Predicting the Probability of Experiencing Clinically Significant Drug–Drug Interactions Involving Boceprevir-Containing Hepatitis C Therapy Among Patients Coinfected with Hepatitis C and HIV

Nimish Patel, PharmD, MS,¹ Michael Veve, PharmD,¹ Mona Nasiri, BS,¹ Steven Bliss, BA,¹ Louise-Anne McNutt, PhD,² Victoria Lazariu, PhD,² and Christopher Miller, PharmD³

Dear Editor:

MANAGEMENT OF HIV is complicated by the presence of hepatitis C (HCV) infection.¹ The recent addition of first-generation nonstructural protein 3/4A (NS3/4A) serine protease inhibitors, such as boceprevir and telaprevir, has significantly enhanced the probability of achieving a sustained virologic response (SVR).² Recently, simeprevir and sofosbuvir have been incorporated into treatment guidelines,³ but availability and uptake in foreign markets is a long process. Therefore, patients with HIV/HCV infection in developing countries may still rely on treatment with first-generation NS3/4A protease inhibitors.

Despite the availability boceprevir and telaprevir, their uptake has been limited by concerns about cost/reimbursement, toxicity, and the risk of drug–drug interactions. Of these, the latter has been among the clinical concerns limiting the use of NS3/4A protease inhibitors among coinfecting patients.

The objectives of this study were to (1) quantify the prevalence of clinically significant drug–drug interactions (CSDDI) when boceprevir-containing triple HCV therapy (BCTT) is added to a patient's medication profile, and (2) determine the predictors of contraindicated drug–drug interactions. This study focused on boceprevir because it has gained licensure in a significant number of developing countries where HCV coinfection is a concern, and is likely to be used.⁴

A cross-sectional study was performed among Veterans' Affairs Medical Center (VAMC) patients receiving care in the Upstate New York Veterans' Healthcare Administration (VISN-2) between January 1, 2000 and July 31, 2011. Inclusion criteria for this study were: (1) age ≥ 18 years, (2) documented HIV infection, and (3) laboratory-confirmed HCV infection. Patients with no medication history were excluded.

From the patients' medical records we extracted social history, demographics (age, sex, race, height, and weight), and clinical data (years since HCV and HIV diagnosis, CD4 cell counts, comorbidities, and medication lists). Further details on the variables that were collected are described elsewhere.⁵

The outcomes of interest in this study were the presence of (1) CSDDI, and (2) contraindicated drug–drug interactions. Drug–drug interactions were identified by Lexi-Interact drug interaction software. The rating system in Lexi-Interact was used to define which drug–drug interactions were considered (1) *clinically significant* and (2) *contraindicated*. Interactions rated by Lexi-interact with a level D or X severity rating were considered clinically significant; those rated only X were considered contraindicated drug–drug interactions.

To determine the effect of BCTT on the excess risk of CSDDI and contraindicated drug–drug interactions, boceprevir, pegylated interferon α , and ribavirin were added to the patients' medications lists in Lexi-Interact, and reanalyzed. Any additional D- or X-rated interactions were documented.

For the bivariate analyses, categorical variables were compared by χ^2 or Fisher's exact tests, and continuous variables were compared by Student's *t* or Mann–Whitney *U* tests. Classification and regression tree (CART) analysis was used to identify break points in continuous variables. McNemar's test was used to compare the frequency of outcome before and after the addition of boceprevir-containing HCV therapy.

Variables in the bivariate analyses that were associated ($p < 0.2$) with contraindicated drug–drug interactions were considered for inclusion in the explanatory multivariate log-binomial regression model with robust variance estimates.⁶ All calculations were computed using SPSS version 11.5 (SPSS Inc., Chicago, IL), SAS version 9.3 (Cary, NC), and CART software (Salford Systems, San Diego, CA).

The mean (standard deviation, SD) age of the 244 patients was 57.4 (6.1) years. The median [interquartile range (IQR)] durations of HIV and HCV infections were 19 (15–24) and 15 (12–19) years, respectively. The most common antiretroviral therapy (ART) regimen types were non-nucleoside reverse transcriptase inhibitor (NNRTI)-based (37.7%) and protease inhibitor (PI)-based (36.9%). The median (IQR) numbers of non-HIV medications and CSDDI per patient were 8 (5–11) and 3 (1–6), respectively.

¹Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, New York.

²Department of Epidemiology and Biostatistics, University at Albany, State University of New York, Rensselaer, New York.

³Department of Medicine and Pharmacy, Upstate University Hospital, Syracuse, New York.

TABLE 1. BIVARIATE ANALYSES OF CLINICAL COVARIATES ASSOCIATED WITH CONTRAINDICATED DRUG-DRUG INTERACTIONS INVOLVING BOCEPREVIR-CONTAINING HEPATITIS C (HCV) THERAPY

<i>Covariate</i>	<i>No contraindicated drug-drug interaction (n = 64)</i>	<i>Contraindicated interaction present (n = 180)</i>	<i>p Value</i>
Demographic characteristics			
Age, mean $\pm$ SD	58.1 (7.0)	57.2 (5.8)	0.32
Age $\geq$ 71 years ^a	4 (6.3)	0 (0)	0.004
Male sex	62 (96.9)	177 (98.3)	0.61
Race			0.91
African American	44 (69.8)	117 (65.0)	
Hispanic	6 (9.5)	18 (10.0)	
White	12 (19.0)	42 (23.3)	
Other	1 (1.6)	3 (1.7)	
History of HIV and HCV infections			
Duration of HIV infection, median [interquartile range (IQR)]	20 (15–25)	19 (14–24)	0.39
Duration of HIV $\geq$ 8 years ^a	64 (100)	165 (91.7)	0.01
Duration of HCV infection, median (IQR)	14 (13–19)	15 (12–19)	0.88
Most recent CD4 count, median (IQR)	515 (328–690)	395 (18–621)	0.01
Most recent log-transformed HIVRNA, mean $\pm$ SD	2.65 (1.14)	2.46 (1.04)	0.24
Antiretroviral medication use			
Receiving antiretroviral therapy	43 (67.2)	179 (99.4)	<0.001
Antiretroviral regimen type			0.02
Non-nucleoside reverse transcriptase inhibitor	14 (32.6)	78 (43.6)	
Protease inhibitor	15 (34.9)	75 (41.9)	
Integrase strand transfer inhibitor	2 (4.7)	1 (0.6)	
Other/mixed class regimen	12 (27.9)	25 (14.0)	
Use of nucleoside reverse transcriptase inhibitors	41 (64.1)	162 (90.0)	<0.001
Zidovudine	17 (26.6)	35 (19.4)	0.23
Lamivudine	33 (51.6)	66 (36.7)	0.04
Emtricitabine	6 (9.4)	78 (43.3)	<0.001
Tenofovir	12 (18.8)	93 (51.7)	<0.001
Abacavir	5 (7.8)	22 (12.2)	0.33
Didanosine	2 (3.1)	11 (6.1)	0.52
Stavudine	12 (18.8)	19 (10.6)	0.09
Use of non-nucleoside reverse transcriptase inhibitor	17 (26.6)	89 (49.4)	0.002
Efavirenz	0 (0)	83 (46.1)	<0.001
Nevirapine	16 (25.0)	3 (1.7)	<0.001
Rilpivirine	1 (1.6)	0 (0)	0.26
Etravirine	0 (0)	3 (1.7)	0.57
Use of protease inhibitor	18 (28.1)	93 (51.7)	0.001
Atazanavir	0 (0)	33 (18.3)	<0.001
Darunavir	0 (0)	13 (7.2)	0.02
Fosamprenavir	0 (0)	5 (2.8)	0.33
Lopinavir	0 (0)	40 (22.2)	<0.001
Saquinavir	3 (4.7)	2 (1.1)	0.12
Indinavir	4 (6.3)	0 (0)	0.004
Nelfinavir	11 (17.2)	3 (1.7)	<0.001
Ritonavir	2 (3.1)	82 (45.6)	<0.001
Integrase inhibitor	2 (3.1)	18 (10.0)	0.11
Raltegravir	2 (3.1)	18 (10.0)	0.11
Enfuvirtide	0 (0)	2 (1.1)	1.00
Non-HIV medication usage			
Total number of medications, median (IQR)	10 (6–13)	12 (9–15)	0.01
Use of $\geq$ 8 medications ^a	39 (60.9)	152 (84.4)	<0.001
Number of non-HIV medications, median (IQR)	8 (5–10)	8 (6–12)	0.17
Antipsychotics	16 (25.0)	34 (18.9)	0.30
Antibiotics	4 (6.3)	7 (3.9)	0.49
Antidepressants	17 (26.6)	62 (34.4)	0.25
Azole antifungals	2 (3.1)	7 (3.9)	1.00

(continued)

TABLE 1. (CONTINUED)

<i>Covariate</i>	<i>No contraindicated drug–drug interaction (n=64)</i>	<i>Contraindicated interaction present (n=180)</i>	<i>p Value</i>
Statins	3 (4.7)	22 (12.2)	0.10
Calcium channel blockers	6 (9.4)	35 (19.4)	0.08
Central nervous system depressants	31 (48.4)	95 (52.8)	0.55
Erectile dysfunction drugs	4 (6.3)	51 (28.3)	<0.001
Antiarrhythmic drugs	3 (4.7)	3 (1.7)	0.19
Corticosteroids	11 (17.2)	33 (18.3)	0.84
Comorbidities			
Median (IQR) number of comorbidities	8 (6–11)	10 (7–13)	0.01
≥11 comorbidities	20 (31.3)	87 (48.3)	0.02
Alcoholism	29 (45.3)	83 (46.1)	0.91
Anxiety	3 (4.7)	20 (11.1)	0.21
Bipolar/mood/personality disorder	11 (17.2)	23 (12.8)	0.38
Cardiovascular disease	6 (9.4)	22 (12.2)	0.54
Chronic kidney disease	5 (7.8)	12 (6.7)	0.76
Chronic obstructive pulmonary disease	8 (12.5)	19 (10.6)	0.67
Depression	24 (37.5)	83 (46.1)	0.23
Diabetes	7 (10.9)	31 (17.2)	0.23
Dyslipidemia	3 (4.7)	41 (22.8)	0.001
Epilepsy/seizures	3 (4.7)	9 (5.0)	1.00
Gastroesophageal reflux disease	7 (10.9)	22 (12.2)	0.79
Hepatitis B infection	3 (4.7)	20 (11.1)	0.21
History of cancer	9 (14.1)	20 (11.1)	0.53
History of substance abuse	47 (73.4)	124 (68.9)	0.50
Hypertension	28 (43.8)	77 (42.8)	0.89
Insomnia	5 (7.8)	18 (10.0)	0.61
Neuropathy	8 (12.5)	23 (12.8)	0.95
Osteoporosis/osteoarthritis/osteogenesis	10 (15.6)	20 (11.1)	0.35
Post-traumatic stress disorder	12 (18.8)	31 (17.2)	0.78
Prostate disease	5 (7.8)	24 (13.3)	0.24
Schizophrenia/psychosis	7 (10.9)	20 (11.1)	0.97

All data presented as *n* (%), mean (standard deviation), or median (interquartile range), unless noted otherwise.

^aClassification and regression tree (CART)-derived break point

The frequency of CSDDI (D- and X-rated interactions) significantly increased after the addition of BCTT from 85.7% (*n*=209) to 97.5% (*n*=238), *p*<0.001. Similarly, the prevalence of contraindicated drug–drug interactions (X-rated interactions) increased from 20.9% (*n*=51) to 73.9% (*n*=180), *p*<0.001, after the addition of BCTT. Clinically significant drug–drug interactions involving ART increased from 74.6% (*n*=182) to 84.8% (*n*=207), *p*<0.001 and contraindicated drug–drug interactions involving ART changed from 6.6% (*n*=16) to 77.9% (*n*=190), *p*<0.001, after the addition of BCTT. In a restricted analysis of patients only receiving ART (*n*=222) the addition of BCTT would have resulted in statistically (*p*<0.05) and clinically significant increases in contraindicated drug–drug interactions for mixed class ART regimens (18.9–67.6%), NNRTI (17.4–84.8%), and PI (25.6–83.3%).

The bivariate analyses of demographic and clinical characteristics associated with a contraindicated drug–drug interaction after the addition of BCTT are described in Table 1. Drug classes with higher frequencies of contraindicated drug–drug interactions were nucleoside reverse transcriptase inhibitors (*n*=162, 90.0%), NNRTIs (*n*=89, 49.4%), PIs (*n*=93, 51.7%), and erectile dysfunction drugs (*n*=51, 28.3%). The results of the multivariate regression analyses are displayed in Table 2. The only variables that were independently associated

with contraindicated drug–drug interactions were atazanavir, darunavir, lopinavir, and efavirenz, and use of eight or more medications (CART-derived break point).

We observed a number of interesting findings in this study. First, the HIV/HCV coinfecting population was highly vulnerable to drug–drug interactions when boceprevir-containing HCV therapy was added to the medication regimen. Second, the two most important drivers of contraindicated drug–drug interactions were polypharmacy (use of at least eight

TABLE 2. CLINICAL COVARIATES INDEPENDENTLY ASSOCIATED WITH THE PRESENCE OF CONTRAINDICATED DRUG–DRUG INTERACTIONS INVOLVING BOCEPREVIR-BASED HEPATITIS C (HCV) THERAPY

<i>Covariate</i>	<i>Adjusted prevalence ratio</i>	<i>95% Confidence interval</i>	<i>p Value</i>
Atazanavir	3.77	2.73–5.19	<0.001
Darunavir	3.27	2.17–4.95	<0.001
Lopinavir	3.17	2.20–4.56	<0.001
Efavirenz	3.73	2.69–5.17	<0.001
Use of ≥8 medications	1.23	1.01–1.50	0.04

medications), and four specific ART medications (efavirenz, lopinavir, atazanavir, and darunavir).

Regarding polypharmacy, treatment of HIV infection alone requires the use of three or more medications and several others to manage other comorbidities in an aging population.⁷ With respect to the four specific ART medications likely to increase the risk of contraindicated drug interactions, three are considered the preferred ART drugs (atazanavir, darunavir, and efavirenz).⁸ More interactions may exist with these agents in the general population because their use is ubiquitous in clinical practice. Other preferred ART medications may be considered in patients who are likely candidates for HCV treatment.³

Some considerations should be noted. First, the HCV guidelines have recently been updated, and no longer advocate the use of boceprevir or telaprevir.³ The issue of drug interactions is still pertinent to simeprevir, and to a lesser extent, sofosbuvir (package inserts). However, boceprevir and telaprevir are still available, and will likely to be relegated to resource-limited areas where prompt therapy is needed. Second, patients in the study did not receive BCTT, and the exposure of interest was theoretical. The theoretical design allowed us to complete the study more quickly than if we had waited for the same number of coinfecting patients to initiate BCTT in clinical practice. A high frequency of CSDDI may be expected for simeprevir, given the similarities in metabolic pathways (package insert). Third, we recognize that boceprevir is only indicated for patients with genotype 1 HCV infection. We did not use genotype as an entry criterion in this study because it was largely unavailable (documented in less than one third of the medical charts). However, the majority of patients would be expected to have genotype 1 infection.⁹ Additionally, the information bias that non-genotype 1 patients would introduce would be negligible, because there is no inherent reason to anticipate genotypic heterogeneity of medication use patterns. Fourth, these findings may underrepresent the magnitude of the issue, as adherence to screening guidelines is imperfect, and more patients may be affected.¹⁰ Finally, BCTT involves the use of pegylated interferon and ribavirin, and these medications can have their own drug–drug interactions, and this could upwardly drive up the number of CSDDI. This was not the case in this study. In a post-hoc analysis, all patients who had an interaction involving pegylated interferon or ribavirin also had interactions involving boceprevir.

Clinicians have a particularly important role in the evaluation of therapeutic agents for HCV against their country's unique backdrop of disease epidemiology, reimbursement, and potential drug interactions. The addition of BCTT in patients with HIV/HCV coinfection was associated with a high prevalence of drug–drug interactions, and was predicted by polypharmacy and specific ART medications. Future research should investigate the population-based risk of drug–drug interactions with emerging HCV agents, and whether

these findings would be more pronounced in the developing world, where BCTT is most likely to be utilized.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Nimish Patel, PharmD, MS
Albany College of Pharmacy and Health Sciences
106 New Scotland Avenue
Albany, NY 12208
E-mail: nimish.patel@acphs.edu