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Liver injury from direct oral anticoagulants

Deven Juneja, Prashant Nasa, Ravi Jain

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Abstract

BACKGROUND

Drug-induced liver injury (DILI) can be caused by any prescribed drug and is a significant reason for the withdrawal of newly launched drugs. Direct-acting oral anticoagulants (DOACs) are non-vitamin K-based antagonists recently introduced and increasingly used for various clinical conditions. A meta-analysis of 29 randomised controlled trials and 152116 patients reported no increased risk of DILI with DOACs. However, it is challenging to predict the risk factors for DILI in individual patients with exclusion of patients with pre-existing liver disease from these studies.

AIM

To determine the risk factors and outcomes of patients who developed DILI secondary to DOACs by systematic review and meta-summary of recent case reports and series.

METHODS

A systematic search was conducted on multiple databases including PubMed, Science Direct, Reference Citation Analysis, and Google Scholar. The search terms included "Acute Liver Failure" OR "Acute-On-Chronic Liver Failure" OR "Acute Chemical and Drug Induced Liver Injury" OR "Chronic Chemical and Drug Induced Liver Injury" AND "Factor Xa Inhibitors" OR "Dabigatran" OR "Rivaroxaban" OR "apixaban" OR "betrixaban" OR "edoxaban" OR "Otamixaban". The results were filtered for literature published in English and on adult patients. Only case reports and case studies reporting cases of DILI secondary to

DOACs were included. Data on demographics, comorbidities, medication history, laboratory investigations, imaging, histology, management, and outcomes were extracted.

RESULTS

A total of 15 studies (13 case reports and 2 case series) were included in the analysis, comprising 27 patients who developed DILI secondary to DOACs. Rivaroxaban was the most commonly implicated DOAC ($n = 20, 74.1\%$). The mean time to onset of DILI was 40.6 d. The most common symptoms were jaundice ($n = 15, 55.6\%$), malaise ($n = 9, 33.3\%$), and vomiting ($n = 9, 33.3\%$). Laboratory investigations showed elevated liver enzymes and bilirubin levels. Imaging studies and liver biopsies revealed features of acute hepatitis and cholestatic injury. Most patients had a favourable outcome, and only 1 patient (3.7%) died due to liver failure.

CONCLUSION

DOACs are increasingly used for various clinical conditions, and DILI secondary to DOACs is a rare but potentially serious complication. Prompt identification and cessation of the offending drug are crucial for the management of DILI. Most patients with DILI secondary to DOACs have a favourable outcome, but a small proportion may progress to liver failure and death. Further research, including post-marketing population-based studies, is needed to better understand the incidence and risk factors for DILI secondary to DOACs.

Key Words: Anticoagulants; Direct-acting oral anticoagulants; Drug induced liver injury; Drug reactions; Hepatotoxicity; Novel oral anticoagulants

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Core Tip: Drug-induced liver injury (DILI) can be ascribed to practically any prescribed drug. The side effect profile of relatively newer direct-acting oral anticoagulants (DOACs) is yet to be completely determined. Even though the data from earlier clinical trials suggested no significant liver toxicity, several case reports and series describing DOAC-induced DILI have been recently published. Most of these cases have been reported in elderly patients, not on concomitant hepatotoxic drugs. However, these patients may have good clinical outcomes, with complete recovery of liver function, if an early diagnosis is made and the offending agent is stopped.

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INTRODUCTION

In general, drug-induced liver injury (DILI) can be ascribed to any sort of prescribed drug. DALI remains a major reason behind the premature termination of the development of a promising therapeutic agent or even the withdrawal of a newly launched drug in the market. On the contrary, the true incidence of DILI remains unknown because of under-reporting, missed diagnosis and the usage of different criteria to define DILI. The incidence of DILI varies from 2.3 and 2.7 per 100000 exposed individuals in the United Kingdom and the United States, respectively[1,2]. The incidence of the drug-induced acute liver failure (ALF) has been reported to be 1.61/1000000 persons-years[3]. However, the incidence varies with geographic, socio-economic, and cultural status of the population. For example, a recent retrospective study from China reported an incidence of 23.8 per 100000 persons. Moreover, DILI is the most common cause of ALF in the United States and Europe, accounting for almost 10% of all the causes of hepatitis. In these countries, the over-the-counter medicines and herbal or dietary supplements are the leading causes of DILI[3,4]. In comparison, the traditional Chinese and herbal medicines, dietary supplements and anti-tubercular drugs remain the major reasons for DILI in China[5]. In case of India, both Ayurvedic medicines as well as anti-tubercular drugs are responsible for most of the DILI cases[6].

Traditionally, the mechanism of DILI can be divided into direct (dose-dependent, predictable) and indirect (idiosyncratic, non-predictable) causes. Further, the idiosyncratic reactions may be immune-mediated (*e.g.*, phenytoin) or metabolic (*e.g.*, isoniazid). Acetaminophen is the best example for dose-dependent DILI. However, the recent studies demonstrated a dose-dependent mechanism in case of idiosyncratic type of DILI. While the exact pathogenesis of DILI remains unknown, genetic risk factors

(including human leucocyte antigen and its associations) have been identified in the literature[7,8]. Female gender, race (higher need for liver transplantation among Asians and chronicity among African Americans), age (elderly or young based on the type of drug), pre-existing liver disease, alcohol abuse, malnutrition, and mutations in the P450 gene are the main risk factors identified for DILI. However, it is challenging to predict the risk factors for DILI in individual patients. High index of suspicion is recommended for DILI, especially among those patients with large number of risk factors and when no other etiology is identified. A detailed review of the drug prescriptions should be performed for at least 3-6 mo. Prompt cessation of the suspected drug(s) is the first step in the management of DILI.

Direct-acting oral anticoagulants (DOACs) are non-vitamin K-based antagonists that have been recently introduced and are increasingly used for varied clinical conditions. Ximelagatran, a direct thrombin inhibitor, was withdrawn from the market because of its hepatotoxicity[9]. There was no signal of hepatotoxicity recorded during the randomised controlled trials (RCTs) of other novel DOACs. However, the patients with significant pre-existing liver diseases were excluded from the pre-approved RCTs for DOACs. Further, these RCTs remain inadequately powered to detect any difference in rare events such as DILI. A meta-analysis conducted by Caldeira *et al*[10], included 29 RCTs and 152116 patients and the study did not find any increased risk of DILI with DOACs. On the contrary, it reported a “protective effect” against hepatotoxicity, when compared with the low molecular weight heparin. Though the meta-analysis overcame the limitations of inadequate power of individual studies, the absence of the individual patient data, variable follow-up among the individual studies, usage of DOACs for different indications and hepatotoxicity being measured as a secondary outcome measure cannot reliably prove the safety of the DOACs. Hence, the post-marketing population-based, case-control, real-world data, and pharmacovigilance reports are required to assess the risk of hepatotoxicity of the DOACs.

More recently, multiple case reports and series have reported DILI secondary to the use of these drugs. However, the incidence, probability, and the risk factors for the development of DILI are not entirely elucidated and may also vary with different DOACs. Hence, the aim of the current study is to collate the data from recent case reports and series and analyse them to determine the risk factors and the outcomes of patients, who developed DILI secondary to DOACs.

MATERIALS AND METHODS

The authors conducted a systematic search for this meta-summary from multiple databases such as PubMed, Science Direct, *Reference Citation Analysis* and Google Scholar. The search terms included were “Acute Liver Failure” OR “Acute-On-Chronic Liver Failure” OR “Acute Chemical and Drug Induced Liver Injury” OR “Chronic Chemical and Drug Induced Liver Injury” AND “Factor Xa Inhibitors” OR “Dabigatran” OR “Rivaroxaban” OR “Apixaban” OR “Betrixaban” OR “Edoxaban” OR “Otamixaban”.

The results were filtered for the literature published in the English language and on adult (> 18 years) humans. All the search results were manually screened by the authors while only those relevant literature for DOAC-induced-DILI was analysed. Duplicate articles from different search databases were excluded (Figure 1). All the case reports and case series were evaluated and the data in terms of patient demographics, clinical symptomatology, type, dose and duration of the DOACs, clinical interventions, intensive care unit course, need for organ support and outcomes was extracted. The concomitant usage of the hepatotoxic drugs was also noted down. A datasheet was prepared for further evaluation.

Statistical analysis

The prepared datasheet was evaluated using MS Excel and Microsoft office, 2019. The categorical variables were presented as frequency and percentage. Median (interquartile range) or mean \pm SD was used for continuous variables. Tabulation and final documentation were done using the MS Office software (MS office 2019, Microsoft Corp, WA, United States).

RESULTS

From the current study search, 27 cases of acute liver damage published between 2011 and 2021[11-25] following DOAC exposure were retrieved (Table 1). There was an equal distribution of males and females (48.1%) while most of the cases were reported from Europe (77.8%) and North America (18.5%). At the time of presentation, the age of the patients was in the range of 41 to 91 years. Out of the total population, 20 (74.1%) patients were aged \geq 65 years or above. The time between the initiation of DOACs and the onset of liver injury ranged from 6 d to 6 mo, while one patient presented with acute condition after accidental ingestion. The major indications for DOACs were prevention of venous thromboembolism (VTE) in patients who were undergoing elective knee surgery and prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). However, three

Table 1 The baseline patient parameters, *n* (%)

Variables	Number of patients (<i>n</i> = 27)
Age (\pm SD), yr	72.7 (\pm 11.4)
Sex	Females, 13 (48.1)
	Males, 13 (48.1)
	Not mentioned, 1 (3.7)
Country of origin	Switzerland, 12 (44.4)
	Italy, 4 (14.8)
	United States of America, 4 (14.8)
	France, 3 (11.1)
	Australia, 1 (3.7)
	Canada, 1 (3.7)
	Ireland, 1 (3.7)
Clinical presentation	Spain, 1 (3.7)
	Jaundice, 15 (55.6)
	Malaise, 9 (33.3)
	Vomiting, 9 (33.3)
	Abdominal pain, 3 (11.1)
	Itching, 3 (11.1)
	Anorexia, 2 (7.4)
	Fatigue, 2 (7.4)
	Dyspepsia, 1 (3.7)
	Breathlessness, 1 (3.7)
	Pruritus, 1 (3.7)
	Weight loss, 1 (3.7)
	Comorbidities
Diabetes, 3 (11.1)	
Coronary artery disease, 3 (11.1)	
Others, 6 (22.2)	
Other drugs causing liver injury	None, 11 (40.7)
	Statins, 4 (14.8)
	Not mentioned, 12 (44.4)
DOACs implicated	Rivaroxaban, 20 (74.1)
	Apixaban, 4 (14.8)
	Dabigatran, 3 (11.1)
Indications of DOACs	Atrial fibrillation, 13 (48.1)
	Pulmonary embolism, 2 (7.4)
	Transient ischemic attack, 1 (3.7)
	Anti-phospholipid antibody syndrome, 1 (3.7)
	Deep vein thrombosis, 1 (3.7)
	Major lower limb surgery, 1 (3.7)
	Sinus node dysfunction, 1 (3.7)
	Accidental, 1 (3.7)

Time to presentation after initiation of DOACs (d)	40.6 ± 42.8
Need for organ support	Renal replacement therapy, 1 (3.7)
	Vasopressors, 1 (3.7)
	Invasive mechanical ventilation, 1 (3.7)
Need for specific antidote	Idarucizumab, 1 (3.7)
Days in hospital (d)	8 ± 9.3
Days in ICU (d)	7 ± 12.1
Outcome	Alive, 26 (96.3)
	Death, 1 (3.7)

SD: Standard deviation; DOAC: Direct-acting oral anticoagulants; ICU: Intensive care unit.

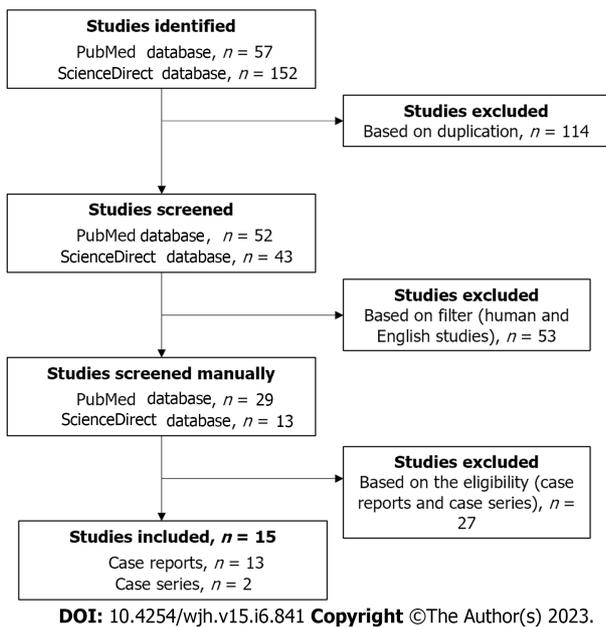


Figure 1 PRISMA flow diagram of the selected literature for the current meta summary.

patients received DOACs for the management of deep vein thrombosis (DVT) and pulmonary embolism (PE). A total of 20 patients (74.1%) received rivaroxaban, four (14.8%) received apixaban, and three (11.1%) received dabigatran. In four cases (14.8%), the consumption of other potential hepatotoxic medications (statins) was reported. The most reported symptom was jaundice in 15 (57.7%) patients, followed by malaise and vomiting in 9 (34.6%) patients. Extracorporeal therapy was initiated in one patient, whereas only one patient with dabigatran-induced DILI received idarucizumab therapy. Table 2 shows the liver function parameters at the time of presentation. Though most of the patients showed complete recovery of the liver function, only 3 (11.1%) patients were reported to have persistent liver dysfunction at the time of discharge, and only one (3.7%) death was reported.

DISCUSSION

Prolonged anticoagulant therapy translates to varied clinical conditions for which vitamin K antagonists are the only therapeutic option. However, the introduction of DOACs has provided the physicians, a safer and an effective alternative. They possess several inherent advantages, including predictable pharmacokinetics and immediate activity after the first dose. This pattern helps in using a fixed dose and obliterates the need for routine laboratory monitoring in most of the patients. However, their side effect profile needs to be fully understood. The first DOAC *i.e.*, ximelagatran was approved for clinical use based on the data from short-term trials. However, the long-term data found DALI in up to 8% of the patients, who received the drug[26]. The fact came into light after its prolonged clinical use. Hence, ximelagatran was withdrawn from the market because of its unfavourable side effect profile. Similarly,

Table 2 Liver function test parameters

Parameter	Mean	Standard deviation	Range
SGOT, at presentation (units/L)	575.5	672.2	90-2304
SGPT, at presentation (units/L)	800.2	1159.6	90-4000
Total bilirubin, at presentation (mg/dl)	6.3	6	0.64-21.8
Direct bilirubin, at presentation (mg/dl)	4.8	4.9	0.3-10.3
Alkaline phosphatase, at presentation (units/L)	269.2	279.5	60-1039

SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase.

significant hepatotoxicity was not reported in the initial trials of other DOACs. However, several case reports have been published in the recent years, describing their hepatotoxic potential.

It is challenging to diagnose DILI with the absence of any specific clinical or biochemical marker. The clinical features of DILI are usually non-specific and may vary from asymptomatic liver enzyme elevation to ALF. Even liver histology is not specific and may also be found in other liver disorders[27]. Hence, a high index of suspicion is warranted to enable early diagnosis. Even though jaundice was present in 55.6% of the study patients, all others presented with non-specific symptoms like malaise, vomiting, anorexia and fatigue. The latency from the exposure to DILI, especially in case of metabolic idiosyncrasies, varies from days to weeks and at times, even months too. The data, from the meta-analysis study that assessed the hepatotoxic potential of DOACs, also reported that the mean age of the patients was in the range of 55 to 71 years. Further, the time to develop DILI after the initiation of DOACs ranged from 2 wk to 2 years[10].

The diagnosis of DILI requires the exclusion of other liver dysfunction etiologies associated with a similar clinical and biochemical picture, along with the documentation of temporal association related to the exposure of the offending agent[28]. The accepted definition for hepatocellular liver injury has been given by an international DILI expert working group; fivefold or greater elevation above the upper limit of normal (ULN) for alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)[29]. The cholestatic picture is defined to be more than twofold elevation above the ULN for alkaline phosphatase with a concomitant elevation of the activity of 5'-nucleotidase or γ -glutamyltranspeptidase [29]. However, when the ratio of elevation, above the ULN for ALT/SGPT and alkaline phosphatase, is more than two-fold yet less than five-fold, it is defined as a mixed pattern of liver injury[29,30]. The use of DOACs has been associated with both hepatocellular and cholestatic patterns of liver injury[11].

As per the clinical studies, DOACs are rarely associated with the development of DILI with the frequency of developing DILI ranging between 0.1%-1%[10]. However, a higher incidence of 2.3% was reported when using rivaroxaban[31]. In the current study analysis, rivaroxaban was reported to be the offending agent in 74% of the cases. This may also be explained by the fact that it is arguably the most prescribed DOAC[32]. However, these clinical trials were neither designed nor powered to detect the risks of rare idiosyncratic adverse reactions like DILI. Moreover, the patients at high risk of developing these complications and with pre-existing liver disease were often not included in these clinical trials.

Several DOACs are approved and prescribed for both prevention and the treatment of DVT or PE. Further, they are also prescribed to prevent stroke and systemic embolism in adults with non-valvular AF and other risk factors. DOACs are also routinely used in the prevention of VTE after hip or knee surgeries. The current study analytical outcomes too depict a similar usage pattern. The patients, who developed DILI, were prescribed DOACs for similar indications, among which the non-valvular AF was the most common indication. The data from the systematic analysis has also shown that the most common indication for initiating DOACs was non-valvular AF[10].

Except for dabigatran and its glucuronide metabolite, which are predominantly excreted through kidneys, all the DOACs are metabolised in the liver. Moreover, dabigatran is also a substrate for P-glycoprotein (P-gp), and hence, dose adjustment needs to be done for patients with renal dysfunction and those on P-gp inhibitors like azole antifungals, amiodarone, macrolides, atorvastatin, digoxin *etc* [33]. Nearly one-third of the administered rivaroxaban is excreted unchanged in the urine, whereas the rest undergoes metabolic degradation. In this context too, half gets eliminated by the kidneys and the other half is eliminated through hepatobiliary route. In the liver, it is mainly metabolised *via* the cytochrome P450 (CYP) 3A4 and some CYP-independent mechanisms. It is also a substrate of P-gp. Apixaban is excreted through multiple pathways such as the renal (25%), intestinal (55%) and the rest through hepatobiliary route (CYP3A4-dependent mechanisms)[34]. Concomitant use of hepatotoxic drugs, or CYP3A4/P-gp inhibitors may increase the risk of hepatotoxicity with DOACs. Hence, these patients require a close monitoring of their liver function. Further, patients may develop hepatotoxicity even in the absence of these drugs. As per the current study analysis, the concomitant use of potentially hepatotoxic drugs was reported in only 14.8% of the cases.

The current study has several strengths to its credit. The authors included DILI associated with all the currently prescribed DOACs and included all the latest case reports and series. However, there exists some limitations to the meta-summary. The studies included, were only case reports and case series without a control arm. Additionally, these studies were heterogeneous, with a high risk of bias and missing data. So, it may affect the generalisability of the results. Further, the authors might have missed some relevant cases too, because those case reports or series that did not have any individual biochemical data were excluded.

CONCLUSION

DOACs may rarely lead to DILI. Most of the cases have been reported among elderly patients, who may be at higher risk of developing DILI. It may develop without the concomitant use of other hepatotoxic drugs. The outcomes of these patients are generally favourable and liver dysfunction is mainly reversible if it is recognised early and the intake of offending agent is stopped. Hence, physicians prescribing these drugs must be aware of such rare complications to ensure early diagnosis and prompt management.

ARTICLE HIGHLIGHTS

Research background

Drug-induced liver injury (DILI) can be caused by any prescribed drug and is a significant reason for the withdrawal of newly launched drugs. Direct-acting oral anticoagulants (DOACs) are non-vitamin K-based antagonists recently introduced and increasingly used for various clinical conditions. It is challenging to predict the risk factors for DILI in individual patients with exclusion of patients with pre-existing liver disease from these studies.

Research motivation

To determine the risk factors and outcomes of DILI in patients taking DOACs and provide clinicians with essential information for the management of DILI secondary to DOACs.

Research objectives

To determine the incidence, probability, and risk factors for developing DILI secondary to DOACs and its outcomes in affected patients.

Research methods

The authors conducted a systematic search of multiple databases for the literature published in English using specific search terms. The results were filtered and analysed to determine the risk factors and outcomes of DILI in patients taking DOACs.

Research results

The analysis of recent case reports and series showed that DOACs can rarely cause DILI, and the incidence, probability, and risk factors for developing DILI varied among different DOACs.

Research conclusions

DOACs can cause DILI, and the incidence, probability, and risk factors for developing DILI vary among different DOACs. Clinicians should have a high index of suspicion for DILI in patients taking DOACs, especially those with multiple risk factors. Prompt cessation of the suspected drug is recommended as the first step in managing DILI.

Research perspectives

The findings of this study provide essential information for clinicians to manage DILI secondary to DOACs. However, further research is required to identify the true incidence of DILI and its risk factors, including genetic associations. Post-marketing pharmacovigilance reports can help to assess the risk of hepatotoxicity associated with DOACs.

FOOTNOTES

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