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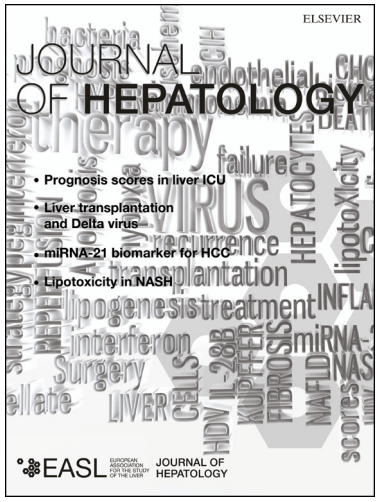

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Rivaroxaban Postmarketing Risk of Liver Injury

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Keywords: rivaroxaban, drug-induced liver injury, hepatotoxicity, adverse drug reactions, postmarketing, pharmacovigilance, anticoagulants, factor Xa inhibitors, drug safety

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ABSTRACT

Background: Rivaroxaban is an oral direct factor Xa inhibitor that has been marketed worldwide since 2008 for the primary and secondary prevention and treatment of thromboembolic disorders. Although liver injury was observed in premarketing trials of rivaroxaban, there are no published postmarketing cases of liver injury associated with rivaroxaban.

Methods: Report of 14 cases of liver injury associated with rivaroxaban, including two with liver biopsy, and search queries in three large international pharmacovigilance databases for comparable cases.

Results: Formal causality assessment classified rivaroxaban as the "highly probable", "probable" and "possible" cause in 4, 7 and 3 patients, respectively. Search results from three large international pharmacovigilance databases revealed a considerable number of additional hepatic adverse events where rivaroxaban was reported as a suspected cause.

Conclusions: We interpret the presented information as a relevant safety signal that should be followed by pharmacoepidemiological studies in order to reliably estimate absolute and relative risks of liver injury associated with rivaroxaban in support of rational risk-benefit assessment. Meanwhile, incident symptoms and signs of liver disease in patients treated with rivaroxaban should be considered as a potential adverse drug reaction, and if no other likely cause can be identified rivaroxaban should be stopped as soon as possible.

INTRODUCTION

Rivaroxaban is an oral direct factor Xa inhibitor that has been marketed worldwide since 2008 for the primary and secondary prevention and treatment of thromboembolic disorders [1, 2]. Although liver injury was observed in premarketing trials of rivaroxaban [3], postmarketing cases of liver injury associated with rivaroxaban have not been published so far. Safety issues of newly marketed drugs including drug-induced liver injury (DILI) are typically identified during the first five years after marketing, and spontaneous reporting systems play an important role as a sensitive source of information for the detection of new postmarketing safety signals. We therefore evaluated postmarketing cases of liver injury associated with rivaroxaban reported to our regional pharmacovigilance center and performed search queries in three large international pharmacovigilance databases for comparable cases.

CASE PRESENTATIONS

Case #1

A 78-year-old male patient had total knee replacement for which he received thromboprophylaxis with dalteparin for 10 days and thereafter rivaroxaban (Xarelto®, Bayer HealthCare) 10 mg/d. Approximately 14 days after start of rivaroxaban the patient developed painless jaundice, pruritus, fatigue, nausea and unintentional weight loss of 5 kg. Rivaroxaban was stopped 19 days after start, but it was not until another 10 days later that the patient was rehospitalized with determination of laboratory values. Upon admission alanine aminotransferase (ALT), alkaline phosphatase (AP) and total bilirubin (TB) were increased 2.5, 2.9 and 15.5 times the upper limit of normal (ULN), respectively. Viral serology and autoantibodies were negative. Abdominal ultrasound and computer tomography (CT) showed cholecystolithiasis but no signs of biliary obstruction. A liver biopsy was performed 20 days after discontinuation of rivaroxaban. Histology showed cholestasis and portal

inflammation with eosinophilic infiltrates, compatible with drug-induced liver injury (Figure). Other recently administered drugs were a single i.v. dose of 2g cefazolin before knee replacement and postoperative analgesic treatment with acetaminophen and metamizole (=dipyrone) up to 4 g/day each for 10 days. During the further course the patient eventually developed a paralytic ileus and died 6 weeks after rehospitalization. The findings are also summarized in Table 1.

According to standardized RUCAM criteria for the assessment of drug-induced liver injuries [4-6] we assigned a causality of “highly probable” (total score: 9) to rivaroxaban. Key criteria for this assessment were a close and plausible temporal relationship, a known and labeled adverse drug reaction, compatible histological findings, and negative differential diagnosis for alternative causes. Specifically, temporal relationship, only mild ALT increase and histology were not compatible with acetaminophen hepatotoxicity; dalteparin and metamizole had been stopped approximately 14 days, and cefazolin single dose was given 24 days before onset of symptoms. Other drugs were therefore classified as unlikely alternative causes.

Case #2

An 83-year-old female patient had total knee replacement for which she received thromboprophylaxis with dalteparin for 9 days and thereafter rivaroxaban 10 mg/d. Approximately 13 days after start of rivaroxaban the patient developed painless jaundice, pruritus, fatigue, nausea and unintentional weight loss of 5 kg. Twenty days after start of rivaroxaban the patient was rehospitalized, and another day later rivaroxaban was replaced by dalteparin. Upon admission ALT, AP and TB were increased 7.8, 6.8 and 13.9 times the ULN, respectively (Table 1). Viral serology and autoantibodies were negative. Abdominal ultrasound and CT showed cholecystolithiasis but no signs of biliary obstruction. A liver biopsy was performed 5 days after stop of rivaroxaban and was compatible with drug-induced liver injury showing a similar histology (Figure) as in case #1. Other recently administered drugs were a single i.v. dose of 2g cefazolin before knee replacement and analgesic treatment with acetaminophen 4 g/day and diclofenac 150 mg/d for 9 days

postoperatively (followed by an on-demand prescription for another 20 days, but unknown actual use), and metamizole 1000 mg and 500 mg on postoperative days 1 and 3, respectively. The patient was treated with cholestyramine and subsequently recovered over the following weeks.

Formal RUCAM assessment classified rivaroxaban‘s causality as “possible” (total score: 5), based on the key criteria of a close and plausible temporal relationship, a known and labeled adverse drug reaction, compatible histological findings and negative differential diagnosis for alternative causes except for diclofenac use. Nevertheless, in contrast to rivaroxaban, fixed-dose diclofenac was stopped 16 days before onset of symptoms, and rivaroxaban therefore remains the most likely cause of liver injury.

Cases #3-14

Over the past 4 years and in our function as a regional pharmacovigilance center we received another 12 reports of liver injury associated with rivaroxaban and an at least possible causal relationship based on RUCAM criteria. In addition to our primary documentation we now performed an extensive reevaluation including formal causality assessment. For that purpose we contacted primary reporters and other treating physicians and hospitals and obtained all available relevant follow-up information. These cases are summarized in Table 1, and their detailed RUCAM classifications are presented in Table 2.

REPORTS IN INTERNATIONAL PHARMACOVIGILANCE DATABASES

Cases of liver injury associated with rivaroxaban should be reported to pharmacovigilance systems worldwide, and we therefore also performed searches in databases of international postmarketing spontaneous reporting systems. The database of the World Health Organization (WHO UMC VigiBase, access date 2013-11-28) contains, including our own cases, reports of 179 cases that are compatible with DILI (classified under 19 selected hepatobiliary WHO-ART reaction terms) where rivaroxaban was reported as a suspected cause; the database of the European Medicines Agency (EMA EudraVigilance, access date

2013-11-03, data censored 30 September 2013) contains 375 events classified under 21 selected hepatobiliary MedDRA reaction terms where rivaroxaban was a suspected cause; and the database of the US Food and Drug Administration (FDA FAERS, data censored 31 December 2012, extracted in November 2013 by the FDA in response to our request under the Freedom of Information Act) contains 87 cases classified under the 21 selected MedDRA terms. For details on searched terms and reported hepatic events see supplementary material (S.1).

These reports have limitations and must therefore be interpreted with caution: in the absence of detailed information the causal role of rivaroxaban regarding the reported hepatic outcomes remains uncertain; due to unknown reporting rates and population exposure spontaneous reporting systems cannot provide reliable quantitative risk estimates; pharmacovigilance systems may contain duplicate reports, and in our EudraVigilance search several adverse events may refer to only one individual case. Nevertheless, these reports can be interpreted as a signal in support of the hypothesis that our cases may represent just the “tip of the iceberg” of a considerably larger number of serious liver injuries worldwide caused by rivaroxaban.

DISCUSSION

Rivaroxaban is an oral direct factor Xa inhibitor that has been marketed worldwide since 2008 for the primary and secondary prevention and treatment of thromboembolic disorders. Five years after market launch we are not aware of any published detailed postmarketing case reports of liver injury associated with rivaroxaban. However, liver injury is known under rivaroxaban, labeled adverse reactions include icterus and increased transaminases, alkaline phosphatase, and total and conjugated bilirubin [7]. Of note, the direct thrombin inhibitor ximelagatran was associated with hepatotoxicity during clinical development, which contributed to non-approval by the US FDA, and in other countries marketing was discontinued after serious cases of liver injury associated with ximelagatran appeared in the postmarketing phase [8]. Looking at premarketing data of rivaroxaban, a published

evaluation of rivaroxaban's hepatic events in clinical trials was based on its phase III RECORD studies and included 6131 patients exposed to rivaroxaban. The featured analysis used state of the art eDISH plots [3] and identified ALT increases ≥3x ULN in 2.3% of patients including 9 apparent "Hy's cases" with a simultaneous ≥2x increase in total bilirubin. Further validations concluded that there was only one "true" Hy's case either caused by rivaroxaban or possibly by other incompletely excluded alternate etiologies [3]. A recent systematic review and meta-analysis of premarketing data on liver injury associated with new oral anticoagulants reported ambiguous results. There were a large number of cases with ALT elevations >3x ULN including many with concomitant total bilirubin >2x ULN subsequent to the use of those drugs. At the same time there were no evident risk differences between the individual studied new oral anticoagulants, and a lower risk of such events when compared to low molecular weight heparins [9]. However, safety analyses of clinical trials' data have intrinsic limitations. According to the "Rule of 3" [10, 11] the 6131 exposed patients in the RECORD studies are insufficient to reliably detect risks of less than approximately 1:2000, which is typical for idiosyncratic drug-induced liver disease (DILI) but can still be relevant for a drug's overall risk-benefit evaluation [12]. Another limitation is that the duration of treatment in these trials was only 35±2 or 12±2 days, respectively [3]. This is shorter than the currently labeled treatment time for some indications, and 12±2 days are also less than the median latency time of 15.5 days in our case series. Risk factors are another issue of particular interest, as they are often underrepresented in clinical trial populations. Rivaroxaban is often started after orthopedic surgery and many patients concomitantly receive potentially hepatotoxic analgesic drugs. Our series included three patients meeting biochemical criteria of Hy's cases but concomitant use of acetaminophen in therapeutic doses. Dose, long latency time and histology were not compatible with acetaminophen-induced hepatotoxicity in these cases. However, according to current mechanistic concepts acetaminophen in doses below the hepatotoxic threshold may attenuate hepatotoxic "downstream" pathways via glutathione depletion and cytokine-mediated signal transduction. Acetaminophen could therefore have acted as a risk factor for rivaroxaban-induced liver

injury [13, 14]. Some patients also received metamizole, but hepatotoxicity is not amongst its labeled adverse reactions. Indeed, we found only one case of metamizole-associated liver injury in the literature [15], but it presented with an allergic skin reaction after short latency, which is different from the pattern observed in our cases. In order to further clarify the causality in our case series, we planned the conduct of lymphocyte transformation tests (LTT) with in-vitro exposure of lymphocytes from our patients to rivaroxaban. This method has been successfully used for the evaluation of DILI in the past [16]. These planned studies have been delayed because we were unable to obtain rivaroxaban pure substance from the manufacturer of Xarelto®, but we now aim to perform these tests with commercially available rivaroxaban.

Possible mechanisms of rivaroxaban-induced hepatotoxicity are unknown and probably involve complex interactions of several rare factors, possibly also immune-mediated reactions. Of further note, previous studies indicated that rivaroxaban is a shared substrate of the drug transport proteins MDR1 and BCRP, whereas anticoagulant vitamin K antagonists are no strong substrates of MDR1 [17-19]. MDR1 inhibitors and loss-of-function BCRP polymorphisms may therefore alter rivaroxaban pharmacokinetics, and further studies may explore the potential role of these factors for rivaroxaban-induced DILI.

The diagnosis of drug-induced liver injury mainly depends on temporal relationship and the exclusion of other causes, which can never be done with absolute certainty. Furthermore, even the widely accepted RUCAM causality scale for DILI has limitations, and discrepancies between expert evaluations vs. standardized scales have been widely discussed and studied [6, 20, 21]. At least all cases reported to our center were evaluated using senior expertise and the most recognized standardized DILI-specific criteria. In contrast, the routine evaluation of cases that are reported to large pharmacovigilance databases usually lacks detailed case information and sufficient resources for standardized DILI-specific causality assessments. In order to avoid over-interpretation it is therefore reasonable that publicly

available search results from those databases only contain the information whether a specific drug is considered as an at least possible cause. Furthermore, we also recognize that some individual cases may have been reported to more than one of the searched databases. Spontaneous reports are neither meant to provide definite proof for the causative role of rivaroxaban in the presented cases, nor can they be used for reliable calculations of quantitative risk estimates. However, we applied the best possible combination of standardized causality assessment plus expert evaluation, and in our long-term experience as a pharmacovigilance center the presented case series of liver injury in association with a newly marketed drug is unusual and reason to raise concern. Premarketing experience and information from international pharmacovigilance databases are also compatible with the possibility that rivaroxaban continues to cause a considerable absolute number of liver injuries worldwide. In conclusion, we therefore interpret the presented case series as a potentially serious signal that requires follow-up by pharmacoepidemiological cohort studies in suitable databases in order to estimate the absolute and relative risks of serious liver injury associated with rivaroxaban versus alternative anticoagulants [12]. Meanwhile, the apparently rare but potentially serious risk of rivaroxaban-induced liver injury should be considered in the risk-benefit evaluation versus alternative antithrombotic drugs with established safety profiles. In patients treated with rivaroxaban incident symptoms and signs of liver disease should be considered as a potential adverse drug reaction, and if no other likely cause can be identified rivaroxaban should be stopped as soon as possible.

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We reported all described cases to the national regulatory authority (Swissmedic), from where they are also forwarded to the WHO Uppsala Monitoring Center. The manuscript was sent to Swissmedic before submission for information, but Swissmedic had no active role in the preparation of this manuscript, and the presented views and interpretations do not necessarily reflect those of Swissmedic.

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FIGURE

see separate file (figure_rivaroxaban_russmann.pdf)

LEGEND FOR FIGURE

Liver histology in cases #1 and #2

Histology in the two patients where needle liver biopsies were performed revealed almost identical morphological findings with more pronounced changes in case #2. Liver parenchyma shows a centrilobular accentuated cholestasis (1A arrow) with prominent Kupffer cells and focal ballooning of periportal hepatocytes (1B). There is a mainly portal inflammation of mixed cellularity, focal with many eosinophilic granulocytes and some periductal reinforcement (2A, 1B). Interlobular bile ducts show an alteration of the epithelium with intraepithelial lymphocytes (2B and inset, arrow) and some ductular reaction (2, inset, arrowhead). No ductopenia or fibrosis is present.

(hematoxylin and eosin stain; inset figure 2: cytokeratin 7 immunohistochemistry stain of bile ducts)

TABLE

Table 1 - Case presentations

see separate file (Table1_rivaroxaban_russmann.pdf)

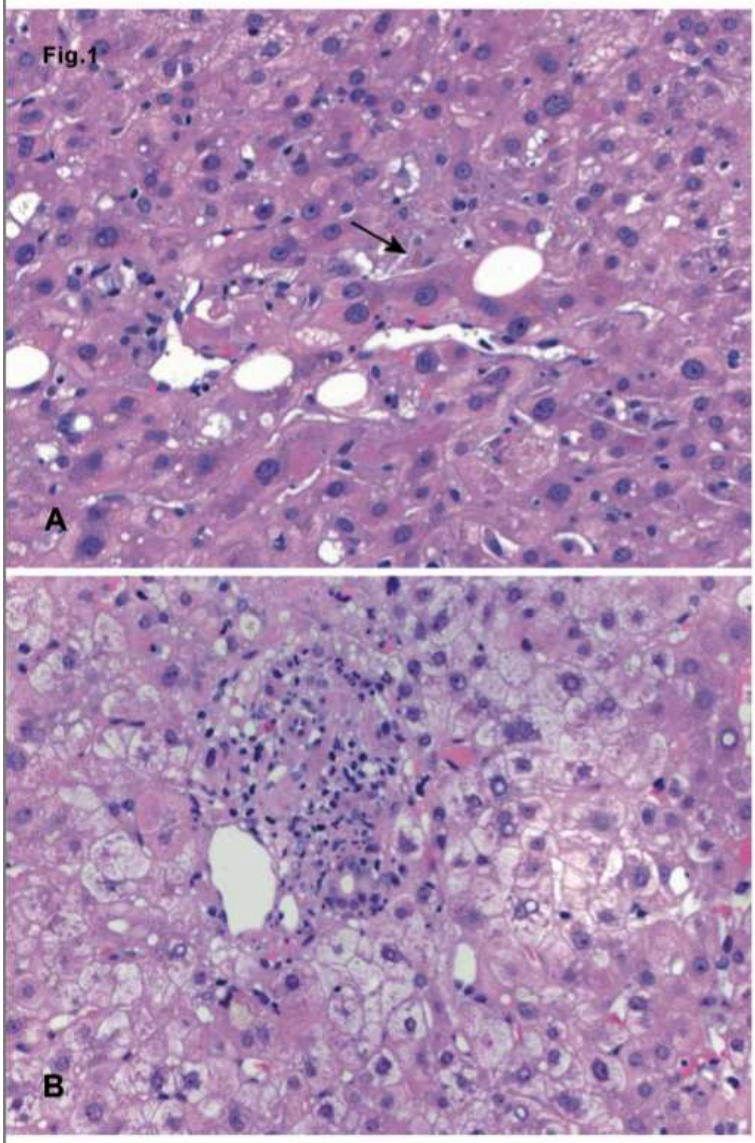
Table 2

Detailed RUCAM causality assessments and scores for all 14 reported cases

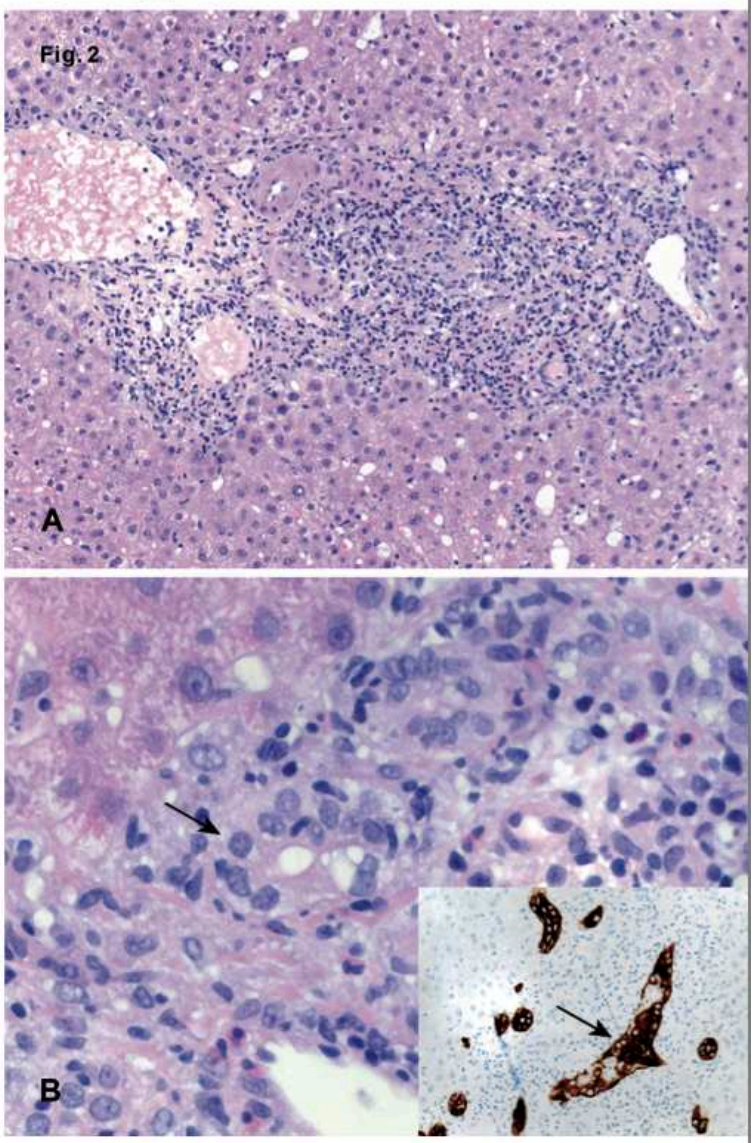
see separate file (Table2_rivaroxaban_russmann.pdf)

Figure (Russmann et al., „Rivaroxaban Postmarketing Risk of Liver Injury")

Liver histology, Case #1



Liver histology, Case #2



(see manuscript for figure legend)

TABLE 1

Case #	Age	Sex	Rivaroxaban indication	Rivaroxaban dose/day	Rivaroxaban treatment duration	Latency time[1]	Symptoms	ALT (xULN)[2] initial max	AP (xULN)[3] initial max	R[4]	TB (xULN)[5] initial max	Outcome	Differential diagnosis	RUCAM[6] causality score	RUCAM[6] causality class	Comments
1	78	m	Knee replacement	20 mg	19 days	14 days	Painless jaundice, nausea	2.5 (day30)	2.9 (day 30)	0.8	15.5 (day 30) 21.6 (day 42)	Death (paralytic ileus)	Vira serology for HBV, HCV, CMV, EBV negative; autoantibodies and imaging negative. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	Liver biopsy performed (see Figure)
2	83	f	Knee replacement	10 mg	21 days	16 days	Painless jaundice, nausea	7.8 (day20)	6.8 (day20) 7.1 (day 29)	1.2	13.9 (day 20) 17.1 (day 27)	Recovery	Viral serology for HAV, HBV, HCV, CMV, EBV negative; autoantibodies and imaging negative. Diclofenac alternative possible cause.	5	Possible	Liver biopsy performed (see Figure)
3	74	m	Atrial fibrillation	20 mg	51 days	<50 days	Painless jaundice	4 (day 51) 5.1 (day 55)	<1 (day 51)	5.1	3.1 (day 51) 3.7 (day 52)	Recovery	Viral serology for HBV negative; IgG and imaging negative. No other suspicious drugs or events causing liver injury identified.	7	Probable	Meets biochemical criteria for Hy's case[7].
4	63	m	Atrial fibrillation	20 mg	6 days	5 days	Nausea and vomiting	7.8 (day 7)	<1 (day 6)	7.8	<1 (day 6)	Recovery	Amiodarone 600 mg/d may be alternative or contributory cause. No other events that suggest alternative cause.	3	Possible	Nausea improved immediately after stop of rivaroxaban while high dose amiodarone was continued (no follow-up of ALT available).
5	91	f	Atrial fibrillation	15 mg	34 days	14 days	Painless jaundice, nausea	2.5 (day 34)	7.8 (day 37)	0.3	8.4 (day 34)	Recovery	Viral serology for HAV, HBV, HCV, HDV, HEV negative; ANA, ANCA, Anti-MPO, Anti-PR3 negative; imaging negative. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	
6	64	f	Atrial fibrillation	20mg	40 days	<40 days	No symptoms	6.3 (day 40)	1.5 (day 40)	4.1	n.a.	Recovery	No other suspicious drugs or events causing liver injury identified.	7	Probable	
7	75	m	Knee replacement	20mg	15 days	15 days	Painless jaundice	10.6 (day 18) 11.3 (day 22)	3.2 (day 18) 6.2 (day 33)	3.4	4.5 (day 18) 9.0 (day 22)	Recovery	Imaging negative; HBV, HCV, EBV, CMV, ANA, Anti-dsDNA and IgG negative. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	
8	69	f	Knee arthroscopy	10mg	10 days	13 days	Fatigue, loss of appetite	2.7 (day 12)	<1 (day 26)	2.7	n.a.	Recovery	No differential diagnostic investigations performed, because presentation and history did not suggest alternative causes. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	"Positive rechallenge": Reexposure to rivaroxaban after knee replacement 6 months later with subsequent increase of AP (2.8 xULN) 11 days after surgery and restart of rivaroxaban; again recovery after stop.
9	61	f	Knee surgery (cruciate ligament plasty)	10mg	24 days	20 days	Jaundice, nausea, pruritus	13.6 (day 24)	1.5 (day 24)	9.3	3.7 (day 24)	Recovery	HBV vaccinated. Acetaminophen possibly contributory but unlikely primary cause (only 3g/day, jaundice and long latency time not typical for intrinsic acetaminophen hepatotoxicity).	6	Probable	Meets biochemical criteria for Hy's case[7]. Acetaminophen may have contributed to ALT increase.
10	60	f	Knee replacement	10mg	17 days	14 days	Jaundice, fatigue, vomiting,	18.6 (day 17) 19.9 (day 20)	n.a.	n.a.	4.2 (day 17) 8.4 (day 13)	Recovery	Imaging negative; HAV, HBV, HCV, ANA, Anti-SLA/SM/mitochondria negative. No other suspicious drugs or events causing liver injury identified.	6	Probable	Meets biochemical criteria for Hy's case[7]. Acetaminophen may have contributed to ALT increase.
11	41	f	Leg surgery after trimalleolar Fx	10mg	27 days	20 days	Jaundice, nausea and vomiting, pruritus	53.7 (day 27)	3.4 (day 27)	15.6	4.8 (day 30)	Recovery	HAV, HBV, HCV, HEV, CMV, EBV, ANA and Anti-sm negative, IgG normal. Imaging negative. No other suspicious drugs or events causing liver injury identified.	7	Probable	Meets biochemical criteria for Hy's case[7]. Acetaminophen may have contributed to ALT increase.
12	78	f	Knee replacement	10mg	62 days	62 days	Jaundice, nausea, diarrhea	14 (day 62)	2.1 (day 62)	6.5	n.a.	Recovery	Acetaminophen postoperatively not documented but possible. No suggestion for alternative causes but no formal exclusion.	5	Possible	
13	73	m	Knee replacement	10mg	3 days	3 days	Jaundice, nausea, mild pain	6.1 (day 5)	2.5 (day 5)	2.5	n.a.	Recovery	Imaging negative. No other suspicious drugs or events causing liver injury identified.	6	Probable	Unusually short latency time. Cefazolin preoperative single i.v. application, but cefazolin previously well tolerated.
14	42	f	Leg surgery after Maisonneuve-Fx	10mg	31 days	29 days	Jaundice, nausea	23.5 (day 30)	3.2 (day 30)	7.3	2.8 (day 30) 3.0 (day 54)	Recovery	Viral serology and autoantibodies negative. No other suspicious drugs or events causing liver injury identified.	8	Probable	

Legend Table 1

[1] Time from start of rivaroxaban to first symptoms or signs of liver injury.

[2] Alanine aminotransferase, expressed as multiples of upper limit of normal. Time in relation to start of rivaroxaban.

[3] Alkaline phosphatase, expressed as multiples of upper limit of normal. Time in relation to start of rivaroxaban.

[4] Laboratory classification of drug-induced liver injury (see also reference 2), where R = ratio ALT/AP, where both are expressed as multiples of upper limit of normal

[5] Total bilirubin, expressed as multiples of upper limit of normal. Time in relation to start of rivaroxaban.

[6] Roussel Uclaf Causality Assessment Method, endorsed by the Council of International Organizations of Medical Sciences (see also references 1 and 2).

[7] Hy's case criteria: ALT >3x ULN and TB >2x ULN without initial AP increase / cholestatic enzyme pattern (see also reference 6).

Supplemental material S1 - Detailed RUCAM causality assessments and scores for all 14 reported cases

Case #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
RUCAM criteria								score						
hepatocell or chol/mix	chol	chol	hepatocell	hepatocell	chol	mix	mix	?	hepatocell	?	hepatocell	hepatocell	mix	hepatocell
1 (temporal relationship)	2	2	2	2	2	2	2	1	2	2	2	2	1	2
2 (course after drug cessation)	2	0	2	0	2	2	1	2	3	2	3	2	2	2
3.1 (risk factors, alcohol)	0	0	0	0	0	0	1	0	0	0	0	0	0	0
3.2 (risk factors, age)	1	1	1	1	1	1	1	1	1	1	0	1	1	0
4 (concomitant drugs)	0	-2	0	-2	0	0	0	-2	-2	-2	-2	-2	0	0
5 (exclusion of non-drug causes)	2	2	0	0	2	0	2	2	0	1	2	0	0	2
6 (labeling / previous information on hepatotoxicity)	2	2	2	2	2	2	2	2	2	2	2	2	2	2
7 (rechallenge)	0	0	0	0	0	0	0	3	0	0	0	0	0	0
TOTAL SCORE	**9**	**5**	**7**	**3**	**9**	**7**	**9**	**9**	**6**	**6**	**7**	**5**	**6**	**8**
Score interpretation	**highly prob**	**possible**	**probable**	**possible**	**highly prob**	**probable**	**highly prob**	**highly prob**	**probable**	**probable**	**probable**	**possible**	**probable**	**probable**

For detailed description of RUCAM criteria see also references 1 (Aithal et al. 2011) and 2 (Danan and Benichou 1993)

SUPPLEMENTAL MATERIAL *(may be used for online only publication)*

S1

Detailed search criteria and results for hepatobiliary disorders compatible with drug-induced liver injury in international pharmacovigilance databases

see separate file (S1_rivaroxaban_russmann.pdf)

Supplemental material S2 - Detailed search criteria and results for hepatobiliary disorders compatible with drug-induced liver injury in international pharmacovigilance databases

WHO UMC VigiBase

Access date 2013-11-28

WHO-ART reaction term	n total events
Cholestasis	10
Hepatitis cholestatic	9
Jaundice	45
Liver disorder	11
Liver injury	7
Acute hepatic failure	5
Hepatic failure	17
Drug-induced liver injury	10
Hepatitis	9
Hepatitis acute	4
Hepatitis toxic	5
Hepatotoxicity	5
Alanine aminotransferase increased	48
Jaundice cholestatic	1
Hepatocellular injury	9
Subacute hepatic failure	1
Blood bilirubin increased	23
Jaundice hepatocellular	1
Mixed liver injury	2
Total WHO-ART reaction terms (events)	**222**
	n total individual cases
after exclusion of several events / case	**179**

EMA EudraVigilance

Access date 2013-11-03, data censored 30 September 2013

MedDRA Preferred Term	n total events
acute hepatic failure	12
cholestasis	20
cholestatic liver injury	6
drug induced liver injury	19
hepatic failure	24
hepatic function abnormal	30
hepatitis	29
hepatitis acute	5
hepatitis cholestatic	9
hepatitis toxic	7
hepatocellular injury	37
hepatotoxicity	8
jaundice	65
jaundice cholestatic	1
jaundice hepatocellular	1
liver disorder	25
liver injury	4
mixed liver injury	3
subacute hepatic failure	1
alanine aminotransferase increased	43
blood bilirubin increased	26
Total Preferred Terms (events)	**375**

no preferred term level access for exclusion of several events/case

(n individual cases for all hepatobiliary disorders = 298)

US FDA FAERS

Extracted in November 2013, data censored 31 December 2012

MedDRA Preferred Term	n total events
acute hepatic failure	2
cholestasis	11
cholestatic liver injury	2
drug induced liver injury	7
hepatic failure	11
hepatic function abnormal	3
hepatitis	16
hepatitis acute	2
hepatitis cholestatic	3
hepatitis toxic	1
hepatocellular injury	2
hepatotoxicity	1
jaundice	20
jaundice cholestatic	1
jaundice hepatocellular	0
liver disorder	10
liver injury	8
mixed liver injury	2
subacute hepatic failure	1
alanine aminotransferase increased	17
blood bilirubin increased	10
Total Preferred Terms (events)	**130**
	n total individual cases
after exclusion of several events / case	**87**