

AM Slišković¹, L Šimičević², M Vrkić Kirhmajer^{1,3}, L Ganoci², H Holik⁴, J Samardžić^{1,3}, T Božina⁵

1 Department of Cardiology, UHC Zagreb, University of Zagreb, School of Medicine, Zagreb; 2 Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, UHC Zagreb, University of Zagreb, School of Medicine, Zagreb; 3 Department of Internal Medicine, “Dr. Josip Benčević” General Hospital, Slavonski Brod; 4 Department of Medical Chemistry, Biochemistry and Clinical Chemistry, School of Medicine, University of Zagreb, Zagreb, Croatia

BACKGROUND

- Rivaroxaban (RIVA) interindividual trough concentration variability could be associated with age, liver and kidney function, concomitant illness and therapy, and pharmacogenetic findings.
- RIVA is a substrate of ABCB1 and ABCG2 drug transporters, and CYP2J2, CYP3A4/5 metabolic enzymes.
- The polymorphisms of these genes may affect the pharmacokinetics of RIVA and consequently its safety profile.
- Pharmacogenetic knowledge is still insufficient for clinical application.

AIM

- To determine possible gene variants [CYP3A4, CYP3A5, CYP2J2, ABCB1 (MDR1), and ABCG2], who may be predictors of RIVA-associated bleeding.
- To evaluate possible clinical and genetic risk factors for RIVA-associated bleeding in patients treated for cardiovascular diseases.

RESULTS

- Sixteen patients (median age 73 years, range 61-80)
- RIVA dose range 5-20 mg, median 17.5 mg, mean 16.6±4.4)
- RIVA-associated bleeding: gastrointestinal (N=9), epistaxis (N=5), haematuria (N=1) and gynaecological (N=1)
- In 9/16 DDI with increased bleeding risk were found.
- Two patients had eGFR>90, while six patients had eGFR<60.
- Two patients were CYP3A4*22 carriers (*1/*22 and *22/*22), three were CYP3A5*3 heterozygous, four were CYP2J2*7 heterozygous, two patients had ABCB1 T/T+T/T genotype, four ABCG2 C/A and one A/A genotype.
- Three patients who experienced bleeding did not have any of investigated risk factors.

Age	Sex	CYP3A4		CYP3A5		CYP2J2		MDR1			ABCG2		RIVA - adverse event	RIVA DD (mg)	eGFR (mL/min)	DDI	Bleeding risk / RIVA conc.	
		*1B	*22	*3	*7	rs11572325	rs1128503	rs1045642	rs2032582	rs4148738	rs2231142	C/A						A/A
1	68	M	*1/*1	*1/*1	*3/*3	*1/*1	A/A	C/C	C/C	G/G	G/G	C/C	C/C	GI bleeding	20	88		/
2	80	F	*1/*1	*1/*1	*3/*3	*1/*1	A/A	T/T	T/T	T/T	A/A	C/A	C/A	GI bleeding	15	38	RIVA-Duloxetine	RIVA-duloxetine
3	64	M	*1/*1	*1/*1	*3/*3	*1/*1	A/A	C/C	C/C	G/G	G/G	C/C	C/C	GI bleeding	20	100		/
4	75	M	*1/*1	*1/*1	*3/*3	*1/*1	A/A	C/T	C/T	G/T	G/A	C/C	C/C	GI bleeding	20	43	RIVA-Indomethacin	Bleeding risk may be increased
5	66	M	*1/*1	*1/*1	*1/*3	*1/*1	A/A	C/T	C/T	G/T	G/A	C/C	C/C	Haematuria	15	89	RIVA-Propafenone	ABCB1 Inhibitors may increase the serum RIVA conc.
6	66	F	*1/*1	*1/*1	*3/*3	*1/*1	A/A	C/C	C/C	G/G	G/G	C/C	C/C	Epistaxis	20	105		/
7	75	F	*1/*1	*1/*1	*1/*3	*1/*7	A/T	C/T	C/T	G/T	G/A	C/C	C/C	Epistaxis	15	35	RIVA-ASA; RIVA-Ketoprofen	Bleeding risk may be increased
8	72	F	*1/*1	*1/*1	*1/*3	*1/*7	A/T	C/C	C/C	G/G	G/G	C/A	C/A	Epistaxis	20	88		/
9	75	M	*1/*1	*1/*1	*3/*3	*1/*1	A/T	C/T	C/T	G/T	G/A	C/C	C/C	GI bleeding	15	54	RIVA-Amiodarone	ABCB1 Inhibitors may increase the serum RIVA conc.
10	76	F	*1/*1	*1/*1	*3/*3	*1/*1	A/A	C/C	C/C	G/G	G/G	C/A	C/A	GI bleeding	15	34		/
11	61	F	*1/*1	*22/*22	*3/*3	*1/*7	A/T	C/T	C/T	G/T	G/A	C/C	C/C	Gynaecological bleeding	10	85	RIVA-ASA	Bleeding risk may be increased
12	75	F	*1/*1	*1/*1	*3/*3	*1/*1	A/T	C/T	C/T	G/T	G/A	C/C	C/C	GI bleeding	15	61	RIVA-Amiodarone RIVA-Clopidogrel	ABCB1 Inhibitors may increase the serum RIVA conc. Bleeding risk may be increased
13	78	M	*1/*1	*1/*1	*3/*3	*1/*7	A/T	T/T	T/T	T/T	AA	C/C	C/C	Epistaxis	5	70	RIVA-ASA	Bleeding risk may be increased
14	74	F	*1/*1	*1/*1	*3/*3	*1/*1	A/A	C/T	C/T	G/G	G/G	C/C	C/C	GI bleeding	20	48	RIVA-Amiodarone	ABCB1 Inhibitors may increase the serum RIVA conc.
15	69	F	*1/*1	*1/*1	*3/*3	*1/*1	A/A	C/T	C/T	G/T*	G/A	C/C	C/C	Epistaxis	20	82		/
16	66	M	*1/*1	*1/*22	*3/*3	*1/*1	A/A	C/C	C/C	G/G	G/A	A/A	A/A	GI bleeding	20	63		/

CONCLUSION

Our results suggest a possible joint role of clinical and pharmacogenetic factors in predicting RIVA-associated bleeding. These findings indicate the need for further comprehensive research.

PATIENTS AND METHODS

- Part of the large prospective nested case-control study “Pharmacogenomics in Prediction of Cardiovascular Drugs Adverse Reaction”.
- Planned study period 4.5 years.
- Subjects with a newly established indication for RIVA administration; as monotherapy or without limitation in relation to any other concomitant therapy.
- Study is going on for 16 months and 450 patients have been recruited.
- Clinical and laboratory data were collected.
- Pharmacogenetic analyses were performed using specific TaqMan® DME and SNP Assays on 7500 Real-Time PCR System (Applied Biosystems, USA) for genotyping of
 - CYP3A4*1B,*22
 - CYP3A5*3,
 - CYP2J2*7, c.1331-2201T>C,
 - ABCB1 (MDR1) c.1236C>T, c.2482-2236G>A, c.2677G>T/A, c.3435C>T
 - ABCG2 (c.421C>A)
- For drug-drug interactions (DDI), The Lexicomp® Clinical Decision Support System was applied.