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Drug-drug interactions with oral anti-HCV agents and idiosyncratic hepatotoxicity in the liver transplant setting

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Summary

Studies of boceprevir and telaprevir based antiviral therapy in liver transplant (LT) recipients with hepatitis C genotype 1 infection have demonstrated dramatic increases in tacrolimus, cyclosporine, and mTOR inhibitor exposure. In addition to empiric dose reductions, daily monitoring of immunosuppressant blood levels is required when initiating as well as discontinuing the protease inhibitors to maximize patient safety. Although improved suppression of HCV replication is anticipated, 20 to 40% of treated subjects have required early treatment discontinuation due to various adverse events including anemia (100%), infection (30%), nephrotoxicity (20%) and rejection (5 to 10%). Simeprevir and faldaprevir will likely have improved efficacy and safety profiles but potential drug interactions with other OATP1B1 substrates and unconjugated hyperbilirubinemia are expected. In contrast, sofosbuvir and daclatasvir based antiviral therapy are not expected to lead to clinically significant drug-drug interactions in LT recipients but confirmatory studies are needed. Liver transplant recipients may also be at increased risk of developing drug induced liver injury (DILI). Establishing a diagnosis of DILI in the transplant setting is very difficult with the variable latency, laboratory features and histopathological manifestations of hepatotoxicity associated with a given drug, the need to exclude competing causes of allograft injury, and the lack of an objective and verifiable confirmatory test. Nonetheless, a heightened awareness of the possibility of DILI is warranted in light of the large number of medications used in LT recipients and the potential adverse impact that DILI may have on patient outcomes.

Introduction

The calcineurin inhibitors (CNI), tacrolimus and cyclosporine, as well as the mammalian target of rapamycin inhibitors (mTORi), sirolimus and everolimus, are the backbone of modern immunosuppression in solid organ transplantation. Both of these drug classes are substrates of cytochrome P450 (CYP) isoenzymes 3A4/5 and the drug-transporter, P-glycoprotein (P-gp). These metabolic pathways are also primarily involved in the elimination of 40 to 60% of all marketed drugs and *in vivo* expression of both *CYP3A4/5* and *P-gp* vary substantially between individuals [1–6]. As a result, administration of a drug that is a CYP3A or P-gp substrate/inhibitor to a liver transplant (LT) recipient can lead to dangerously high immunosuppressant blood levels, while intake of CYP3A inducers can predispose to subtherapeutic dosing and rejection [4,5]. Therefore, transplant practitioners must be knowledgeable of the pharmacokinetic and potential drug-drug interaction (DDI) profiles of many drugs.

The azole antifungals and non-dihydropyridine calcium channel blockers are commonly prescribed drugs that can increase the blood levels of CNI's and mTORi's. For example, a 200 mg dose of fluconazole will increase the area under the curve (AUC) of cyclosporine by 1.8-fold and increase the tacrolimus trough concentration by 5-fold in transplant recipients [7]. Similarly, intake of CYP3A inducers such as carbamazepine, St. John's wort, and rifampin can lead to increased metabolism and reduced bioavailability of both CNI's and mTORi's [8]. Boceprevir (BOC) and telaprevir (TPV) are NS3 protease inhibitors approved for use in combination with peginterferon (PegIFN) and ribavirin (RBV) for patients with chronic hepatitis C virus (HCV) genotype 1 infection. Both BOC and TPV are potent substrates and inhibitors of CYP3A and have demonstrated significant interactions with the CNI's and mTORi's in healthy volunteers as well as LT recipients. In this article, potential drug-interactions of BOC and TPV with immunosuppressants and other commonly used medications will be reviewed. In addition, preliminary safety and efficacy data of these drugs as well as other newer direct acting antiviral agents (DAA's) in LT recipients will be provided.

Keywords: Hepatitis C; Immunosuppression; Calcineurin inhibitors; Cytochrome P450; Antiviral therapy.

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Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AUC, Area under the curve; BOC, Boceprevir; BSEP, Bile salt export pump; C_{max}, Maximum concentration; CNI, Calcineurin inhibitors; CYP, Cytochrome P450; DAA, Direct acting antivirals; DDI, Drug-drug interaction; DILI, Drug induced liver injury; DILIN, Drug induced liver injury network; FCH, Fibrosing cholestatic hepatitis; HCV, Hepatitis C virus; HDS, Herbal and dietary supplements; LT, Liver transplantation; mTORi, Mammalian target of rapamycin inhibitors; OATP, Organic anion transporting polypeptide; PegIFN, peg-interferon; P-gp, P-glycoprotein; RBV, Ribavirin; SVR, Sustained virological response; TB, Tuberculosis; TMP-SMZ, Trimethoprim-sulfamethoxasole; TPV, Telaprevir.

Lastly, a review of the incidence, presentation, and outcomes of drug induced liver injury (DILI) in LT recipients will be provided.

The first generation HCV protease inhibitors: Boceprevir and telaprevir

Hepatitis C remains the leading indication for LT in most western countries and is associated with nearly universal recurrence of HCV replication and damage in the allograft [9,10]. The rate of liver disease and fibrosis progression in LT recipients is greatly accelerated compared to non-transplant patients with ~20% developing cirrhosis within 5 years of transplant and ~1 to 5% developing rapidly progressive and frequently fatal fibrosing cholestatic hepatitis (FCH) [11]. As a result, PegIFN and RBV combination therapy is frequently used in selected LT recipients [12,13]. However, many LT recipients have contraindications to PegIFN therapy and rates of sustained virologic response (SVR) are substantially lower in LT recipients compared to non-transplant patients (e.g., 20% to 30% *vs.* 45% in HCV genotype 1) [12,13]. The lower observed SVR rates are attributed to the use of immunosuppressant agents that enhance viral replication and the need for frequent antiviral dose reductions (50 to 70%) and early antiviral treatment discontinuation (20 to 40%) [12,14]. Furthermore, there are increasing reports of immune-mediated allograft dysfunction due to PegIFN that may not only require early discontinuation of treatment, but also lead to premature graft failure and/or death [15–17]. However, since LT recipients who achieve SVR have a significantly improved survival compared to non-responders, there is an urgent unmet medical need to develop safer and more effective therapies for LT recipients [18,19].

BOC and TPV in combination with PegIFN and RBV significantly improve SVR rates in both treatment naïve and previously treated patients with HCV genotype 1 infection compared to PegIFN and RBV alone [20,21]. In addition, only 6 months of response guided therapy is required in 50 to 60% of non-cirrhotic patients [20,22–25]. However, use of these agents is also associated with various adverse events including rash (50%), anorectal symptoms (30%), and anemia (50%) with TPV, and dysgeusia (30%) and anemia (50%) with BOC treatment [26,27]. Although both of these agents carry warnings regarding the potential for DDI's with CNI's and mTORi's, the anticipated improvement in antiviral efficacy has generated a great deal of interest in using them in the transplant setting [28].

Drug-drug interactions with boceprevir and telaprevir

Boceprevir and TPV are extensively metabolized in the liver and both drugs are substrates and inhibitors of CYP3A. Telaprevir is also a potent substrate and inhibitor of P-gp. Since elimination of BOC is dependent on multiple routes of metabolism, BOC is anticipated to be associated with less severe DDI's with CYP3A substrates compared to TPV [28,29].

Co-administration of BOC and TPV with drugs metabolized by CYP3A can lead to increased pharmacodynamic effects of those concomitant drugs, due to reduced metabolism and increased bioavailability in the non-transplant setting [30–34]. For example, the area-under the curve (AUC) and maximum concentration (C_{max}) of a 20 mg dose of atorvastatin increased 7.9 and 10.6-fold, respectively, with TPV co-administration, while BOC increased the AUC and C_{max} of a single 40 mg dose of atorvastatin by 2.3- and 2.7-fold, respectively [33,35]. Therefore, atorvastatin should not be co-administered with TPV and the lowest possible dose of atorvastatin should be used in patients receiving BOC. Alternatively, pravastatin which is a weak inhibitor of CYP3A may be a suitable alternative [33]. Similarly, the dose of intravenous midazolam should be reduced by at least 50% in patients receiving BOC or TPV [30,36]. Digoxin levels are increased 18% when co-administered with BOC and increased 85% when co-administered with TPV [30,36]. These latter data suggest that TPV is a moderate inhibitor of P-gp while BOC appears to be a mild P-gp inhibitor [31].

Use of BOC and TPV may also alter the bioavailability and pharmacodynamic effect of some concomitantly administered medications. For example, both BOC and TPV lower the AUC of ethinyl estradiol by approximately 25%, which may result in the loss of contraceptive efficacy [30,37]. In addition, BOC and TPV have differing effects on the bioavailability of the progestin component of oral contraceptives [30]. Since ribavirin is highly teratogenic, two alternative forms of contraception, such as an intrauterine device and barrier methods, are recommended during and after treatment with BOC or TPV based therapy [26,27,30].

Concomitant administration of CYP3A inhibitors and inducers may also alter the pharmacokinetics and pharmacodynamics of BOC and TPV during antiviral therapy (Supplementary Table 1). For example, administration of carbamazepine, a CYP3A inducer, may lower serum BOC and TPV levels and increase the risk of drug resistant variants developing in HCV patients. In contrast, drugs that are CYP3A inhibitors, such as the macrolide antibiotics, may lead to increased BOC or TPV exposure and increase the severity and frequency of adverse events [26,27,34]. Therefore, reviewing all concomitant medications prior to BOC or TPV based therapy is required. If (a) concomitant medication(s) metabolized by CYP3A or P-gp is required, the lowest effective dose should be used or an agent that is not heavily dependent on CYP3A could be considered (Table 1).

Effects of telaprevir and boceprevir on immunosuppressant drug levels

One of the greatest challenges of using BOC and TPV in the LT population is the dramatic effect that BOC and TPV have on CNI and mTORi blood levels [28,30,38]. In one study of healthy volunteers, the AUC of cyclosporine increased 4.6 and 2.7-fold when co-administered with TPV and BOC, respectively (Supplementary Table 2). In addition, the AUC of tacrolimus increased 70.3- and 17.1-fold when co-administered with TPV and BOC in healthy individuals, respectively [39,40]. Lastly, a study of BOC with single dose sirolimus in healthy volunteers showed a significant increase in the AUC and C_{max} of sirolimus by 8.1 and 4.8-fold, respectively [41]. Currently, use of BOC and TPV in subjects receiving CNI's and mTORi is considered a relative to absolute contraindication until additional safety data are obtained [26,27].

Despite the aforementioned concerns, several studies have begun to explore the use of BOC and TPV in combination with PegIFN and RBV in carefully monitored LT recipients (Table 2). A substantial reduction in the clearance of tacrolimus (~80%), cyclosporine (~50%), and everolimus (53%) was reported in LT