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Drug-drug interactions and Idiosyncratic Hepatotoxicity in the Liver Transplant setting

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Abstract

Preliminary studies of boceprevir and telaprevir based antiviral therapy in liver transplant (LT) recipients with hepatitis C have demonstrated dramatic increases in tacrolimus, cyclosporine, and the 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 faldepravir are 2nd generation protease inhibitors which may have improved efficacy and tolerability profiles but potential drug interactions with other OATP1B1 substrates and unconjugated hyperbilirubinemia are expected. In contrast, sofosbuvir and daclatasvir based therapies 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.

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

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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 (PEG-IFN) 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. 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, PEG-IFN and RBV combination therapy is frequently used in selected LT recipients (12, 13). However, many LT recipients have contraindications to PEG-IFN 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 PEG-IFN 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 PEG-IFN and RBV significantly improve SVR rates in both treatment naïve and previously treated patients with HCV genotype 1 infection compared to PEG-IFN 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 are considered investigational in LT recipients due to potential 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 Pg-p. 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 Pg-p 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 (Supplemental 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 (Supplemental 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 PEG-IFN 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 recipients receiving BOC with PEG-IFN and RBV (42). In addition, a significant reduction in the clearance of both cyclosporine and tacrolimus in LT recipients receiving TPV and PEG-IFN and RBV therapy was reported (43). The median weekly dose of tacrolimus and cyclosporine during TPV treatment was 4% and 14% of the pretreatment dose, respectively (43). Similarly, the AUC of sirolimus increased 26-fold and the mean terminal half-life increased 1.5-fold in 5 patients receiving TPV and PEG-IFN and RBV (44). During the 12 weeks of TPV therapy, patients required only 3 to 33% (mean 11%) of the pretreatment sirolimus dose with doses ranging from 0.5 to 1 mg every 5 to 22 days (44).

Prednisone and methylprednisolone are also substrates of CYP3A and one study demonstrated a 37% increase in prednisolone AUC when co-administered with BOC (26, 27, 31, 45). However, the increase in prednisolone concentration is unlikely to be clinically significant, so no dose adjustments are recommended (26,27, 45).

Boceprevir and Telaprevir based antiviral therapy in LT recipients

There are several ongoing studies of BOC and TPV in combination with PEG-IFN and RBV in LT recipients with recurrent HCV genotype 1 (Table 2) (46–52). In one study, 35 patients treated with TPV, PEG-IFN and RBV were followed for a mean of 32 weeks and 25 BOC treated patients were followed for a mean of 39 weeks (46). Prior to initiation of treatment, 92% of the patients were converted to cyclosporine. Thus far, 14 (67%) TPV and 10 (45%) BOC treated patients had undetectable HCV RNA at week 24 and 3 (5%) had developed viral breakthrough. Despite restricting the initial ribavirin dose to 800 mg/day, anemia was encountered in 100% of the patients and 50% required a blood transfusion. In addition, biopsy-proven rejection due to subtherapeutic cyclosporine levels occurred in two patients during TPV therapy and another patient following discontinuation of BOC. Of the two

patients that died, one with FCH developed sepsis after treatment of rejection and the other patient had decompensation prior to starting antiviral therapy.

The preliminary results of a multicenter French study of 37 LT recipients treated with either BOC or TPV were recently published (47). Sixteen percent of these patients had FCH and 51% had received prior antiviral therapy post LT. A 4-week lead-in of PEG-IFN and RBV was given to 84% of patients and all of the patients were hospitalized when BOC or TPV was started to monitor CNI levels. Quite remarkably, 89% of the BOC and 58% of the TPV treated patients had an undetectable HCV RNA at week 16. However, early discontinuation of therapy was required in 58% of the TPV treated patients due to severe infections or a lack of response, while only 28% of the BOC treated patients required early discontinuation of therapy. Although follow-up is ongoing, 71% of the BOC treated patients and 20% of the TPV treated patients with a week-48 response have remained HCV RNA negative at post-treatment week 12. Anemia was encountered in 100% of the patients and 35% required a blood transfusion. Only one episode of mild rejection was reported, but 8% died of liver-related complications.

The week 12 results of the ongoing REFRESH study demonstrate more promising outcomes with TPV use in LT recipients with 47% and 82% of patients achieving undetectable HCV RNA at weeks 4 and 12, respectively (48). The most frequent adverse events include anemia (39%) and rash (35%) but follow-up is ongoing.

Overall, these preliminary data suggest that the addition of TPV or BOC to PEG-IFN and RBV can lead to increased rates of HCV RNA suppression in LT recipients compared to historical controls. However, the dose of CNI needs to be markedly reduced during BOC and TPV therapy with highly variable dosing intervals necessitating the need for frequent therapeutic drug monitoring. In addition, a rapid increase in the CNI dosing and frequency is required within 1 to 2 days of discontinuing BOC or TPV to minimize the risk of under immunosuppression and rejection (53).

Adverse effects of Boceprevir and Telaprevir in LT recipients

Anemia has been a universal and potentially severe adverse event with BOC and TPV therapy in LT recipients (46–54). This is, in part, due to the impaired clearance of RBV in LT recipients with renal insufficiency as well as the bone marrow suppressive effects of PEG-IFN, BOC, and TPV (54,55). Despite a lower starting dose of RBV, aggressive RBV dose reductions have been needed and erythropoietin stimulating agents (ESA) have been used in 60 to 90% of treated patients (46–52). Skin rashes have also been frequently noted but they have not been severe (46–51). Mild to moderate renal insufficiency has also been reported during triple antiviral therapy, which may, in part, be due to drug-drug interactions with the CNI's. (44–49,52,56). However, recent studies in non-transplant patients have demonstrated significant but reversible reductions in renal function with TPV and BOC therapy attributed to renal tubular transporter effects (56,57). Due to these safety concerns, frequent therapeutic drug monitoring and assessment of renal function is recommended in LT recipients receiving these agents. Bacterial infections resulting in hospitalization or even death have also been reported in up to 33 % of LT recipients further highlighting the need for frequent and vigilant clinical assessment of all treated patients (46,47,59,50).

CNI and mTORi dosing during and after Telaprevir and Boceprevir therapy

Empiric adjustments of the CNI and mTORi dose and interval must be made at the time of initiation of BOC or TPV to minimize the risk of toxicity. Currently, prospective studies to provide safe and accurate estimates of the extent of CNI dose reduction are ongoing (43). However, since the severity of the CYP3A interaction is less with cyclosporine compared to tacrolimus, many centers have opted for conversion to cyclosporine prior to initiating BOC or TPV therapy in LT recipients. Regardless of the CNI or mTORi used, immunosuppressant blood levels should be stable and within therapeutic range for at least 1 month prior to starting antiviral therapy (Supplemental Table 3). Most studies have withheld CNI dosing after the initiation of TPV and then checked daily morning CNI blood levels to guide future doses (46,48,49). When using tacrolimus with TPV, it is suggested to use 10% of the initial total daily dose once the morning trough level goes below 3 or 4 ng/ml. In the ongoing REFRESH study, the reported dosing interval of tacrolimus ranged from once every 4 to 25 days. In contrast, the cyclosporine dose is usually 25% of the initial total daily dose and the dosing interval ranged from once every 1 to 7 days (48). There is less data available with BOC in LT recipients, but one study suggested that cyclosporine could be administered at 50% of the initial total daily dose and given once a day, while the tacrolimus dose should be started at approximately 25% of the initial dose and the interval guided by daily assessment of trough levels (46).

It is also critical to resume dosing of the CNI and mTORi to at least the pre-treatment dose within 1 to 2 days of BOC and TPV discontinuation and frequently monitor immunosuppressant blood levels for the first two weeks after BOC and TPV discontinuation. Since LT recipients with suppression of HCV replication have improved hepatic metabolic function, higher daily doses of the CNI's and mTORi's may be required early after discontinuation of BOC and TPV in up to 30% of patients (46,58–60). Therefore, close monitoring of immunosuppressant blood levels is imperative throughout antiviral therapy as well as after discontinuation of BOC and TPV to prevent rejection.

Direct acting antivirals in the pipeline

Several DAA's are in phase 3 development and may gain regulatory approval in the near future. Drugs that will likely reach the marketplace soon include the NS3 protease inhibitors, simeprevir and faldaprevir; the NS5A replication complex inhibitors daclatasvir; and the nucelos(t)ide NS5B polymerase inhibitor, sofosbuvir. In addition, an IFN-free regimen consisting of ritonavir boosted ABT-450, a protease inhibitor, ABT-267, a NS5A inhibitor, and ABT-333, a non-nucleoside polymerase inhibitor, is demonstrating promising efficacy results in both treatment naïve and experienced patients (61,62). However, IFN-free regimens may have reduced efficacy in LT recipients wherein the high frequency of HCV genotype 1a, advanced fibrosis, high levels of HCV replication, and altered drug pharmacokinetics pose substantial therapeutic challenges (63).

The new DAA's offer several potential therapeutic advantages over the currently approved protease inhibitors, including improved antiviral efficacy, shorter duration of therapy, and fewer side effects. Studies of faldaprevir, simeprevir, daclatasivr and sofosbuvir in combination with PEG-IFN and RBV have demonstrated SVR rates, of ~70–90% in

treatment naïve non-transplant, HCV genotype 1 patients treated for 12 to 48 weeks (64–71). Furthermore, the addition of two DAA's to PEG-IFN and RBV has demonstrated an almost 100% SVR even in historically difficult to treat populations (72,73). In addition, sofosbuvir combined with ribavirin alone for 12 weeks is associated with a 97% SVR in genotype 2 and 67% SVR in genotype 3 patients (74,75). The use of ledipsavir in combination with sofosbuvir and ribavirin may be particularly attractive in LT recipients with genotype 1 infection (76,77). Many of the new DAA's also have improved bioavailability and longer half-lives requiring less frequent dosing and do not require administration with food.

Available data also suggest a lower likelihood of clinically significant DDI's with some of the new DAA's compared to BOC and TPV (Table 3) (32, 82,83, 88–89). However, several are CYP3A and drug transporter substrates and inhibitors. For example, the AUC of tacrolimus decreased by 17% and that of cyclosporine increased by 19% with simeprevir co-administration (78). ABT-450 is an inhibitor of OATP1B1 that leads to unconjugated hyperbilirubinemia and the boosting of its bioavailability with ritonavir, a potent CYP3A4 substrate, may create difficulties in the LT population (79). Although, sofosbuvir does not undergo metabolism via CYP3A, dose adjustments are anticipated for patients with moderate or severe renal impairment. Faldaprevir can lead to unconjugated hyperbilirubinemia via inhibition of UGT1A1 (80). Lastly, simeprevir is a substrate of OATP1B1 and results in an increase in total bilirubin levels in subjects treated with ribavirin (81).

Data regarding the safety and efficacy of the new DAA's in various special patient populations will likely be lacking at the time of their approval. Therefore, careful scrutiny of available pharmacokinetic and clinical data will be essential for successful use of these new drugs in the transplant setting. Administration of daclatasvir with PEG-IFN and RBV for 24 weeks in an LT recipient with severe cholestatic HCV infection led to an SVR (82). In addition, the first ever successful use of an IFN-free regimen consisting of sofosbuvir and daclatasvir for 24 weeks in a LT recipient with FCH was recently reported (83). However, large, prospective, multicenter studies are needed to determine the optimal agent(s), duration of therapy, and safety profile in LT recipients (86).

Idiosyncratic drug induced liver injury in the transplant setting

Drug-induced liver injury (DILI) is an increasingly recognized cause of clinically significant acute and chronic liver disease in both children and adults (90,91). DILI is a leading cause of acute liver failure (ALF) in western countries and the most common reason for removal of approved medications from the marketplace (92, 93). However, most cases of DILI are "idiosyncratic" and not associated with the dose or duration of medication administered nor obvious clinical risk factors Furthermore, the protean clinical and laboratory presentations of liver injury due to a particular drug coupled with the lack of an objective and confirmatory diagnostic test frequently leads to a delay in diagnosis (94, 95).

DILI in the general population

The incidence of DILI in the general population is not well known. However, DILI accounts for < 1% of consecutive acute liver disease cases seen in referral centers with viral hepatitis,

pancreaticobiliary disease, hepatic ischemia, and alcohol being much more common (96, 97). The incidence of DILI in a prospective cohort study from Northern France was 14 cases per 100,000 patient years (98). More recently, the incidence of DILI in the 250,000 adult inhabitants of Iceland was estimated to be 19.1 cases per 100,000 patient years (99). In western countries, the majority of DILI cases are attributed to antibiotics, anticonvulsants and psychiatric medications (Table 4) (100, 101). However herbal and dietary supplements (HDS) can also cause clinically significant liver injury (102). The Drug Induced Liver Injury Network (DILIN) demonstrated that 73% of DILI cases in the United States were attributed to a single prescription medication while 9% were attributed to a single or multiple HDS products and 18% were attributed to multiple medications (100).

The diagnosis of DILI rests on finding abnormalities in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or total bilirubin levels while on the drug compared to pretreatment baseline values. Causality assessment is largely a diagnosis of exclusion that relies on 1) time from drug initiation to DILI onset, 2) clinical and laboratory features at presentation, 3) the time and course of recovery after drug discontinuation (i.e. de-challenge), 4) presence of established risk factors, 5) exclusion of competing causes of liver injury, and 6) previous reports on the hepatotoxicity of the implicated agent. Recently, a checklist of the essential elements to consider in investigating a possible DILI case was published (103). Causality assessment instruments can assist with DILI case recognition, but expert opinion appears to be a more reliable and accurate diagnostic method but is not widely available nor generalizable (104–106). The LIverTox website was recently established by the NIH and National Library of Medicine to provide up-to-date and evidence based information on the hepatotoxicity profile of over 600 marketed drugs (107). The website also provides useful information on the proposed mechanism, risk factors, and overall likelihood of bonafide injury attributed to a particular drug.

The clinical course of DILI can be categorized as hepatocellular, cholestatic or mixed based upon the presenting laboratory profile and liver histology (90). The severity of a DILI episode can vary from asymptomatic to severe and life threatening. DILIN has established a 5-point system for grading severity based on symptoms, jaundice, need for hospitalization, and signs of hepatic failure (108). DILIN and other groups have demonstrated that subjects who present with severe hepatocellular injury that are jaundiced at the time of hospitalization may have as high as a 10% mortality rate validating “Hy’s law (100, 101).

Studies of DILI in the transplant setting

In the LT setting, exclusion of biliary, infectious, vascular, and immunological causes of allograft dysfunction is essential since they are more likely to cause liver injury than DILI (109). Furthermore, LT recipients may also develop recurrent disease in their allograft (110). In addition, idiopathic “alloimmune hepatitis” can develop at any time post-LT even in previously stable patients (111, 112). Finally, some solid organ transplant recipients may be chronically infected with hepatitis E virus and misdiagnosed as having DILI (113, 114). Therefore, a thorough evaluation for competing causes of liver injury using molecular

diagnostic assays, liver imaging, and liver histology is required to exclude the myriad causes of allograft dysfunction in LT recipients.

Patients with liver disease may be at increased risk of developing DILI due to altered pharmacokinetics, up-regulated intrahepatic cytokine expression, and alterations in drug-metabolizing pathways (115, 116). For example, subjects with HIV and HCV or HBV co-infection are at greater risk of developing serum ALT elevations during anti-retroviral therapy compared to HIV mono-infected patients (116). However, it can be exceedingly difficult to reliably distinguish a flare in the underlying liver disease from a DILI episode.

Case series

Currently, there is a paucity of data on the frequency, etiologies, and outcomes with DILI in the LT setting. Recently, DILI was implicated in 131 Chinese LT recipients undergoing protocol liver biopsies at a single center over a 6-year period (117). Of note, 44% of the DILI cases occurred within the first 30 days of LT and antifungal agents were the leading suspect drug (29%). All of the patients survived and improved during follow-up. However, the criteria used to establish a diagnosis of DILI and the extent to which other causes of allograft dysfunction were excluded are unclear. In addition, many of the liver biopsy samples demonstrated evidence of hepatic steatosis and necrosis, which are commonly encountered in the early post-LT setting.

The frequency and risk factors for DILI in 1689 consecutive LT recipients from Mayo Clinic seen over a 15 year period were also recently reported (118). A diagnosis of “Definite DILI” was based on the presence of clinical criteria and a compatible liver biopsy after rigorous exclusion of competing causes using expert opinion for causality assessment (103). Of the 79 patients with suspected DILI based upon pathology records, there were only 28 individuals who met clinical criteria for “definite DILI” leading to an overall DILI incidence of 1.7%. The mean age of the DILI patients was 52 years and 52% were women. The major indications for LT in these 28 patients were primary sclerosing cholangitis (28%), cholangiocarcinoma (14%) and hepatocellular carcinoma (14%) with the former being over-represented compared to non-DILI LT recipients. The DILIN severity scores were mild (1) or moderate (2) in 92% of the patients (Table 4). The median duration of suspect medication use was 57 days and the most frequently identified drugs were antibiotics (48%), immunosuppressive agents (14%) and hypolipidemics (7%). Trimethoprim-sulfamethoxazole (TMP-SMZ) was the single most commonly implicated drug. The serum aminotransferase levels normalized during a median follow-up of 34 days after drug withdrawal. There was no clear relationship between donor characteristics nor time interval since LT and DILI diagnosis.

These intriguing data suggest that the incidence of DILI in LT recipients of 1.7% is substantially higher (i.e. 100 fold) than that reported in the general population (0.02%). Prior studies of immunosuppressed patients with HIV infection have also demonstrated that they are at increased risk of developing hepatotoxicity from TMP-SMZ and isoniazid (119). There are also prior case reports of LT recipients acquiring food allergies from the donor (120). Therefore, immunosuppressed LT recipients may be at increased risk of developing DILI.

Hepatotoxicity of frequently used drugs in LT recipients

Immunosuppressants—Azathioprine, a prodrug of mercaptopurine that inhibits T-cell maturation, has been a backbone of immunosuppressive regimens in LT recipients for several decades. Patients with low levels or deficiency in thiopurine methyltransferase, which affects ~10% of the population, have a higher rate of myelotoxicity with azathioprine use but do not appear to have a higher incidence of DILI. Azathioprine leads to hepatotoxicity in up to 1 to 5% of non-transplant patients treated for prolonged periods of time (121, 122). Many of these patients present with mild hepatocellular injury or cholestasis which resolves with drug discontinuation. Individual case reports have also described nodular regenerative hyperplasia with prolonged exposure to high dose azathioprine in LT recipients whom frequently present with a cholestatic laboratory profile (123, 124). The pathophysiology of this lesion is believed to be due to endothelial cell damage that leads to sinusoidal dilatation and obliterative pericentral veno-occlusive changes. Despite its widespread use, acute hepatocellular injury attributed to mycophenolate mofetil has been only rarely reported (133–135).

Hepatotoxicity attributed to cyclosporine and tacrolimus also appears to be uncommon in light of their near universal use in hundreds of thousands of solid organ transplant recipients. Individual cases of cholestatic liver injury following the use of tacrolimus have been reported that usually improved with dose reductions or switching to an alternative agent (128–131). Severe acute hepatocellular injury with jaundice was previously reported in kidney transplant patients receiving high doses of cyclosporine with histological features of cholestasis and pericholangitis (130, 131). The mechanism of this intrahepatic cholestasis may be due to inhibition of canalicular bile flow and inhibition of bile salt export pump (BSEP) (132). However, testing for HCV and other causes of viral infection were not routinely done in these early studies and many of the patients appeared to improve with cyclosporine dose reduction. Sirolimus has been reported to cause liver injury in HCV patients but clinically apparent DILI attributed to everolimus has not been reported (133–135).

Antibiotics—Antibiotics are commonly used to prevent and treat bacterial and fungal infections post-transplant. Amoxicillin- clavulanate is a leading cause of DILI in the general population and has also been associated with DILI in a pediatric LT recipient (100, 136). TMP-SMZ can cause a cholestatic liver injury within a few days to weeks of drug initiation with prominent hypersensitivity features of skin rash, fever and eosinophilia (137). A minority of patients treated with TMP-SMZ may also develop life-threatening DRESS syndrome (Drug rash and eosinophilia and systemic symptoms) while others have mild biochemical liver injury and hepatic granulomas on biopsy (138). The presenting liver injury pattern is typically cholestatic or mixed and may be associated with prolonged jaundice. As with other sulfonamides, TMP-SMZ has also been linked to cases of severe acute hepatocellular injury that may be severe and even fatal.

The azole antifungals are frequently used to treat and prevent systemic and superficial fungal infections in LT recipients. In addition to being potent inhibitors of CYP3A4, fluconazole can cause mild to moderate serum aminotransferase elevations in up to 5% of

treated patients. Fluconazole, as well as the other azole antifungals (itraconazole, voriconazole, ketoconazole), can also rarely lead to severe acute hepatocellular injury with jaundice (139, 140).

Isoniazid is a leading cause of severe acute DILI that may result in emergency LT (92). In these instances, anti-tuberculosis (TB) prophylaxis with an alternative regimen containing a quinolone, rifampin, or amikacin may be required in the early post-LT setting to prevent TB reactivation (141). The optimal time and duration of isoniazid therapy for LT recipients with latent TB remains unclear, but should generally be deferred until at least 6 months post-LT to reduce the risk of inadvertent hepatotoxicity (142, 143).

Antiviral agents—Ganciclovir and valganciclovir are frequently used to treat and prevent cytomegalovirus infection in the LT setting. Neither agent has been associated with clinically apparent liver injury, but intravenous administration of ganciclovir is associated with mild to moderate increases in serum ALT levels in ~ 2% of treated patients that are typically self-limited (144).

Other agents—Individuals who consume weight loss products that contain green tea extract with variable amounts of catechins may develop severe acute hepatocellular injury with jaundice including LT recipients (145, 146). Other drugs associated with DILI in LT recipients include sorafenib to treat recurrent liver cancer and intravenously administered amiodarone for peri-operative atrial fibrillation (147–149).

Summary and conclusions

The introduction of potent and highly effective DAA's has ushered in a new era in the management of both LT candidates and recipients with HCV infection. Knowledge of the metabolic pathways involved in the elimination of these agents will be critical for their optimal and safe use in the LT population. Clinically significant DDI's have consistently been reported in LT recipients treated with TPV and BOC, which mandate empiric CNI dose reductions and intensive monitoring of immunosuppressant blood levels during and after their discontinuation. It is anticipated that several of the HCV polymerase inhibitors, NS5A replication complex inhibitors, and 2nd generation protease inhibitors will be associated with fewer DDI's and adverse effects but prospective studies of these agents in LT recipients are needed. Finally, LT recipients appear to be at increased risk of developing DILI from various antibiotics, immunosuppressants, and hypolipidemics. An improved awareness of the potential for DILI in the LT setting will hopefully lead to earlier discontinuation of the suspect drug and help minimize allograft injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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
PEG-IFN	peg-interferon
P-gp	P-glycoprotein
RBV	Ribavirin
SVR	Sustained virological response
TB	Tuberculosis
TMP-SMZ	Trimethoprim-sulfamethoxasole
TPV	Telaprevir

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KEY POINTS

- Boceprevir and telaprevir based antiviral therapy are associated with improved response rates in liver transplant (LT) recipients with HCV infection compared to historical controls but side effects including anemia are also more frequent and potentially severe.
- Clinically significant drug interactions of boceprevir and telaprevir with the calcineurin inhibitors mandate empiric dose reductions and frequent immunosuppressant blood level monitoring during and after treatment to prevent toxicity and subtherapeutic dosing/rejection, respectively.
- The protease inhibitors, simeprevir and faldeprevir, as well as daclatasvir and sofosbuvir based antiviral therapy will likely be associated with improved antiviral response rates in LT recipients as well as fewer side effects; studies to identify the optimal agent(s) and duration of therapy are needed.
- Liver transplant recipients appear to be at increased risk of developing drug-induced liver injury (DILI) from a multitude of agents with antibiotics, immunosuppressants and hypolipidemic agents most frequently implicated.
- Differentiating DILI from other causes of allograft dysfunction is diagnostically challenging but important so that the suspect drug can be promptly discontinued.

Table 1

Selected drugs that should be used with caution in subjects receiving boceprevir or telaprevir based antiviral treatment

Drug Class	Effect on concomitant drug bioavailability (Clinical impact)	Alternative agent(s) and management
Macrolide antibiotics		
Clarithromycin Erythromycin Telithromycin	Increased (QT prolongation; Torsade de Pointes)	Amoxicillin Cefazolin Clindamycin Trimethoprim/sulfamethoxazole Ciprofloxacin Levofloxacin Metronidazole
Antidepressants		
Escitalopram*	Decreased (Decreased efficacy)	Citalopram Sertraline Venalfaxine Duloxetine
Trazodone Despiramine**	Increased (Dizziness, hypotension, nausea)	As above Use lower dose of trazodone
Anti-fungals		
Itraconazole Ketoconazole Posaconazole Voriconazole ***	Increased (QT prolongation, diarrhea, vomiting)	Ketoconazole dose not to exceed 200 mg/day Fluconazole Micafungin Caspofungin
Calcium channel blockers		
Amlodipine Diltiazem Nicardipine Nifedipine Verapamil	Increased (Hypotension, bradycardia)	Consider amlodipine dose reduction Metoprolol, atenolol Hydrochlorothiazide Lisinopril, benazepril Losartan, valsartan Clonidine
Immunosuppressants		
Cyclosporine Everolimus Sirolimus Tacrolimus	Increased (Nephrotoxicity, hypertension, neurotoxicity)	Significant dose reductions and close monitoring of drug levels
Prednisone Methylprednisolone	Increased (hyperglycemia, osteoporosis, insomnia)	Risk verses benefit Use lowest effective dose.
Anti-arrhtymic		
Amiodarone Propafenone Lidocaine Quinidine	Increased (Proarrhtymic)	
Digoxin	Increased (Digoxin toxicity)	Use lowest dose and monitor digoxin levels.

* Only reported with TPV

** Only reported with BOC

*** Not recommended to be used with TPV. TPV co-administration may increase or decrease voriconazole.

Adapted from boceprevir and telaprevir package insert (26, 27)

Please consult package inserts for complete list of known drug interactions and recommended management.

Table 2

Ongoing studies of Boceprevir and Telaprevir with PEG-IFN and RBV in LT recipients with HCV genotype 1

Study (ref)	Antiviral regimen	Immunosuppressant	% HCV-RNA undetectable	Immunosuppressant dose adjustments	% Adverse events
Coily (Ref #47) N=37	**BOC** 4 week PEG-IFN + RBV then BOC + PEG-IFN/RBV N=18 Mean Rx = 41 weeks **TPV** 4 week PEG-IFN + RBV; TPV + PEG-IFN + RBV × 12 week then PEG-IFN + RBV N=19 Mean Rx = 41 weeks	**BOC** CSA =12 TAC =6 **TPV** CSA =10 TAC =9	**BOC** 56% Week 8 89% Week 16 72% Week 48 11% early viral breakthrough **TPV** 47% Week 8 58% Week 16 21% Week 48 21% early viral breakthrough	**BOC** CSA 36% of original dose TAC 22% of original dose **TPV** CSA 54% of original dose TAC 5% of original dose All patients hospitalized for CNI dose adjustments	**BOC** 100 % Anemia 61% Neutropenia 50% Thrombocytopenia 5% Rash 5% Nephrotoxicity 26% Infections 33% Hospitalization 11% Death**TPV** 84% Anemia 21% Neutropenia 15% Thrombocytopenia 5% Rash 21% Nephrotoxicity 27% Infections 31% Hospitalization 5% Death
Pungpapong, (Ref #46) (n=60)	**BOC** 4 week PEG-IFN + RBV then BOC + PEG-IFN/RBV (n=25) Mean Rx=39 wk **TPV** TPV + PEG-IFN/RBV × 12 wk then PEGIFN/RIB (n=35) Mean Rx = 32 wk	**BOC** CSA = 23 TAC= 2 **TPV** CSA = 33 SRL =1 TAC =1	**BOC** 24% Week 8 40% Week 12 12% early viral breakthrough **TPV** 17% Week 4 80% Week 12 8% early viral breakthrough	**BOC** CSA 33–100% (mean 56%) of original dosed every 12 hours TAC 86% reduction of original dose dosed twice weekly to every 48 hours **TPV** CSA 50–100% (mean 70%) of original dose every 12 hours SRL = 0.5 mg every 4 days TAC = 0.5 mg every 7 days	**BOC** 100% Anemia 76% Leukopenia 36% increase SCr > 0.5 mg/dL 32% Rash 4 % Infections 4% Acute rejection 4% Death **TPV** 88% Anemia 77% Leukopenia 11% SCr increase > 0.5 mg/dL 31% Rash 6% Infections 6% Acute rejection 3% Death
Werner (Ref #49) (n=9)	**TPV** TPV + PEG-IFN/RBV × 12 weeks then PEG-IFN/RBV Mean Rx= 12 wks	**TPV** CSA = 4 TAC = 4 SRL = 1	**TPV** 44% Week 4 88% Week 12	**TPV- Fold dose reduction** TAC = 22 (96%) SRL = 7 (86%) CSA = 2.5 (60%) Immunosuppressant interval TAC – single dose per week SIRL – single dose per week CSA – single dose daily	**TPV** 66% Anemia 66% Leukopenia 44% Thrombocytopenia 33% Rash 44% Hospitalized infection 11% Renal failure
Brown (Ref #48) (n=26)	**TPV** TPV+PEG-IFN/RBV × 12 wks then PEG-IFN/RBV Mean Rx = 12 wks	**TPV** TAC = 23 CSA =3	**TPV** 47% Week 4 82% Week 12	**TPV** CSA reduced 4-fold TAC reduced 10-fold Med time to 1st TAC dose =71 hrs	**TPV** 39% Anemia 35% Rash (mild) 17% Anorectal symptoms

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Study (ref)	Antiviral regimen	Immunosuppressant	% HCV-RNA undetectable	Immunosuppressant dose adjustments	% Adverse events
				Median TAC dose =0.5 mg every 7 days Med time to 1st CSA dose 22 hrs Med CSA dose =25 every 24 hrs	13% Pruritus 13% Renal insufficiency 4% Supratherapeutic CNI level (discontinued TPV)
O'Leary (Ref #44) (n= 120**)	**TPV/BOC** TPV (n=107) or BOC (n=13) + PEG/IFN ± PEG-IFN/RBV lead-in (n=116) Median Rx = 148 days	**TPV/BOC** TAC =35 CSA = 73	**TPV/BOC** 63% Week 4 78% Week 12 72% Viral breakthrough	**TPV/BOC** Median daily dose prior and after initiation of TPV or BOC CSA = 200 mg/50 mg TAC = 1.0 mg/0.19 mg	**TPV/BOC** 79% Anemia 45% Blood transfusion 43% GCSF 20% Hospitalization 33% Scr increased > 0.5 mg/dL 6% Acute rejection 2% Death

Abbreviations: BOC, boceprevir; CSA, cyclosporine; EVRL, everolimus; IS, immunosuppression; MMF, mycophenolate mofetil; PEG-IFN, peginterferon; RBV, ribavirin; Rx, treatment duration; Scr, serum creatinine; SIRL, sirolimus; TAC, tacrolimus; TPV, telaprevir

*One patient received prolonged-release (once daily) tacrolimus

**6 liver-kidney transplant recipients

Table 3

Pharmacokinetic and metabolic parameters of selected direct acting antiviral agents for hepatitis C

Drug and dose	Metabolism / excretion route	CYP inducer or inhibitor	Transporter substrate or inhibitor	Comments
NS3 Protease inhibitors				
ABT-450/ Ritonavir (150 mg q day/100 mg q day)	Hepatic (CYP3A)	Strong CYP3A inhibition by ritonavir	Inhibitor of OATP1B1	Unconjugated hyperbilirubinemia
Boceprevir 800 mg tid	Hepatic (CYP3A, aldoketoreductase)	Moderate CYP3A inhibitor	Weak P-gp inhibitor	Significant DDI's with other CYP3A substrate drugs
Faldaprevir 120 mg q day (BI 20335)	Hepatic (CYP3A)	Moderate CYP3A inhibitor; weak CYP2C9 inhibitor	Inhibits OATP1B1, OATP1B2, OATP2B1; Substrate of P-gp and MRP2	Inhibition of UGTA1 results in unconjugated hyperbilirubinemia
Simeprevir 150 mg q day (TMC-435)	Hepatic (CYP3A)	Mild CYP1A2 inhibitor; mild intestinal/ hepatic CYP3A inhibitor	Inhibitor of OATP1B1 and MRP2	Unconjugated hyperbilirubinemia commonly seen
Telaprevir 750 mg tid	Hepatic (CYP3A)	Strong CYP3A inhibitor	Moderate P-gp inhibitor	Significant DDI's with other CYP3A and P-gp substrate drugs
NS5A replication complex inhibitors				
ABT-267 25 mg q day	No data	No data	No data	AUC and C_{Max} increased 62% and 67% by ritonavir, respectively
Daclatasvir 60 mg q day (BMS-790052)	Hepatic (CYP3A)	Not a inducer or inhibitor of CYP3A4	Moderate inhibitor of P-gp and OATP1B1	
Ledipasvir 90 mg q day (GS-5885)	Feces (major); hepatic and renal (minor)	Not a CYP inhibitor or inducer	Weak inhibitor of P-gp, OATP1B1	
Nucleos(t)ide polymerase inhibitors				
Sofosbuvir 400 mg q day (GS-7977)	Renal	No clinical evidence of CYP inhibition or induction	Substrate of P-gp	Dose reduction if moderate to severe renal impairment
Non-nucleoside polymerase inhibitors				
ABT-333 400 mg BID	Hepatic CYP2C8 (60%); CYP3A4 (30%); CYP2D6 (10%)	Not a CYP3A inducer		
Deleobuvir 600 mg BID (BI-207127)	No data	No data	Substrate of P-gp, BCRP, OATP1BI, OATP1B3	

Abbreviations: BCRP, breast cancer resistance protein; BID, two times a day; CYP, cytochrome P450; MRP, multiple drug resistance protein; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; q, every day; UGT, uridine glucuronly transferase

Adapted from Kiser JJ, et al. Ref #32

Table 4

Presentation and outcomes with DILI in the general population and LT recipients

Feature	DILIN US N=300 (ref #100)	Spain N=446 (ref #101)	Mayo-Liver transplant N= 29 (ref #118)
Study Design	Prospective Multicenter (8 sites) '04 to '08	Prospective Multicenter (32 sites) '94-'05	Retrospective LT center (1 site) '85-'10'
Causality method	DILIN Expert opinion	RUCAM	DILIN Expert opinion
F/U duration (mon)	6 to 24	3	NA
Mean age (yrs)	48	53	52
% Female	60%	49%	52%
Race			
% Caucasian % African American % Asian % Other	79% 11% 4% 6%	100%	NA
Liver injury type			
% Hepatocellular % Mixed/ Cholestatic	57% 20%/23%	58% 22%/20%	7% 4%/89%
% Jaundice	69%	71%	24%
% Liver biopsy	50%	25%	96%
% Hospitalized	60%	53%	8%
% Died or transplanted	10%	7%	0%
Median duration medication use (d)	42	105	57
Suspect drugs			
% Antibiotics % Psychotropic % HDS products % Hypolipidemic % Immunosuppressants	45% 15% 9% 3% 1%	32% 17% 0% 3% 0%	58% 4% 4% 7% 14%

NA= Not available