EVIDENCE-BASED MINIREVIEW

Direct oral anticoagulants to treat deep venous thrombosis and pulmonary embolism in patients with cirrhosis: are we there yet?

Amber Afzal[1] and Jordan Schaefer[2]

[1]Division of Hematology, Department of Medicine, Washington University, St Louis, MO
[2]Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

A 59-year-old female with Child-Pugh class B cirrhosis attributed to nonalcoholic steatohepatitis complicated by hepatic encephalopathy, portal hypertension with esophageal varices, and thrombocytopenia is seen for management of an acute segmental right lower lobe pulmonary embolism in a clinic. She is hemodynamically stable. Complete blood count is notable for hemoglobin 11.6 g/dL and platelets 80 K/μL. Prothrombin time is 12.6 seconds; partial thromboplastin time, 33.7 seconds; and fibrinogen, 221 mg/dL. She was referred to discuss if a direct oral anticoagulant (DOAC) can be used for anticoagulation. What would you suggest?

LEARNING OBJECTIVES

- Review the limited data on the use of the DOACs to treat deep vein thrombosis and/or pulmonary embolism for patients with cirrhosis
- Understand considerations for optimizing bleeding risk for patients with cirrhosis receiving anticoagulation

CLINICAL CASE

A 59-year-old female with Child-Pugh class B cirrhosis attributed to nonalcoholic steatohepatitis complicated by hepatic encephalopathy, portal hypertension with esophageal varices, and thrombocytopenia is seen for management of an acute segmental right lower lobe pulmonary embolism in a clinic. She was referred to discuss if a direct oral anticoagulant (DOAC) can be used for anticoagulation. What would you suggest?

Introduction

Patients with cirrhosis are at a higher risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) than is the general population.[1] Therefore, initiation of anticoagulation and choice of anticoagulant are frequently encountered clinical questions, but limited data are available to guide these clinical decisions in patients with cirrhosis. Most of the oral anticoagulants depend on liver metabolism for excretion; hence, liver disease raises concerns for drug accumulation and toxicity. Traditionally, vitamin K antagonists (VKA) and low molecular weight heparins have been used for outpatient management of DVT and PE in patients with cirrhosis. VKA, although dependent on liver metabolism for excretion, can be dose-adjusted reliably based on international normalized ratio (INR) measurements for patients with an acceptable baseline INR. The direct oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban undergo some degree of hepatic metabolism and variable degrees of renal clearance (Table 1). The prospective clinical trials that led to the Food and Drug Administration (FDA) approval of the DOACs for treatment of DVT and PE in the United States largely excluded patients with cirrhosis and/or those with modest elevations in liver enzymes or bilirubin (Table 1). Therefore, we have limited data on the pharmacokinetics, pharmacodynamics, safety, and efficacy of DOACs in patients with cirrhosis. Patients with compromised liver function have 3%-10% risk of bleeding per year, which increases as liver disease progresses. Oral anticoagulants can further multiply this risk of bleeding.[2] The anticoagulant effect of DOACs may get enhanced in patients with advanced cirrhosis.[3-5] The risk of spontaneous bleeding

Table 1. Exclusion criteria for liver disease of select randomized clinical trials of the direct oral anticoagulants for VTE

Trial	Population	Exclusion criteria
AMPLIFY (2013)	Acute VTE	ALT or AST >2 x ULN, bilirubin >1.5 x ULN (unless an alternative factor is identified [eg, Gilbert's syndrome]), active and clinically significant liver disease (eg, hepatorenal syndrome)
AMPLIFY-EXT (2013)	Extended VTE	ALT or AST >2×ULN, bilirubin >1.5×ULN (unless an alternative factor is identified [eg, Gilbert's syndrome]), active and clinically significant liver disease (eg, hepatorenal syndrome)
EINSTEIN CHOICE (2017)	Extended VTE	Hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk
EINSTEIN DVT (2010)	Acute DVT	Significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3×ULN
EINSTEIN-EXT (2010)	Extended VTE	Significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3×ULN
EINSTEIN PE (2012)	Acute PE	Significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3×ULN
Hokusai VTE (2013)	Acute VTE	Significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis) or ALT ≥2×ULN, or total bilirubin 1.5×ULN
RE-COVER (2009)	Acute VTE	Liver disease with aminotransferase level that was >2×ULN, known liver disease expected to have an impact on survival
RE-COVER II (2014)	Acute VTE	Liver disease with aminotransferase level that was >3×the ULN, known liver disease expected to have an impact on survival
RE-MEDY (2013)	Extended VTE	AST or ALT >2×ULN, liver disease expected to have any potential impact on survival (eg, acute hepatitis or possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery)
RE-SONATE (2013)	Extended VTE	Active liver disease or liver disease decreasing survival (eg, acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3×ULN
Drug	**CYP metabolism**	**Degree of renal clearance[a]**
Apixaban	Mostly CYP3A4	~27%
Dabigatran	No	~80%
Edoxaban	Minimal	~50%
Rivaroxaban	CYP 3A4/5, CYP2J2	~66%

[a]The exact hepatic portion of DOAC clearance cannot be directly estimated given variable elimination via biliary excretion and direct intestinal excretion.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP, cytochrome P; DVT, deep vein thrombosis; ULN, upper limit of normal; VTE, venous thromboembolism.

with DOACs can be of paramount significance for patients with Child-Pugh B and Child-Pugh C cirrhosis.[3] We should, therefore, examine the available data carefully to inform clinical practice regarding treatment of DVT and PE in patients with cirrhosis and to identify areas in need of research.

DOACs for DVT and PE in patients with cirrhosis

Recently, meta-analyses of smaller retrospective studies and prospective pilot studies assessed efficacy and safety of DOACs for treatment of atrial fibrillation and/or splanchnic vein thrombosis in patients with cirrhosis.[6-8] Available data, however, are limited for the use of DOACs to treat extremity DVT and PE in this population. A review of available literature suggests that the efficacy of DOACs is comparable to traditional anticoagulants when measured by rates of thrombus resolution and recurrent thrombosis. Most of these studies report the risk of bleeding with DOACs to be similar to or even lower than the risk with traditional anticoagulation; however, these studies are limited by potential selection bias, sample sizes too small to detect significant differences, short follow-up times, and concerns about publication bias (Table 2). The risk of recurrent thrombosis and bleeding correlate with the severity of liver disease, and patients with Child-Pugh C cirrhosis were unlikely to receive DOACs in these observational studies. Moreover, these studies report pooled outcomes for DOACs when used for any indication (ie, DVT, PE, splanchnic vein thrombosis and/or atrial fibrillation; Table 2) despite the potential for these groups to be clinically dissimilar. When used for splanchnic vein thrombosis, DOACs recanalize splanchnic vasculature, hence reducing portal pressures, risk of variceal bleeding, and progressive liver dysfunction.[9] The outcomes for treatment of splanchnic vein thrombosis may not correlate with outcomes for DVT/PE treatment. Given these differences, caution should be exercised extrapolating data on use of DOACs for splanchnic vein thrombosis or atrial fibrillation to make treatment decisions in patients with cirrhosis presenting with DVT and/or PE until better data are available.

Prediction of anticoagulant-related bleeding and optimizing bleeding risk in patients with cirrhosis

Available risk-prediction models for anticoagulant-related bleeding are unlikely to guide safe selection of cirrhotic patients for initiation of DOACs[10] because they were developed in a general noncirrhotic population and most of these models were for traditional anticoagulants. These risk-prediction models incorporate conventional coagulation abnormalities, including thrombocytopenia, that are suboptimal predictors of hemostasis in cirrhosis. Moreover, these risk-prediction models do not account

Table 2. Retrospective cohort studies comparing direct-acting oral anticoagulants to traditional anticoagulation for patients with cirrhosis including those with deep venous thrombosis and pulmonary embolism

Retrospective study	DOACS (n)	Traditional anticoagulation (n)
Intagliata[12]		
N	20	19
DVT/PE n (% of N)	**4** (20)	**12** (63)
Child Pugh-B (n)	11	10
Child Pugh-C (n)	0	0
Bleeding (n)	4	3
Thrombosis (n)	N/A	N/A
Hum[13]		
N	27	18
DVT/PE n (% of N)	**12** (39)	**8** (44)
Child Pugh-B (n)	12	9
Child Pugh-C (n)	4	2
Bleeding (n)	8	10
Thrombosis (n)	1	1
Jones[14]		
N	42	37
DVT/PE n (% of N)	**9** (21)	**8** (22)
Child Pugh-B (n)	8	19
Child Pugh-C (n)	0	2
Bleeding (n)	7	8
Thrombosis (n)	3	3
Davis[14]		
N	27	82
DVT/PE n (% of N)	**19** (70%)	**62** (76%)
Child Pugh-B (n)	16	49
Child Pugh-C (n)	0	15
Bleeding* (n)	2	11
Thrombosis (n)	3	10
Coons[15]		
N	44	41
DVT/PE n (% of N)	**11** (25)	**8** (20)
Child Pugh-B (n)	24	17
Child Pugh-C (n)	8	9
Bleeding (n)	10	14
Thrombosis (n)	1	2
Aquite[15]		
N	48	52
DVT/PE n[1] (% of N)	**10** (21)	**11** (21)
Child Pugh-B (n)	N/A	N/A
Child Pugh-C (n)	N/A	N/A
Bleeding (n[2])	9.1/100-patient years	14.4/100 patient years
Thrombosis (n)	N/A	N/A

Table 2. Retrospective cohort studies comparing direct-acting oral anticoagulants to traditional anticoagulation for patients with cirrhosis including those with deep venous thrombosis and pulmonary embolism (*Continued*)

Retrospective study	DOACS (n)	Traditional anticoagulation (n)
Oldham[16]		
N	67	32
DVT/PE n[1] (% of N)	**45** (65)	**9** (28)
Child Pugh-B (n)	59	30
Child Pugh-C (n)	0	0
Bleeding (n)	25	7
Thrombosis (n)	3	0

DOACs, direct acting oral anticoagulants; DVT, deep venous thrombosis; PE, pulmonary embolism; traditional anticoagulation refers to low-molecular weight heparin or vitamin K antagonists.
*Only major bleeding was reported.
[1]Number includes splanchnic vein thrombosis.
[2]Only reported patient-years of bleeding.
Child-Pugh class, bleeding, and thrombosis have been reported for the entire study population (N).

for severity of liver disease, class of anticoagulant, or site of prior bleeding, which are relevant considerations. Most of bleeding in patients with cirrhosis originates in the gastrointestinal tract, and this is the very site where some DOACs are associated with more bleeding than are traditional anticoagulants.[11]

Efforts should be made to mitigate the bleeding risk in any patient on anticoagulation. In the setting of cirrhosis, this may entail frequent endoscopies to manage varices and other potential bleeding lesions, use of beta-blockers for portal hypertension, considering proton pump inhibitors or H2 receptor antagonists when appropriate, limiting use of drugs with antiplatelet activity, and close monitoring for changes in liver function over time. This requires a multidisciplinary approach and shared decision-making between patients, gastroenterologists, and hematologists. Selection of the safest anticoagulant should be based on renal function, need for invasive procedures, anticipation of liver transplant, and potential drug interactions. For example, calcineurin inhibitors, frequently used after liver transplants, may interact with most DOACs.

Future research

Considering the complex hemostatic changes of cirrhosis, with higher baseline risks of thrombosis and bleeding, well-designed studies are needed to better define the role of DOACs in management of DVT/PE and understand the hemostatic impact of these drugs. Studies should focus on the indications for DOACs (eg, initial treatment versus extended secondary prevention of venous thromboembolism) to help balance risks and benefits. Dose reduction of DOACs, initiation of DOACs after initial management with parenteral anticoagulation, and use of novel anticoagulants deserve further investigation in this population. A validated tool that predicts DOAC-related bleeding in patients with cirrhosis may facilitate safe selection of patients for DOAC use and prioritize modifiable risk factors that could be addressed to maximize net anticoagulant benefit. Such a tool could also promote clinical trial participation for some cirrhotic patients. In addition, evidence-based strategies for optimizing risk factors for gastrointestinal bleeding, monitoring patients on anticoagulation, and managing anticoagulation around the time of liver transplant need to be developed.

Recommendations

- Discuss the risks and benefits of DOACs compared to traditional anticoagulants (low-molecular weight heparin/VKA) and the limitations of available literature with patients with cirrhosis as part of shared decision-making. The Child-Pugh score should be considered as part of a comprehensive assessment of anticoagulant candidacy and selection. (Strong recommendation, low quality evidence)
- Avoid use of DOACs to treat DVT or PE in patients with Child-Pugh C cirrhosis. (Strong recommendation, low quality evidence)
- Consider DOACs to treat DVT or PE in patients with Child-Pugh A cirrhosis without significant liver enzyme or bilirubin elevation. (Strong recommendation, low quality evidence)
- DOAC use is controversial for Child-Pugh B cirrhosis; FDA package inserts do not recommend use of edoxaban and rivaroxaban for this population. Selective and cautious use of the other DOACs may be reasonable in individual cases after estimation of risk versus benefit. (Weak recommendation, low quality evidence).

Conflict-of-interest disclosure

Amber Afzal: no competing financial interests to declare.
Jordan Schaefer: no competing financial interests to declare.

Off-label drug use

The prescribing information for apixaban does not provide dose adjustment recommendations for Child-Pugh class B or moderate hepatic impairment but notes limited experience of clinical use in this population. It suggests avoiding use in Child-Pugh class C. Edoxaban advises against use in moderate to severe hepatic impairment (Child-Pugh B and C). Rivaroxaban suggests avoiding use in Child-Pugh B and C and in hepatic disease associated with coagulopathy.

Correspondence

Amber Afzal, Division of Hematology, Department of Medicine, Washington University in St Louis, 660 S. Euclid Avenue, St Louis, MO 63110; e-mail: afzalamber@wustl.edu.

References

1. Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. *Clin Gastroenterol Hepatol.* 2010;8(9):800-805.e1805e1.
2. Serper M, Weinberg EM, Cohen JB, Reese PP, Taddei TH, Kaplan DE. Mortality and hepatic decompensation in patients with cirrhosis and atrial fibrillation treated with anticoagulation. *Hepatology.* 2021;73(1):219-232.
3. Semmler G, Pomej K, Bauer DJM, et al. Safety of direct oral anticoagulants in patients with advanced liver disease. *Liver Int.* 2021;41(9):2159-2170.
4. Potze W, Arshad F, Adelmeijer J, et al. Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. *PLoS One.* 2014;9(2):e88390.
5. Kubitza D, Roth A, Becka M, et al. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct factor Xa inhibitor: rivaroxaban pharmacokinetics and pharmacodynamics in hepatic impairment. *Br J Clin Pharmacol.* 2013;76(1):89-98.
6. Koh JH, Liew ZH, Ng GK, et al. Efficacy and safety of direct oral anticoagulants versus vitamin K antagonist for portal vein thrombosis in cirrhosis: a systematic review and meta-analysis. *Dig Liver Dis.* 2022;54(1):56-62.
7. Kim S-A, Lee JY, Lee J-O, Bang S-M. Preliminary result of a pilot study of apixaban in the treatment of splanchnic vein thrombosis. *Blood.* 2022;140(Supplement 1):5678-5679.
8. Chen S, Pürerfellner H, Meyer C, et al. Anticoagulation in atrial fibrillation and liver disease: a pooled-analysis of >20 000 patients. *Eur Heart J Cardiovasc Pharmacother.* 2022;8(4):336-345.
9. Jarboe L, D.A., Bandikatla S, et al., Drug use evaluation of direct oral anticoagulants (DOACs) in patients with advanced cirrhosis. *Cureus.* 2022;14(4):e24029.
10. Afzal A, Suhong L, Korenblat K, Sanfilippo KM. Modest performance of available risk prediction models when used to predict hemorrhage in patients with chronic liver disease. *ISTH Congress*. 2022. Abstract Number: OC 24.5.
11. Radadiya D, Devani K, Brahmbhatt B, Reddy C. Major gastrointestinal bleeding risk with direct oral anticoagulants: does type and dose matter? - a systematic review and network meta-analysis. *Eur J Gastroenterol Hepatol.* 2021;33(1s suppl 1):e50-e58.
12. Intagliata NM, Henry ZH, Maitland H, et al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. *Dig Dis Sci.* 2016;61(6):1721-1727.
13. Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. *Eur J Haematol.* 2017;98(4):393-397.
14. Jones K, Pham C, Aguilar C, Sheth S. Retrospective review on the safety and efficacy of direct oral anticoagulants compared with warfarin in patients with cirrhosis. *Fed Pract.* 2020;37(10):479-485.
15. Munevar Aquite O, Hayes M, Beyene K, et al. Bleeding risk of oral anticoagulants in liver cirrhosis. *N Z Med J.* 2022;135(1563):52-61.
16. Oldham M, Palkimas S, Hedrick A. Safety and efficacy of direct oral anticoagulants in patients with moderate to severe cirrhosis. *Ann Pharmacother.* 2022;56(7):782-790.

DOI 10.1182/hematology.2023000514