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Review and Management of Drug Interactions with Boceprevir and Telaprevir

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Abstract

Boceprevir and telaprevir, when added to pegylated interferon and ribavirin for the treatment of chronic hepatitis C virus infection, increase the rates of sustained virologic response in treatment naïve persons to approximately 70%. While these agents represent an important advance in the treatment of chronic hepatitis C virus, they present new treatment challenges to the Hepatology community. Boceprevir and telaprevir are both substrates and inhibitors of the hepatic enzyme cytochrome P450 3A and the drug transporter, P-glycoprotein, which predisposes these agents to many drug interactions. Identification and appropriate management of potential drug interactions with telaprevir and boceprevir is critical for optimizing therapeutic outcomes during hepatitis C treatment. This review highlights the pharmacologic characteristics and drug interaction potential of boceprevir and telaprevir and provides guidance on the management of drug interactions with these agents.

Keywords

boceprevir; telaprevir; pharmacology; pharmacokinetics; drug interactions

The Hepatitis community has eagerly awaited regulatory approval of new agents with direct acting antiviral activity against chronic hepatitis C virus (HCV) infection. In 2011, two inhibitors of the non-structural (NS) 3/4A viral protease, boceprevir and telaprevir, reached the market changing the standard of care for the treatment of chronic HCV to triple therapy with peginterferon alfa, ribavirin, and an HCV protease inhibitor. These agents increase the rates of sustained virologic response (SVR) in treatment naïve patients by 30% when added to pegylated interferon and ribavirin(1–3) and offer a new treatment option for patients who failed prior therapy(4, 5). However, because of the clinical pharmacology of these agents, hepatology providers are faced with new challenges in treating persons with HCV. Owing to their short half-lives and insolubility, telaprevir and boceprevir require frequent dosing (every 8 hours) with a large number of pills (6 and 12 per day, respectively) in the fed state which may adversely impact adherence. Additionally, their routes of metabolism and transport predispose them to drug-drug interactions. Herein, we review the pharmacologic characteristics and drug interaction potential of boceprevir and telaprevir and provide guidance on the management of drug interactions with these agents.

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BOCEPREVIR

When combined with peginterferon alfa 2b and ribavirin, boceprevir demonstrated superior efficacy to peginterferon alfa 2b and ribavirin alone in phase 3 clinical trials.(1, 4) In trials, the following adverse effects were reported more frequently in patients on boceprevir, peginterferon alfa 2b and ribavirin relative to those on peginterferon alfa 2b and ribavirin alone: fatigue, anemia, nausea, dysgeusia, chills, insomnia, alopecia, neutropenia, diarrhea, decreased appetite, irritability, vomiting, arthralgias, dizziness, dry skin, rash, asthenia, thrombocytopenia, and dyspnea on exertion.(6)

Boceprevir is dosed as 800mg (4–200mg capsules) every 8 hours. Boceprevir area under the concentration time curve (AUC) is increased up to 65% in the fed relative to fasted state, so the drug should be taken with food, but bioavailability is similar whether taken with a high or low fat meal.(6) Boceprevir is administered as an approximately equal mixture of two diastereomers, SCH534128 (pharmacologically active) and SCH534129 (inactive), but in plasma the ratio of active to inactive form is 2:1.(7) Boceprevir is metabolized by aldoketoreductase (AKR) 1C2 and 1C3 and cytochrome P450 3A (CYP3A).(7) After a single 800-mg oral dose of ^{14}C-boceprevir, a diastereomeric mixture of ketone-reduced metabolites predominate with a mean exposure approximately 4–fold greater than that of boceprevir.(6) Boceprevir is a potent inhibitor of CYP3A.(6) Boceprevir is also a substrate and inhibitor of the drug transporter, P-glycoprotein (P-gp).(7) In vitro, at concentrations up to 52,000 ng/mL, boceprevir did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1.(6) After incubation with 520–52,000 ng/mL of boceprevir in cultured human hepatocytes, there was little (<2 fold) or no induction of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4/5.(6) Seventy-nine percent and 9% of the dose is excreted in the feces and urine, respectively following a single oral 800mg dose of ^{14}C-boceprevir.(6) Boceprevir is 75% protein bound in human plasma.(6) The pharmacokinetics of boceprevir is shown in Table 1. (6) Following a single 400mg boceprevir dose, SCH534128 AUC and maximum concentration (Cmax) were increased 32% and 28%, respectively in those with moderate (Child Pugh 7–9) and 45% and 62%, respectively in those with severe hepatic impairment (Child Pugh 10–12), relative to subjects with no impairment. (6) No dosage adjustment is necessary for patients with renal impairment. Boceprevir AUC is 10% lower in patients with end-stage renal disease requiring hemodialysis.(6)

The boceprevir concentration required to inhibit 50% of HCV replication (IC_{50}) in vitro is 100 ng/mL.(7) Early studies (boceprevir monotherapy or combined with peginterferon alone) found boceprevir pharmacokinetics to be associated with HCV decline.(8) However, an FDA exposure-response analysis of limited Phase 3 data found no exposure-response relationship between boceprevir trough or AUC with antiviral activity, but an upward trend of increasing anemia with increasing boceprevir AUC. The predicted incidence of anemia at the lowest and highest boceprevir exposure quartiles (3.2 and 6.3 μg·hr/mL) was 43% and 58%, respectively.(7) However, ribavirin demonstrated a steeper exposure-response relationship with incidence of anemia compared to boceprevir.(7)

TELAPREVIR

When combined with peginterferon alfa 2a and ribavirin, telaprevir demonstrated superior efficacy to peginterferon alfa 2a and ribavirin alone in phase 3 clinical trials.(2, 3, 5) In trials, the following adverse effects were reported more frequently in patients on telaprevir, peginterferon alfa 2a and ribavirin relative to those on peginterferon alfa 2a and ribavirin alone: hyperuricemia, rash, fatigue, thrombocytopenia, pruritus, hyperbilirubinemia, nausea, anemia, diarrhea, lymphopenia, vomiting, hemorrhoids, anorectal discomfort, dysgeusia, and anal pruritus.(9)

Telaprevir is dosed as 750mg (2–375 mg tablets) every 8 hours. Telaprevir 1125mg twice daily dosing demonstrated similar rates of SVR (82.3% vs. 82.9%) to thrice daily dosing in a trial of 161 patients.(10) Telaprevir should be taken with a high (≥20 grams)-fat meal or snack for optimal absorption.(11) Examples of foods with at least 20 grams of fat are shown in Table 2.(11, 12) Telaprevir interconverts to an R-diastereomer, VRT-127394, which is the major metabolite in plasma and is about 30-fold less potent than telaprevir.(9) Telaprevir's primary route of metabolism is CYP3A, but non-CYP mediated metabolism may play a role after multiple doses.(9) Following a single ^{14}C-telaprevir 750mg dose, 82% was recovered in feces, 9% in exhaled air, and 1% in urine.(9) Telaprevir is a substrate and inhibitor of P-gp.(9) Telaprevir is 59–76% protein bound primarily to alpha-1 acid glycoprotein and albumin.(13) The pharmacokinetics of telaprevir is shown in Table 1.(9) In vitro, telaprevir did not inhibit CYP1A2, 2C9, 2C19, or 2D6 and the drug has a low potential to induce CYP2C, 3A, or 1A.(9) Relative to participants with no hepatic impairment, telaprevir AUC and Cmax were reduced 46% and 49%, respectively in those with moderate (Child Pugh B) hepatic impairment following multiple doses of telaprevir.(14) This is counterintuitive, but has also been observed with the HIV protease inhibitor, ritonavir, and attributed to reduced absorption.(15) Thus the appropriate dose of telaprevir in those with moderate or severe hepatic impairment has not been determined. The reduction in telaprevir AUC and Cmax was less for those with Child Pugh A hepatic impairment, 15% and 10%, respectively, so no dose adjustment is necessary in those with mild hepatic impairment. A single dose study of telaprevir in subjects with creatinine clearances less than 30 mL/min found a 10% higher Cmax and 21% higher AUC compared to those without renal impairment, thus no dosage adjustment is necessary for those with mild, moderate, or severe renal impairment, but telaprevir has not been studied in persons with end stage renal disease or those requiring hemodialysis.(9)

The telaprevir IC_{50} against wildtype HCV is 190 ng/mL and 241 ng/mL in HCV subtype 1a and 1b replicon assays, respectively.(9) Telaprevir trough concentrations were associated with HCV viral decline in an early study of telaprevir monotherapy(16), but higher telaprevir exposure was only weakly associated with increased SVR in the pivotal trials. Telaprevir exposures were not significantly associated with the development of rash, but were significantly associated with an increased risk of anemia and hemoglobin toxicity, defined as hemoglobin less than 10 g/dL or any decrease from baseline of more than 3.5 g/dL. As with boceprevir, the association between ribavirin exposures and hemoglobin toxicity was stronger than the association with telaprevir.(17)

DRUG INTERACTIONS

Drug interactions have the potential to increase drug toxicity and/or decrease drug efficacy. For drugs with a narrow therapeutic index (i.e., the range between the minimally efficacious concentration and the maximum tolerable concentration is small), drug interactions can have important clinical implications. There are also patient populations or clinical scenarios where maintenance of adequate drug concentrations is critical to treatment success not only for the HCV drugs a patient may be taking, but also other concomitant medications. For example, in the treatment of persons with human immunodeficiency virus (HIV) coinfection or post-transplantation, maintenance of appropriate antiretroviral and immunosuppressant concentrations, respectively, is a necessity.

Sixty percent of marketed medications are metabolized by CYP3A(18), so there are many interactions to consider with boceprevir and telaprevir which are both substrates and inhibitors of CYP3A. Studies with CYP3A probes support that many drug interactions with telaprevir and boceprevir are mediated by CYP3A. Rifampin, a potent CYP3A inducer, when dosed to steady state, reduced the single dose telaprevir AUC and Cmax by 92% and

86%, respectively.(19) Thus, rifampin should not be used with telaprevir or boceprevir. Rifabutin 150mg daily or every other day is used with ritonavir-boosted HIV protease inhibitors, but requires study with boceprevir and telaprevir. Ketoconazole, a potent CYP3A inhibitor, increased single dose telaprevir AUC and Cmax by 62% and 24%, respectively following a single dose of ketoconazole.(19) Single dose boceprevir AUC and Cmax were increased 131% and 41%, respectively when administered following six days of ketoconazole 400mg twice daily.(20) Midazolam is a selective CYP3A substrate. Boceprevir increases the AUC_{0-12} of oral midazolam by 430%.(20) Oral midazolam is increased to a greater extent by telaprevir than intravenous midazolam. Oral midazolam AUC and Cmax were increased 8.96-fold and 2.86-fold, respectively, when combined with telaprevir. Intravenous midazolam AUC was increased 3.4-fold, but Cmax was unchanged. (21) Oral midazolam should not be used with telaprevir or boceprevir, but halving the dose of intravenous midazolam could be considered with monitoring for therapeutic and toxic effects.

In addition to interactions mediated by CYP3A, telaprevir and boceprevir are susceptible to membrane transporter-mediated interactions. Both agents are substrates and inhibitors of P-gp. Digoxin is not metabolized, but is a selective substrate of P-gp. Telaprevir increased digoxin Cmax and AUC by 1.5-fold and 1.85-fold, respectively, so lower doses of digoxin may be needed in patients on telaprevir and digoxin concentrations should be monitored during telaprevir treatment.(21) In vitro, boceprevir is an inhibitor of the hepatic uptake transporter organic anion transporting polypeptide (OATP) 1B1 (IC_{50}=18 μM) and the efflux transporter breast cancer resistance protein (BCRP) (IC_{50}=81 μM).(7)

Following are summaries of the available interaction data with telaprevir and boceprevir and other classes of medications which may be used in persons with HCV. When possible, recommendations on therapeutic alternatives are provided. This is not an exhaustive list of potential interactions, and new information accrues continuously. Additional information may be available in the product information for both agents or through the University of Liverpool website, www.hep-interactions.org.

Immunosuppressants

HCV recurs in nearly 100% of patients who undergo liver transplantation. Thus, it is imperative to determine the safest and most effective doses of telaprevir and boceprevir to use in this setting. Multi-dose boceprevir and telaprevir have been studied with single dose cyclosporine and tacrolimus in healthy volunteers. The pharmacokinetic data from these studies are shown in Table 3. Boceprevir and telaprevir slow the clearance of cyclosporine and tacrolimus. The AUC of cyclosporine is increased 4.64-fold and 2.7-fold by telaprevir and boceprevir, respectively.(22, 23) The AUC of tacrolimus is increased 70.3-fold and 17.1-fold by telaprevir and boceprevir, respectively.(22, 23) Boceprevir and telaprevir pharmacokinetics are not affected by cyclosporine or tacrolimus. Sirolimus is expected to behave similarly to tacrolimus, but has not been studied. These preliminary data suggest cyclosporine may be preferred to tacrolimus in the setting of telaprevir or boceprevir-based HCV treatment, but it may still be possible to use tacrolimus in a very controlled manner. When initiating telaprevir or boceprevir-based HCV therapy in patients on cyclosporine, one may consider empirically reducing the cyclosporine dose by 75%, then using therapeutic drug monitoring to further refine the cyclosporine dose and frequency. Another option may be to hold the doses of cyclosporine and tacrolimus after telaprevir or boceprevir have been introduced and re-dose these medications when the immunosuppressant concentrations are in the desired range. This has been done with ritonavir-boosted HIV protease inhibitors.(24–27)

Antiretroviral Drugs

Thirty percent of persons with HIV are coinfected with HCV.(28) HIV/HCV coinfected patients have higher baseline HCV viral loads, more rapid progression of liver disease and fibrosis, and are at increased risk for cirrhosis, end stage liver disease and hepatocellular carcinoma.(29) Preferred agents for the treatment of HIV include two nucleos(t)ide reverse transcriptase inhibitors, tenofovir disoproxil fumarate (TDF) and emtricitabine; the non-nucleoside reverse transcriptase inhibitor, efavirenz; two ritonavir boosted protease inhibitors, darunavir and atazanavir; and the integrase inhibitor, raltegravir.(30) Results from healthy volunteer drug interaction studies performed with boceprevir or telaprevir and antiretroviral drugs are shown in Table 4. TDF does not affect the pharmacokinetics of boceprevir or telaprevir, but the Cmax of tenofovir is increased about 30% with both HCV protease inhibitors.(31, 32) This effect has also been observed with some HIV protease inhibitors.(33–35) Data suggest those on HIV protease inhibitors with TDF may have greater declines in renal function from TDF than those on non-PI containing antiretroviral regimens(36), though renal adverse events from TDF are uncommon(37). Concentrations of both telaprevir and boceprevir are reduced by efavirenz.(20) A higher dose of telaprevir, 1125mg thrice daily, is being used in combination with efavrienz in clinical trials of HIV/HCV coinfected patients with promising initial results.(38) In the treatment of HIV, ritonavir is used at a low dose (100mg once or twice daily) to inhibit CYP3A metabolism of other HIV protease inhibitors and pharmacokinetically enhance their levels. This strategy was investigated for both boceprevir and telaprevir. Unfortunately ritonavir-boosting does not appear to decrease telaprevir or boceprevir pill burden or dosing frequency(20, 39) Telaprevir has some deleterious bi-directional interactions with ritonavir-boosted protease inhibitors.(31) Ritonavir-boosted darunavir, fosamprenavir, and lopinavir all significantly reduce telaprevir concentrations (AUCs decreased by 32–54%). Atazanavir also reduces telaprevir levels, but the effect is smaller (AUC reduced 20%). In addition to the telaprevir levels being reduced, telaprevir also reduces darunavir and fosamprenavir by 40% and 47%, respectively whereas lopinavir is essentially unchanged and atazanavir AUC is slightly increased (17%) and trough is increased 85%. Ritonavir-boosted atazanavir is being studied in HIV/HCV coinfected patients on telaprevir without dose adjustment of either agent(38), but whether telaprevir can be safely combined with darunavir, fosamprenavir, and lopinavir requires additional study. Darunavir, fosamprenavir, and lopinavir have CYP-induction properties, so they may induce telaprevir metabolism, but the shapes of the telaprevir pharmacokinetic profiles suggest a possible interaction at the level of protein binding displacement or at the level of bioavailability. In vitro data do not show telaprevir to be a CYP-inducer, so the mechanism for the reduction in darunavir and fosamprenavir is unclear. Raltegravir is an attractive agent for use in the treatment of HCV in the HIV/HCV coinfected patient because it does not inhibit or induce CYP enzymes and its primary route of metabolism is glucuronidation. In combination with telaprevir, raltegravir AUC was increased 31%, presumably due to telaprevir's inhibition of P-gp. Telaprevir levels were unchanged. Raltegravir has a wide therapeutic index and a 31% increase in AUC is not expected to have clinical relevance. Studies of the interaction potential of boceprevir with ritonavir-boosted protease inhibitors and raltegravir are ongoing. A Phase 2 trial of boceprevir in 98 HIV/HCV coinfected participants allowed the use of NRTIs, ritonavir-boosted HIV protease inhibitors, raltegravir, and the chemokine coreceptor 5 antagonist maraviroc, but excluded those on non-nucleoside reverse transcriptase inhibitors. SVR data are not yet available, but at 24 weeks of treatment, 70.5% of those on boceprevir, peginterferon alfa 2b, and ribavirin had undetectable HCV RNAs.(40)

HMG-CoA Reductase Inhibitors

Simvastatin and lovastatin are highly dependent on CYP3A for metabolism. There are multiple reports in the literature of myopathy and rhabdomyolysis in patients whose

simvastatin concentrations were raised by a drug interaction with a potent CYP3A inhibitor.(41) Thus, simvastatin and lovastatin use should be avoided in patients on boceprevir or telaprevir. Administered as 20mg daily, atorvastatin Cmax and AUC are increased 10.6-fold and 7.88-fold by telaprevir.(42) Atorvastatin AUC and Cmax, when administered as a single 40mg dose, were increased 2.3-fold and 2.7-fold, respectively by multidose boceprevir.(43) Atorvastatin use should be avoided with telaprevir and the lowest dose used then titrated to effect with boceprevir. Pravastatin is metabolized by multiple pathways. In combination with boceprevir, pravastatin AUC and Cmax are increased 1.6-fold and 1.5-fold respectively.(43) The mechanism for the interaction with pravastatin is unclear but may relate to boceprevir's inhibition of OATP1B1. Rosuvastatin, which is not extensively metabolized by CYP3A, could be considered for use in combination with telaprevir and boceprevir, but has not been studied to date. Unexpected increases in rosuvastatin concentrations were noted when used in combination with several HIV protease inhibitors(44–46), so increased monitoring for symptoms of myopathy may be necessary.

Oral contraceptives

Ribavirin is highly teratogenic(47) so prevention of pregnancy during antiviral treatment of HCV is critical. Boceprevir and telaprevir lower ethinyl estradiol AUC by about 25%.(32, 48) With telaprevir, the reduction in ethinyl estradiol levels increases follicle stimulating hormone and luteinizing hormone and decreases endogenous progesterone levels, suggesting this pharmacokinetic alteration could result in loss of contraceptive efficacy.(48) Boceprevir and telaprevir have different effects on the progestin-component of oral contraceptives. Telaprevir reduces norethindrone slightly (~11%), whereas boceprevir increases drosperinone AUC and Cmax 99% and 57%, respectively.(32) Progestin-only contraception is effective(49), but it is difficult to know with certainty whether boceprevir would increase the levels of all progestins or if it is unique to drosperinone. There may also be more progestin-associated adverse effects with increased progestin concentrations. Furthermore, since drosperinone inhibits potassium excretion in the kidneys, the increase in drosperinone concentrations could theoretically cause hyperkalemia. Thus, considering the potential for increased adverse effects (with boceprevir) and loss of contraceptive efficacy (with telaprevir), use of ethinyl estradiol and progestin-based hormonal contraception should not be relied upon during triple therapy for HCV and for 2 weeks following the discontinuation of boceprevir or telaprevir.

Antidepressants

The selective serotonin reuptake inhibitors (SSRIs) are generally chosen as first line treatment for depression due to their safety in overdose and improved tolerability.(50) Boceprevir and telaprevir have been studied with escitalopram. Escitalopram is metabolized by CYP2C19, with minor contribution by CYP3A4 and CYP2D6. The single dose AUC of escitalopram was reduced 21% (with a reduction in half-life from 31 to 22 hours) following multiple doses of boceprevir.(51) Multiple dose escitalopram exposures were reduced an average of 35% by multiple doses of telaprevir.(52) The mechanism for this interaction is unclear. With HIV protease inhibitors, paroxetine and sertraline exposures are reduced(53, 54). There are no obvious concentration-effect data for the SSRIs, so it is unknown if reductions in exposures translate into reduced ability to control depressive symptoms but providers should be aware of the potential for reductions in SSRI exposures with telaprevir and boceprevir and increase the anti-depressant doses as needed.

Anti-psychotics

There are no formal drug interaction studies between telaprevir or boceprevir and anti-psychotics, thus predictions must be made based on knowledge of the clinical pharmacology of each agent. Quetiapine relies solely on CYP3A for metabolism and the potent CYP3A

inhibitor, ketoconazole, increases quetiapine exposures by 335%.(55) There are case reports of quetiapine toxicity when combined with HIV protease inhibitors.(56) Aripiprazole concentrations are increased 63% by ketoconazole(57) and there is a case of presumed aripiprazole toxicity in a patient taking the ritonavir-boosted HIV protease inhibitor, darunavir.(58) Ketoconazole increases the iloperidone AUC by 57%.(59) If possible, quetiapine use should be avoided in patients undergoing boceprevir and telaprevir-based HCV treatment, and the dosage of aripiprazole and iloperidone should be empirically reduced by half when telaprevir or boceprevir are initiated and the anti-psychotic dose then titrated to effect. When available and when therapeutic concentrations have been established (e.g., clozapine plasma concentration >350 ng/mL), therapeutic drug monitoring of the anti-psychotic may have clinical utility.

Anxiolytics and Sleep Aids

Benzodiazepines are commonly used as anxiolytics and sleep aids. Flurazepam, quazepam, and triazolam are highly dependent on CYP3A for metabolism and their use should be avoided with boceprevir and telaprevir. Alprazolam AUC is increased 35% with telaprevir.(60) Zolpidem, zaleplon, eszopiclone are non-benzodiazepine hypnotics that induce sleepiness. Zolpidem AUC is reduced 42% by telaprevir and zolpidem half-life shortened from 4.32 to 3.37 hours, so a higher dose of zolpidem may be required with telaprevir.(60) The antidepressant trazodone is also used as a sleep aid. With the HIV protease inhibitor ritonavir, trazodone exposures are increased with nausea, dizziness, hypotension and syncope.(61)

Opioid-Replacements

Methadone and buprenorphine do not inhibit or induce CYP enzymes, but their pharmacokinetics and pharmacodynamics can be affected by drugs that do affect CYP enzymes. Methadone, administered as a combination of the R- and S-isomers, is 85% plasma protein bound and is metabolized by CYP2B6, CYP2C19, and CYP3A.(62) Buprenorphine is 96% plasma protein bound and is metabolized by CYP3A, CYP2C8, and glucuronidation.(63) Telaprevir has been studied with methadone and buprenorphine. Total R-Methadone (the isomer responsible for opioid effect) AUC and minimum concentration (Cmin) in plasma were reduced about 30%, but unbound (free) methadone concentrations were unchanged with telaprevir. There were no symptoms of withdrawal in the 18 study participants. Thus, telaprevir displaced methadone from its plasma protein binding sites, but since free concentrations were unchanged a methadone dose adjustment is likely unnecessary with the addition of telaprevir.(64) Telaprevir has no effect on buprenorphine pharmacokinetics.(65)

Anti-hypertensive Agents

CYP enzymes are not involved in the metabolism of ace inhibitors or diuretics, thus CYP-mediated drug interactions with these classes of antihypertensives and boceprevir and telaprevir are unlikely. Among the beta blockers, only carvedilol and nabivolol are metabolized to some extent by CYP3A4.(66) There is a contribution of CYP3A4 to the metabolism of the angiotensin II receptor blockers irbesartan and losartan.(66) Thus, dose reductions could be considered for carvedilol, nabivolol, irbesartan, and losartan in patients initiating telaprevir and boceprevir. The calcium channel blockers are highly reliant on CYP3A for metabolism(66) and are therefore susceptible to increases in exposure from boceprevir and telaprevir. Amlodipine Cmax and AUC are increased 1.27-fold and 2.79-fold by telaprevir, so a reduced dose of amlodipine should be considered in patients on telaprevir.(42)

CONCLUSION

Telaprevir and boceprevir represent important advances in the treatment of chronic HCV, but their optimal use requires a significant appreciation for their clinical pharmacology and drug interaction potential. Table 5 provides a summary of drugs to avoid and drugs to use with caution with boceprevir and telaprevir. While several drug interaction studies have been conducted, there is a relative paucity of information on the management of the interactions identified and still much to learn about concentration-effect relationships for these agents. This knowledge is essential for increasing the probability of virologic response while minimizing toxicities from HCV treatment.

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Table 1

Pharmacokinetics of Telaprevir and Boceprevir

	Boceprevir 800mg Q8H	**Telaprevir 750mg Q8H**
AUC_{0-8} (ng*hr/mL)	5408	22,300
Cmax (ng/mL)	1723	3510
Ctrough (ng/mL)	88	2030
Tmax (hours)	2	4–5
Half-life (hours)	3.4	9–11
CL/F (L/hr)	161	32.4
V/F (L)	772	252
PB (%)	75	59–76

Table 2

Examples of Foods with at Least 20g of Fat

Bagel with cream cheese
½ cup of nuts
3 tablespoons of peanut butter
1 cup of ice cream
2 ounces of American or cheddar cheese
2 ounces of potato chips
½ cup of trail mix
1 cup of granola (33 g)
3 slices of homemade French toast
2 cups 3.3% whole milk
2 oz. chocolate candy bar with almonds or peanuts
2 2oz. plain doughnuts
1 slice pecan pie
1 medium avocado
3.5 oz. lean hamburger in bun
3.5 oz. salami
4 slices of bologna
1 3.5 oz broiled pork chop
3 3.5 oz. sausage patties
2 cups chow mein noodles
1 7 oz. fried chicken breast
2 small roasted chicken legs

Table 3

Cyclosporine and Tacrolimus Pharmacokinetics with and without Concomitant Boceprevir and Telaprevir Administration

		Mean (SD) CL/F (L/hr)	Mean (SD) $t_{1/2}$ (hr)	Mean (SD) $AUC_{0-\infty}$ (ng*hr/mL)	Mean (SD) Cmax (ng/mL)
	Cyclosporine				
Telaprevir Study	CSA 100mg (n=10)	56.3 (14)	12 (1.67)	1880 (489)	489 (142)
	CSA 10mg + TVR (n=9)	12.5 (3.33)	42.1 (11.3)	853 (218)	62.2 (18.9)
	DN GLS Mean Ratio (90% CI)			4.64 (3.9, 5.51)	1.32 (1.08, 1.6)
Boceprevir Study	CSA 100mg (n=10)	58.8 (15.3)	11.3 (4.1)	1800 (468)	388 (186)
	CSA 100mg+ BOC (n=10)	21 (3.36)	15.7 (3.6)	4870 (779)	737 (199)
	GMR (90% CI)			2.7 (2.39, 3.05)	2.01 (1.69, 2.4)
	Tacrolimus				
Telaprevir Study	TAC 2mg (n=10)	32 (10.2)	40.7 (5.85)	67.3 (17.3)	3.97 (1.82)
	TAC 0.5mg + TVR (n=9)	0.48 (0.19)	196 (159)	1310 (866)	8.7 (3.23)
	DN GLS Mean Ratio (90% CI)			70.3 (52.9, 93.4)	9.35 (6.73, 13)
Boceprevir Study	TAC 0.5mg (n=12)	29.6 (16.9)	36.7 (8.1)	21.8 (11.6)	0.81 (0.29)
	TAC 0.5mg + TVR (n=12)	1.6 (0.5)	61.3 (11)	345 (110)	7.8 (1.95)
	GMR (90% CI)			17.1 (14, 20.9)	9.9 (7.96, 12.3)

CSA=cyclosporine, TAC=tacrolimus, DN GLS=dose normalized geometric least square means, GMR=geometric mean ratio

Table 4

Interactions with Boceprevir and Telaprevir and Antiretroviral Drugs

	Boceprevir			Antiretroviral			Telaprevir			Antiretroviral		
	Cmax	**AUC**	**Cmin**	**Cmax**	**AUC**	**Cmin**	**Cmax**	**AUC**	**Cmin**	**Cmax**	**AUC**	**Cmin**
Tenofovir	1.05	1.08	1.08	1.32	1.05	NR	1.01	1.00	1.03	1.3	1.3	1.41
Efavirenz	0.92	0.81	0.56	1.11	1.2	NR	0.91	0.74	0.53	0.84	0.93	0.98
Atazanavir/Ritonavir	-	-	-	-	-	-	0.79	0.8	0.85	0.85	1.17	1.85
Darunavir/Ritonavir	-	-	-	-	-	-	0.64	0.65	0.68	0.6	0.6	0.58
Fosamprenavir/Ritonavir	-	-	-	-	-	-	0.67	0.68	0.7	0.65	0.53	0.44
Lopinavir/ritonavir	-	-	-	-	-	-	0.47	0.46	0.48	0.96	1.06	1.14
Raltegravir	-	-	-	-	-	-	1.07	1.07	1.14	1.26	1.31	1.78

Data are presented as the geometric mean ratios (GMR) of boceprevir, telaprevir, and the antiretroviral drugs when given in combination relative to when given alone, -=no data, NR=not reported, Cmax=maximum concentration, AUC=area under the concentration time curve for the dosing interval, Cmin=minimum concentration

Table 5

Summary of Drugs to Avoid and Drugs to Use with Caution in Combination with Boceprevir and Telaprevir. Interactions unique to one of the HCV Protease Inhibitors are indicated in parentheses (e.g, TPV or BOC).

	AVOID	**USE WITH CAUTION**	
		↑ Concentration of Concomitant Med or HCV PI	↓ Concentration of Concomitant Med or HCV PI
Alpha-1 adrenoreceptor antagonist	Alfuzosin	Doxazosin, terazosin, tamsulosin, silodosin	
Anticonvulsants	Carbamazepime, phenobarbital, phenytoin		
Antifungals		Ketoconazole, itraconazole, posaconazole, voriconazole	
Antimicrobials		Clarithromycin, erythromycin	
Antimycobacterials	Rifampin, rifapentine	Rifabutin	
Antiretroviral Drugs	lopinavir **(TPV)**, darunavir **(TPV)**, fosamprenavir **(TPV)**, efavirez **(BOC)**		efavirenz **(TPV)** *
Benzodiazepines and Sleep Aids	Flurazepam, quazepam, triazolam, oral midazolam	Alprazolam, trazodone	
Cardiovascular	Amiodarone, bosentan, dofetilide, flecainide, lidocaine, propafenone, quinidine, sildenafil and tadalafil for pulmonary arterial hypertension	Calcium channel blockers, digoxin, carvedilol, nabivolol, irbesartan, losartan	
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine		
Herbal products	St John's wort		
HMG-CoA reductase inhibitors	Lovastatin, simvastatin, atorvastatin **(TPV)**	Atorvastatin **(BOC)**, pravastatin, rosuvastatin	
Immunosuppressants	Tacrolimus, sirolimus	cyclosporine	
Oral contraceptives		Drosperinone **(BOC)**	Ethinyl estradiol
Respiratory		Fluticasone, salmeterol	
Second Generation Antipsychotics	Quetiapine	Iloperidone, aripiprazole	

* a higher dose of telaprevir 1125mg every 8 hours has been studied with efavirenz with promising preliminary rates of SVR