

Non-hemorrhage-related adverse effects of rivaroxaban

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Abstract

The direct oral anticoagulant rivaroxaban is useful in various indications that include venous deep vein thrombosis prophylaxis/treatment after knee/hip replacement surgery and prevention of stroke in patients with non-valvular atrial fibrillation. Its mechanism of action has been mostly associated with hemorrhage-related adverse effects; thus a number of non-hemorrhage-related adverse effects of the drug have received less attention or go unrecognized. These adverse effects mainly include liver injury, hypersensitivity reactions, leukocytoclastic vasculitis and hair loss. Clinicians should be aware of these rare adverse reactions and advise their patients to contact them as soon as they observe any unexpected clinical response.

Key words: rivaroxaban, adverse effects, liver, anaphylaxis, hypersensitivity, vasculitis, hair loss.

Introduction

Direct oral anticoagulants (DOACs) have predictable anticoagulant effects, the ability to administer fixed doses without a need for routine anticoagulant monitoring, fast onset and offset of action, and relatively low potential for food and drug interactions compared to warfarin. Therefore, DOACs have broadened the options for anticoagulation and have been widely used since 2011 [1–3]. Rivaroxaban is an anti-factor Xa DOAC used for the prevention of thromboembolic complications in patients with non-valvular atrial fibrillation, for prophylaxis of deep venous thrombosis (DVT) in patients undergoing knee or hip surgery, and for acute treatment and secondary prevention of DVT and pulmonary embolism (PE) [4]. It is also approved by the European Medicines Agency, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers [5]. Due to the mechanism of action of rivaroxaban, much consideration has been given to hemorrhage-related adverse effects; thus non-hemorrhage adverse effects receive less attention and some of them go unrecognized.

The aim of this review is to present the non-hemorrhage-related adverse effects of rivaroxaban.

Material and methods

We searched for eligible publications published in PubMed (last search in November 2017) by using the following search algorithm: rivaroxaban

AND (side effects OR adverse effects OR safety OR pancreas OR liver OR cardiovascular OR skin OR allergy OR angioedema OR immune system OR renal OR kidney OR infection OR central nervous system OR malignancy OR cancer).

The search was limited by the following criteria: published in the English language, published as clinical trial, meta-analysis, case report, comparative study, observational study, evaluation study, or validation study.

The initial search identified 680 articles in PubMed, which were scrutinized for relevance. Data presented in meta-analyses or large clinical trials were given more weight in the analysis than those from smaller studies. Of note, hemorrhagic manifestations following rivaroxaban administration were not the subject of this review and were not included.

Adverse effects other than hemorrhage-related (Table I)

Hepatobiliary disorders

The first oral direct thrombin inhibitor, ximelagatran, was associated with liver toxicity [6, 7] and was withdrawn from the market; thus, the new DOACs were thoroughly investigated regarding the possibility of hepatotoxicity. Rivaroxaban administration was rarely associated with liver injury in the randomized clinical trials [8]. Specifically, four randomized, double-blind phase III studies (RECORD 1–4) were performed [9–12]. Using data from these studies, liver injury (defined as ≥ 3 times the upper limit of normal (ULN) of alanine transaminase (ALT) or aspartate aminotransferase (AST) and ≥ 2 ULN of total bilirubin [13]) was present in 2.33% of the patients treated with rivaroxaban, whereas it was observed in 3.64% of enoxaparin-treated subjects [8]. It should be mentioned that the dosage of rivaroxaban in the above studies was lower than the standard 20 mg dose used in atrial fibrillation, and thus the possibility of dose-related liver adverse effects was lower. According to a systematic review of 29 randomized clinical trials evaluating 152,116 patients (mean follow-up of 16 months), including RECORD 1, 3 and 4, DOACs did not show an increased risk of drug-induced liver injury (DILI) compared to the control group (relative risk (RR) 0.90, 95% confidence interval (CI): 0.72–1.13 compared to low molecular weight heparin (LMWH), vitamin K antagonist, placebo or non-pharmacological treatment) [14]. The results were similar for each individual DOAC. Of note, a 29% risk reduction of transaminase elevations was apparent among DOAC-treated patients in comparison with LMWH (RR = 0.71, 95% CI: 0.59–0.85) [14]. In addition, according to a recently published study,

the hospitalization rate for liver injury was higher among patients who received warfarin compared with DOACs [15].

However, in case reports, case series as well as in pharmacovigilance data, a post-marketing safety signal has arisen concerning the hepatotoxicity of rivaroxaban. A recent prospective study of 113,717 patients with atrial fibrillation included in the MarketScan Commercial and Medicare Supplemental databases (median follow-up of 12 months; 56,879 initiated warfarin, 17,286 initiated dabigatran, 30,347 initiated rivaroxaban and 9,205 initiated apixaban) identified 960 hospitalizations associated with liver injury [15]. The rate of liver injury hospitalization per 1000 person-years was 9.0 for warfarin, 4.0 for dabigatran, 6.6 for rivaroxaban and 5.6 for apixaban. The lower liver injury hospitalization rates in initiators of DOACs compared with warfarin remained after multivariable adjustment (hazard ratio (HR) (95% CI): dabigatran 0.57 (0.46–0.71), rivaroxaban 0.88 (0.75–1.03) and apixaban 0.70 (0.50–0.97)). Rivaroxaban initiators showed a 56% increased risk of liver injury hospitalization compared with dabigatran initiators (HR = 1.56, 95% CI: 1.22–1.99). Other significant factors predicting liver injury hospitalization included prior liver, gallbladder and kidney disease, cancer, anemia, heart failure and alcoholism [15]. It should be mentioned that this was an observational study and other factors, for example prescriber preferences, could affect the results. Additionally, through an analysis using data from the US Food and Drug Administration Adverse Event Reporting System (FAERS database), among the 17,097 reports concerning a DOAC, 3985 were treated with rivaroxaban. Overall liver injury reports related to rivaroxaban represented 3.7% of all reports and 1.4% of all drug-associated liver injury reports [16].

A total of 28 cases of rivaroxaban-related hepatotoxicity have also been published with a time lapse between initiation of treatment and onset of hepatic injury ranging from 2 to 180 days (median: 15 days). In the majority of these cases liver injury was classified as hepatocellular (approximately 40%), whereas in the other cases the pattern was cholestatic (approximately 27%) or mixed (approximately 15%) [17]. The severity of hepatotoxicity ranged from asymptomatic liver injury with a cholestatic pattern [18] to symptomatic and severe [19–26]. Some of the symptomatic patients developed jaundice and nausea [20, 22, 26] and

Table I. Non-hemorrhage-related adverse effects of rivaroxaban

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| <ul style="list-style-type: none"> • Hepatobiliary disorders • Allergy and hypersensitivity reactions • Skin side effects • Hair loss |
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1 patient developed acute liver failure and hepatic encephalopathy with a fatal outcome [25].

The overall incidence of DILI is considered to be between 1 in 10,000 and 1 in 1,000,000, making it difficult to study the etiopathogenesis of this condition [27]. It should be mentioned that rivaroxaban-induced hepatotoxicity is commonly an idiosyncratic adverse drug reaction, as it cannot be explained by its pharmacological action and is observed in therapeutic doses [21, 27]. Idiosyncratic reactions can be divided into two large groups, the immunological and non-immunological (metabolic) ones [28]. Immunologic reactions present with systemic features, such as fever, rash, and eosinophilia. They have an early onset (1–6 weeks) and rapid re-injury with the reintroduction of the drug [28]. The biopsies taken from 2 patients being treated with rivaroxaban showed a perivenular hepatic necrosis, corresponding to a higher density of CYP3A4 [23, 29]. Considering the fact that rivaroxaban is metabolized via CYP3A4 [1, 30], the rivaroxaban-induced liver injury is probably associated with a metabolic-related mechanism [23]. However, an immunological-mediated mechanism causing liver injury cannot be excluded since rivaroxaban administration has also been associated with the DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) [31]. A patient 6 weeks after the initiation of rivaroxaban therapy presented with fever, leukocytosis, fatigue and arthralgia and three days later a maculopapular rash appeared. The biopsy of the aforementioned patient revealed non-zonal areas of necrosis and neutrophilic inflammation infiltrate in portal tracts with no presence of eosinophils. A skin biopsy was also performed, indicating a dermal hypersensitivity reaction with the perivascular presence of lymphocytes, eosinophils and neutrophils. Symptoms and biochemical markers improved with methylprednisolone [31].

However, in patients receiving rivaroxaban, or other DOACs in general, due to atrial fibrillation, the atrial fibrillation itself can predispose to episodes of low cardiac output leading to ischemic liver injury and elevation of aminotransferases. Moreover, elderly subjects receiving DOACs after surgery for hip/knee replacement might also exhibit liver injury through low cardiac output syndrome due to the intervention [32].

Although DILI associated with the use of rivaroxaban is rare, patients being treated with the drug should be advised to visit their physician immediately if they develop symptoms such as jaundice and malaise [21].

Allergy and hypersensitivity reactions

According to product information, immunological side effects due to rivaroxaban occur at a rate of 0.1–1%. In the ROCKET-AF study (7,111 patients

treated with rivaroxaban) observed hypersensitivity reactions were: toxic skin eruption (0.03%), cutaneous vasculitis (0.01%), erythema multiforme (0.0%), exfoliative rash (0.01%) and anaphylaxis (0.01%) or anaphylactic shock (0.01%) [33].

A case of DRESS syndrome probably induced by rivaroxaban has already been mentioned above [31]. DRESS is a rare but severe drug reaction, characterized by fever, skin eruption, eosinophilia, lymphocyte activation and internal organ involvement. It is a late-onset reaction, usually noticed 3–8 weeks after the initiation of the drug [34]. Another plausible association between rivaroxaban administration and DRESS development was reported [35]. The patient experienced fever (up to 40.5°C) 10 days after the initiation of rivaroxaban therapy for prophylaxis of DVT following hip replacement surgery, and generalized skin erythema 5 days later. Rivaroxaban was stopped 10 days after the beginning of the symptoms. One day after the discontinuation hypotension and bradycardia were present and the patient was admitted to the intensive care unit. Neutrophilia, eosinophilia (peak up to 1065/mm³), acute renal failure and increased levels of ALT, γ -glutamyl-transferase and direct bilirubin were observed. The radiology examination showed pulmonary infiltrates and lumbar and pulmonary lymphadenopathy. Symptoms were improved with corticosteroid treatment [35].

Two more cases of probable hypersensitivity reactions after administration of rivaroxaban have been published. The first patient developed a bumpy rash after taking one dose of rivaroxaban. He took two more doses and 7 days after the discontinuation of the drug he was admitted to the hospital with erythema, blisters and tense bullae on his lower extremities, eczematous plaques on his thighs and desquamating skin over his lower extremities, neck, ears, trunk and arms. Upon admission, blood count revealed no leukocytosis or eosinophilia and mild elevation of inflammatory markers. Punched biopsy showed only fibrin deposition in the dermis. After treatment with topical triamcinolone the rash resolved [36]. The second patient received rivaroxaban after knee-replacement surgery. Seven days after the administration of the drug he developed a maculopapular rash on the groin, anterior chest, upper back, upper limbs and face. Several pustules on the upper arms and back as well as leukocytosis with neutrophilia and eosinophilia were present. Cessation of rivaroxaban, oral antihistamines and topical mometasone improved the symptoms and biochemical tests [37]. Generally, hypersensitivity reactions are rare.

Two cases of leukocytoclastic vasculitis associated with rivaroxaban administration have been reported. A palpable non-blanching purpuric rash

developed 7 and 10 days after initiation of rivaroxaban due to deep venous thrombosis. Apart from the palpable purpura, examination findings were unremarkable in both patients. Other medications were excluded as the etiologic trigger, as well as infections (e.g. hepatitis B, hepatitis C and human immunodeficiency virus) and rheumatology diseases. Rivaroxaban therapy was stopped at admission with resolution of the rash within a week in both patients [38, 39].

Hair loss

Hair loss during anticoagulant therapy has been previously described with heparins [40, 41] and vitamin K antagonists [42]. In the study of Gelbricht *et al.*, 9 out of the 730 patients treated with rivaroxaban reported hair loss with a mean time 68 ± 76 days after the administration of the drug [43]. Additionally, a case of rivaroxaban-induced hair loss was reported in a 26-year-old woman, observed 3 months after the initiation of rivaroxaban therapy. A few months after the cessation of rivaroxaban her hair grew spontaneously [44].

The traditional anticoagulants are thought to share a common mechanism for hair loss as a similar pattern is observed. The mechanism is named telogen effluvium and is a process of anagen hair shifting into the catagen phase prematurely, leading to visible alopecia commonly 2–4 months after drug administration [45]. Hence, if hair loss is related to DOAC anticoagulant activity, rivaroxaban can also share the same underlying mechanisms.

Conclusions

Rivaroxaban, a DOAC, is widely used in various indications including DVT prophylaxis/treatment after knee/hip replacement surgery and prevention of stroke in subjects with non-valvular atrial fibrillation. Since its release in 2011, some non-hemorrhage-related adverse effects of the drug have been reported. Mainly, they referred to liver injury, hypersensitivity reactions, leukocytoclastic vasculitis and hair loss. Clinicians must be aware of these adverse reactions and advise their patients to contact them as soon as they observe any unexpected clinical response. However, careful post-marketing surveillance should be continued in order to establish actual event rates.

Conflict of interest

This review was written independently. Professor MS Elisaf reports personal fees from AstraZeneca, grants and personal fees from MSD, personal fees from Pfizer, Abbott, Sanofi, Boehringer Ingelheim, Eli Lilly, GSK. The authors have given talks and attended conferences sponsored by various

pharmaceutical companies, including Bristol-Myers Squibb, Pfizer, Lilly, Abbott, Amgen, AstraZeneca, Novartis, Vianex, Teva and MSD.

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