CASE REPORT

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A case example of direct oral anticoagulant use in a patient following right lobe living-donor liver transplantation

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ABSTRACT Thromboembolic complications can significantly impact patient and allograft outcomes following liver transplantation. A variety of surgical, medication, and patient specific risk factors can alter the tenuous balance of pro- and anti-thrombotic risk factors in patients with cirrhotic liver disease leading to the formation of acute thrombi. Historically, warfarin was the only oral anticoagulant available to manage these patients; however, in recent years, direct acting oral anticoagulants have increasing replaced warfarin in clinical practice due to their more predictable pharmacokinetic profile and lack of requirement for regular therapeutic drug monitoring. By comparison, use of these agents in the liver transplant population has been infrequent due to a paucity of data as well as concern for drug–drug interactions, lack of reversibility, and ongoing bleeding concerns. As a result, we describe a case of successful direct oral anticoagulant use in a patient receiving a right lobe living-donor allograft and also examine the various transplant and pharmacokinetic considerations that may influence anticoagulant treatment selection in this population.

KEYWORDS

liver transplantation, anticoagulants, pharmacokinetics

ABBREVIATIONS: CT, computed tomography; CYP450, cytochrome P450; DOACs, direct oral anticoagulants; INR, international normalized ratio; IR, interventional radiology; JP, Jackson-Pratt; mTOR, mammalian target of rapamycin; NASH, non-alcoholic steatohepatitis; Pgp, P-glycoprotein; PE, pulmonary embolism; VTE, venous thromboembolism

INTRODUCTION

Thromboembolic complications can significantly impact patient and allograft outcomes following liver transplantation. While much of the focus post-operatively is on managing acute blood loss and monitoring for ongoing signs of bleeding, liver transplant recipients demonstrate a tenuous balance of pro- and anti-thrombotic factors that can also precipitate the formation of acute thrombi in 2–10% of patients.[1] A variety of surgical thrombotic risk factors including release of tissue factor, ischemia reperfusion injury, venous stasis due to immobility and surgical clamping, and platelet hyper-reactivity can potentiate thrombus formation. Additionally, the excessive administration of hemostatic agents intraoperatively such as fresh frozen plasma or cryoprecipitate can tilt the hemostatic balance toward thrombosis, and corticosteroid administration post-transplant to prevent acute allograft rejection can impair fibrinolysis.[1] Patient specific risk factors can also contribute to overall thrombotic risk peri-transplant as a number of etiologies of chronic liver disease are associated with an increased risk for systemic thrombosis including Budd–Chiari syndrome, hepatocellular carcinoma, primary sclerosing cholangitis, primary biliary cirrhosis, and metabolic syndrome associated non-alcoholic steatohepatitis.[1]

In the setting of an acute thrombus or multiple prothrombotic risk factors, systemic anticoagulation remains the treatment of

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choice to prevent thrombus progression and to limit sequelae associated with chronic thrombosis.[2] Historically, warfarin, a vitamin K antagonist, was the only available oral anticoagulant; however, in recent years, direct oral anticoagulants (DOACs) have increasingly replaced warfarin due to their more predictable pharmacokinetic profiles (summarized in Table 1) and lack of requirement for regular therapeutic drug monitoring. Two classes of DOACs are currently available, direct thrombin inhibitors (dabigatran) and anti-factor Xa inhibitors (rivaroxaban and apixaban). While these agents are an attractive therapeutic option for patients and providers owing to their relative ease of administration, concerns still remain regarding the use of these products in the liver transplant population. Each of these agents is at least partially metabolized via the P-glycoprotein (Pgp) or cytochrome P450 (cyp450) enzyme system which can be altered by calcineurin inhibitor-based immunosuppression resulting in increased drug exposure.[3] Additionally, pharmacokinetic studies have demonstrated altered cyp450 enzymatic activity following liver transplantation when compared with healthy controls, suggesting that enzyme expression, even in a functioning allograft, does not return entirely to baseline.[4] Variable renal and hepatic function post-transplant can also serve as a source of inter- and intrapatient variability and complicate the management of DOACs.[3] Finally, lack of routine access to timely therapeutic drug monitoring and rapid reversal therapies presents potential safety concerns when utilizing these agents in patients who recently underwent major operative procedures. These factors, in combination with the relative paucity of data describing the use of DOACs following liver transplantation, have so far limited DOAC uptake in the liver transplant population.[5–8] This trend may change as more data become available and providers become more comfortable managing patients on chronic DOAC therapy. Here, we describe the case of a patient receiving a right lobe living-donor liver allograft that was subsequently successfully managed with DOAC therapy, and examine the various pharmacokinetic considerations that may influence anticoagulant treatment selection in liver transplant recipients.

CASE SUMMARY

A.P. is a 50 year-old male who underwent living-donor right lobe liver transplantation on September 5, 2017 secondary non-alcoholic steatohepatitis (NASH). Prior to transplant, the patient was diagnosed with a portal vein thrombus on computed tomography (CT) for which he received 3 months of systemic anticoagulation with warfarin, resulting in partial resolution of the thrombus. The patient had no prior history of venous thromboembolism (VTE), and no additional hypercoagulable mutations were identified during pre-transplant work-up. The operative procedure was uncomplicated but notable for complex portal reconstruction with interposition of a donor iliac vein graft to the recipient's native main portal vein. The donor right hepatic artery was anastomosed to the native right hepatic artery, and a roux-en-y hepaticojejunostomy was performed to the donor right anterior hepatic biliary duct over a stent. The recipient received 5 units of packed red blood cells and 7 units of fresh frozen plasma in the operating room but did require any vasopressor support. The post-operative course was additionally uncomplicated, and the patient was eventually discharged from the hospital on September 18 with a total bilirubin of 2.1 mg/dL, serum creatinine of 1.0 mg/dL, and international normalized ratio (INR) of 1.1. No polyclonal or monoclonal antibody induction therapy was employed, and the patient received a standard maintenance immunosuppression regimen consisting of tacrolimus, mycophenolate mofetil, and tapering corticosteroids.

The patient was re-admitted to the hospital on October 4 with fevers, and bilious output noted from an intraperitoneal Jackson-Pratt (JP) drain. At this time, the patient's total bilirubin and INR had increased to 3.8 mg/dL and 2.0, respectively. CT imaging demonstrated an acute portal vein thrombus and subsegmental pulmonary embolism (PE), in addition to a large peri-hepatic biloma. The patient was subsequently started on a heparin drip and broad-spectrum antibiotics. The biloma was managed by interventional radiology (IR) drainage on October 5 and a further 7 days of piperacillin/tazobactam. On October 8, the patient's heparin drip was switched to enoxaparin 1 mg/kg twice daily with the plan to switch to oral dabigatran 150 mg twice-daily once insurance approval was obtained. The patient was eventually discharged on October 16 still receiving therapeutic enoxaparin with a total bilirubin of 1.6 mg/dL, serum creatinine of 1.1 mg/dL, and INR of 1.4.

A.P was next re-admitted on October 20 for diarrhea and worsening abdominal pain. He was found to be positive for clostridium difficile by PCR for which he received 10 days of oral vancomycin, and repeat CT imaging found a new right upper quadrant collection that was not communicating with the current JP drain. A.P. underwent repeat IR drainage of the collection on October 24 and endoscopic retrograde cholangiopancreatography with stent placement in the common bile duct on October 28. During this hospitalization, the patient was maintained on therapeutic enoxaparin until November 2 at which time he was switched to dabigatran with the plan to complete a minimum of 3 months of systemic anticoagulation. Labs at discharge were notable for a total bilirubin of 1.1 mg/dL, a serum creatinine of 1.2 mg/dL, an INR of 1.5, and a hemoglobin of 8.8 mg/dL.

A.P. had one subsequent hospital admission from November 5 to November 16 for worsening abdominal pain, during which time he had his IR drain upsized due to leaking around the drain exit site. Throughout the entire course of this hospitalization, he was maintained on therapeutic dabigatran 150 mg twice daily without acute signs or symptoms of bleeding and did not require any blood product transfusions. The remainder of the patient's post-transplant course has been uneventful, and at last outpatient follow-up on February 26 he was still receiving dabigatran 150 mg twice daily without any clinically significant bleeding or progression of thrombosis.

Table 1 Pharmacokinetics of direct oral anticoagulants

Characteristics	Dabigatran	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Bioavailability (%)	6	80–100	50
Volume of distribution (L)	50–70	50	21–61
T_{max} (hours)	0.5–2	2–4	3–4
Protein binding (%)	35	95	87
Half-life (hours)	14–17	5–13	6–15
Metabolism	Hydroxylase	CYP3A4 and 2J2, hydrolysis	CYP3A4, 1A2, 2C9, 2C8
Renal excretion (%)	85	33	27

DISCUSSION

Direct oral anticoagulants have increasingly replaced warfarin in the therapeutic landscape for managing thromboembolic diseases and risk factors. Since their inception in 2010, DOAC use has steadily grown among clinicians, and by 2014 DOACs accounted for approximately half of all anticoagulant prescriptions.[9] DOAC uptake has not been as swift in the field of organ transplantation owing to the relative paucity of data in this population, high potential for drug–drug interactions, and variable end-organ function. Liver transplant recipients represent a particularly complicated population owing to their unique hemostatic physiology and variable metabolic function. Patients with clinically significant liver disease were universally excluded from the large, randomized-controlled trials that lead to FDA approval of the DOACs, and to date, experience with DOAC use in liver transplant recipients has been limited to one small case series and several single case reports.[3,5,7,8] Here, we present the first case report of DOAC use in a recipient of a living-donor liver allograft, who tolerated therapy without any significant bleeding or thrombotic complications. This case highlights the potential for DOAC use in liver transplant recipients as well as a variety of factors that bear consideration when selecting among the available systemic oral anticoagulants in this population.

Variable hepatic function post-liver transplantation is a significant concern for anticoagulant use as this may alter drug pharmacokinetics and metabolism and in turn overall exposure to the various anticoagulants. Hypoalbuminemia can increase the free-fraction of highly protein bound medications like warfarin, rivaroxaban, and apixaban thus potentiating the anticoagulant effects, while portal hypertension can decrease first-pass metabolism of high hepatic extraction drugs increasing bioavailability.[4] These pharmacokinetic parameters are primarily a concern in the setting of significant allograft dysfunction and should be considered when selecting between a hepatically or non-hepatically metabolized anticoagulant. There are a variety of early and late risk factors for the development of hepatic allograft dysfunction that can be used to help prognosticate the risk of future hepatic injury including donor characteristics (macrosteatosis >30%, prolonged cold ischemia time >10 hours, increased donor age >50, deceased cardiac donor status), recipient characteristics (prior transplantation, increased MELD score at time of transplant, body mass index >25 kg/m^2, history of medication non-compliance, and prior immune sensitization), likelihood of underlying liver disease recurrence, and transplant technique.[10,11] When compared to the standard technique of orthotopic whole-liver transplantation, living-donor transplant with a split allograft poses unique concerns due to higher rates of biliary and vascular complications.[12] This may be influenced by the small-for-size syndrome and reduced when the allograft-recipient weight ratio is >0.8–1%. In patients demonstrating a number of these risk factors for early or late allograft dysfunction, caution should be employed when selecting a hepatically metabolized anticoagulant due to potential intrapatient variability in drug exposure. Rivaroxaban and apixaban rely primarily on oxidative metabolism and biliary excretion, and subsequently exposure may be markedly increased in the setting of significant allograft dysfunction. Both agents are contraindicated in the setting of Child–Pugh class B or C liver disease and should be used with caution in well-compensated cirrhosis.[2] Warfarin also undergoes significant hepatic metabolism but offers the advantage of routinely available and well-validated therapeutic drug monitoring to assess fluctuations in drug exposure. However, in patients with advanced cirrhosis and an elevated INR at baseline, drug monitoring may not be reliable, and there is little evidence currently available to help guide dose titration in this setting.[13] Alternatively, low molecular weight heparins and dabigatran do not require oxidative metabolism via the CYP450 enzyme system, have low protein binding, and are primarily renally excreted, making these agents viable options for patients with irregular or underlying hepatic dysfunction.

Renal function may also be subject to wide variability following liver transplantation, and more than half of patients will experience some degree of renal dysfunction post-transplant.[14] Many patients have some element of renal injury going into transplant due to portal hypertension and resulting renal arterial vasoconstriction, which can manifest or be exacerbated post-transplantation.[15] Additionally, significant hemodynamic shifts can occur during the operative and early post-operative course due to bleeding/transfusions or sepsis that can precipitate pre-renal acute kidney injury. Calcineurin inhibitors prescribed to prevent allograft rejection can also contribute to renal injury by causing afferent renal arteriole vasoconstriction and subsequent renal hypoperfusion.[15] Calcineurin inhibitor nephrotoxicity can be at least partially ameliorated by early conversion to mammalian target of rapamycin (mTOR) inhibitors with subsequent calcineurin inhibitor reduction or withdrawal.[16] Other risk factors that deserve consideration when assessing a patient's risk for development of acute or chronic renal injury include mostly recipient characteristics: increased age, elevated BMI > 25 kg/m^2, history or development of diabetes, elevated MELD at time of transplant, systemic infection prior to transplant, requirement for surgical revision post-transplant, and vasopressor requirement post-transplant.[14,15] For patients with marked kidney disease or significant chronic kidney disease risk factors, warfarin remains the anticoagulant of choice for the management of VTE. Apixaban may be an option as it relies minimally on renal excretion (< 30%) and is the only DOAC approved for use in hemodialysis or a creatinine clearance < 30 mL/min; however, this is based on a single pharmacokinetic study in less than 10 hemodialysis patients and should be extrapolated to liver transplant recipients with caution.[17] Rivaroxaban, dabigatran, and low molecular weight heparins are all contraindicated in patients with a creatinine clearance < 30 mL/min and should be avoided in these patients.[2]

Drug–drug interactions are another frequent concern in solid organ transplant recipients prescribed anticoagulation due to the requirement for calcineurin inhibitor or mTOR inhibitor-based immunosuppressive therapy. Both of these classes of medications have a narrow therapeutic window and undergo significant hepatic metabolism via the CYP450 3A4/5 enzyme family as well as excretion through Pgp making them highly susceptible to clinically significant drug–drug interactions. Common enzyme and Pgp inhibitors including macrolide antibiotics, azole antifungals, non-dihydropyridine calcium channel blockers, and protease inhibitors can reduce the metabolism and excretion of medications that rely upon these pathways thus increasing overall drug exposure. Alternatively, enzyme and Pgp inducers such as first-generation anti-epileptics and rifamycins can increase drug metabolism and excretion decreasing target medication exposure. These drug interactions require careful consideration and monitoring as potency and timing of the interaction can differ significantly across and within medication classes. To further complicate matters, calcineurin inhibitors are both substrates and inhibitors of CYP450 3A4/5 and Pgp, and as such could reduce excretion of DOACs metabolized through these pathways. Pharmacokinetic studies have found cyclosporine to be a much more potent inhibitor of CYP450 and Pgp than tacrolimus or sirolimus, and in one study of rivaroxaban use post-liver transplantation, this translated to significantly more clinical bleeding in patients receiving cyclosporine and rivaroxaban when compared with

tacrolimus (60 vs 25%).[5,17] Based on these data, DOACs may be a consideration with concomitant tacrolimus but should be used with extreme caution in patients receiving cyclosporine until more data become available.

Post-operative bleeding and surgical re-exploration are always potential concerns following liver transplantation and can complicate anticoagulant selection and management. Retrospective data suggest re-operative rates approach 10–20% following liver transplantation, and as a result, anticoagulant reversibility should be considered for patients at high risk of needing another invasive procedure.[18] Common risk factors for surgical re-operation include the following: increased MELD at time of transplant, history of prior renal dysfunction in the recipient, and high-risk donor characteristics (living-donor or deceased cardiac donor).[18,19] In patients with these risk factors, warfarin or dabigatran may be more appropriate anticoagulant choices owing to the reversibility of these agents. Dabigatran may be of particular interest as it is the only available DOAC with a reversal agent that has been studied in the setting of emergent surgery. In the RE-VERSE-AD trial, idarucizumab, a monoclonal antibody targeting dabigatran, was administered to 36 patients who subsequently underwent emergent operative procedures. The ecarin clotting time was normalized in 88% of these patients, and normal intraoperative hemostasis was reported in 92% of cases.[20] However, there are still no data currently available to suggest that reversal of these surrogate markers correlates with improved patient-oriented outcomes. Furthermore, due to the relatively short half-lives of the available DOACs, these agents are generally excreted completely from the body within 1–2 days once therapy is discontinued. As a result, by the time surgical intervention is necessary reversal of anticoagulant effect may no longer be necessary in many cases.[2]

Finally, patient comfort and institutional experience should always be considered when prescribing any new medication. Transplant recipients must adhere to a complex medication regimen that requires diligent compliance and routine therapeutic drug monitoring. Shared-decision-making with patients to address desired route of therapy and frequency of administration can help to improve patient adherence and foster a good working relationship between patient and provider. Rivaroxaban and warfarin are currently the only available once-daily oral anticoagulant options, and in one study this dosing schedule was found to result in a 39% greater likelihood of compliance when compared to twice-daily dosing.[21,22] Low molecular weight heparins require daily self-injection and should only be considered in patients who are willing to comply with this regimen and who have the manual dexterity to perform the injections. Liver transplant patients are also managed by a large multidisciplinary team consisting of transplant surgeons, hepatologists, various consultants, nutritionists, and clinical pharmacists. Ensuring that other clinicians providing care to the patient are aware of the anticoagulant therapy and have some institutional experience or knowledge of the medication characteristics can help to limit errors related to prescribing or administration of therapy.

CONCLUSIONS

Liver transplant recipients are a very complex patient population with respect to anticoagulant selection and administration. Currently, experience with DOACs in these patients is limited to small case series and single case reports. A variety of factors bear consideration when selecting between the various DOACs and more traditional anticoagulant options including hepatic allograft function, risk for renal injury, drug–drug interactions, risk for re-operation, and patient and physician preferences. In order to optimize anticoagulant treatment selection, decision-making should be based on multidisciplinary assessment of the risks and benefits of the various anticoagulants in the setting of specific patient and transplant characteristics.

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