brought to the marketplace.

Despite this rapid advancement in therapy, the Phase 3 trial met its primary goals and moved the field forward in a number of key aspects. First, it again demonstrated the importance of Phase 3 trials which often reveal efficacy levels that fall short of their Phase 2 predecessors. The Phase 2 HCV/HIV coinfection trial of the boceprevir/PEG-IFN/RBV regimen yielded an SVR rate of 63%. This is significantly higher than what we observed in the Phase 3 trial which enrolled a population more representative of the United States HCV/HIV population at large in terms of racial distribution. Indeed, the proportion of black participants in this study (49%) is higher than the imputed racial distribution of HCV/HIV coinfecting patients in United States (23%-33%) based upon a 2002 analysis^[10]. It also exceeds the black representation in the previously reported Phase 2 trial^[6]. Our treatment population was more male, more non-white, with a higher representation of the IL28b T allele and with more advanced fibrosis/cirrhosis than the population enrolled

in the previously reported Phase 2 study. Our findings of a lower SVR in this population is similar to that reported in "real world" analyses using first generation protease inhibitors^[11].

Interestingly, we observed a higher SVR12 among treatment-naïve subjects whose cART regimen consisted of ritonavir boosted atazanavir + a dual NRTI backbone. Pharmacokinetic data indicates that boceprevir AUC was reduced 32% when administered with ritonavir-boosted darunavir while atazanavir AUC decreased only 5%^[12]. While we cannot categorically state that this difference affected overall SVR, we suspect it represents an important factor in treatment outcomes among treatment naïve patients. The lack of this finding in treatment experienced participants may represent the overall decreased effectiveness of the PEG-IFN component in that group which masks more subtle effects related to HCV protease inhibitor pharmacokinetics.

Interferon-based therapy is difficult to tolerate and this is clearly demonstrated by the high drop-out rate seen in our study cohort. Though some guidelines and insurers still encourage use of PEG-IFN in some treatment groups, this approach may be particularly detrimental in the HIV-infected patient where tolerability to interferon-based regimens seems to be lower than that observed in comparable Phase 3 trials in monoinfected patients.

Though the treatments utilized in this Phase 3 multicenter trial will not be utilized in general practice, our study provided several important principles and observations that may guide future trials in the field. First, we provide additional support to the concept that Phase 3 trials represent a more accurate representation of true response rates compared to Phase 2 trials. We also note that outcomes in HCV/HIV coinfecting patients may be related to the background HIV antiretroviral regimen and that this effect may be a drug effect rather than a class effect. Finally, we note the systematic delays in initiation of clinical trials for those with underlying HIV infection vs those without HIV. Phase 3 trials of first generation HCV protease inhibitors lagged significantly behind drug approvals in HCV monoinfected patients. More recent drug development programs have attempted to remedy this situation, but the HIV research community should remain vigilant to reduce this bias going forward, particularly in rapidly moving developmental fields.

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COMMENTS

Background

Hepatitis C virus (HCV) coinfection is a major cause of morbidity and mortality among those with human immunodeficiency virus (HIV) infection. Prior to the emergence of new HCV targeted direct acting antiviral agents in 2011, response to standard therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) was poor, both in terms of efficacy and medication tolerability. The approvals of first generation serine protease inhibitors of HCV replication initiated a revolution in terms of the care and management of HCV infected patients. Phase 2 trials in HCV/HIV coinfecting patients suggested improved efficacy with moderate drug tolerability for treatment regimens that combined either boceprevir or telaprevir with PEG-IFN + RBV. In an effort to define treatment efficacy with response- and cirrhosis- guided regimens in HCV/HIV coinfecting, the authors conducted a prospective, multicenter, open-label Phase 3 trial in both HCV treatment naïve and treatment experienced participants with comparison to historical controls in the same clinical trials network.

Research frontiers

The treatment of hepatitis C is a rapidly moving and dynamic field. Introduction of new agents has led to expansion of indications prior to completion of comprehensive Phase 3 trials in some cases. This study provides data regarding a large Phase 3 trial of a first generation protease inhibitor of HCV which was utilized in combination with PEG-IFN and RBV in HCV/HIV coinfecting patients.

Innovations and breakthroughs

This is the largest study to investigate the efficacy and safety of this first generation protease inhibitor therapy in HCV/HIV coinfecting patients. The treatment was not optimal, but it did meet criteria for treatment success compared to historical controls treated with PEG-IFN plus RBV.

Applications

While this study demonstrates efficacy of a first generation HCV protease inhibitor in the treatment of HCV/HIV coinfecting patients, the regimen is unlikely to be widely used due to rapid development of all-oral regimens that have supplanted the use of PEG-IFN-based regimens. The importance of conducting Phase 3 trials was emphasized by the lower rates of efficacy than were observed in Phase 2 trials that included highly selected patients.

Terminology

Treatment naïve patients are those who have never been treated with a hepatitis C active agent while treatment experienced are those who may have been exposed to interferon or PEG-IFN with or without RBV in the past. Therapies for HIV are collectively called cART which includes combinations of drugs used for antiretroviral therapy.

Peer-review

The authors report data on efficacy and safety of HCV protease inhibitor boceprevir with PEG-IFN alfa and weight-based RBV in a phase 3 trial in patients with HCV plus HIV. The result, in terms of RBV, is similar to that reported by other studies in the real world and reflects the limits of this treatment. The authors, correctly, described the chronology of their trial, born before the entry in the clinical practice of the new treatments.

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