Rivaroxaban

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Rivaroxaban (BAY 59-7939) is an oral anticoagulant invented and manufactured by Bayer; in a number of countries it is marketed as Xarelto. In the United States, it is marketed by Janssen Pharmaceutica.

It is the first available orally active direct factor Xa inhibitor. Rivaroxaban is well absorbed from the gut and maximum inhibition of factor Xa occurs four hours after a dose. The effects last approximately 8–12 hours, but factor Xa activity does not return to normal within 24 hours so once-daily dosing is possible [1)].

Indications

Rivaroxaban is a direct factor Xa inhibitor used to prevent and treat various thromboembolic events, such as those in atrial fibrillation, deep vein thrombosis, and pulmonary embolism.

Thrombolysis and/or endovascular thrombectomy might be safe for patients treated with the new anticoagulant rivaroxaban [2)].

Rivaroxaban for deep-vein thrombosis treatment

Complications

Rivaroxaban complications.

Andexanet alfa, an antidote for the anticoagulant medications rivaroxaban and apixaban, is used in cases of uncontrolled bleeding requiring rapid reversal of anticoagulation. This decoy molecule neutralizes the anticoagulant effects of these medications by binding to them in the bloodstream. Andexanet alfa is administered intravenously in emergency situations and should be closely monitored by healthcare professionals. It is essential for patients on direct oral anticoagulant therapy to be aware of this antidote's availability in emergencies or surgeries.

Case series

Although rivaroxaban is widely prescribed to reduce their risk of stroke in patients with nonvalvular atrial fibrillation (NVAF), the real-world evidence on rivaroxaban treatment is limited. Minematsu et al. aimed to examine the outcomes of rivaroxaban treatment in NVAF patients with prior ischemic stroke/transient ischemic attack (TIA) by using the data of the Xarelto Post-Authorization Safety and Effectiveness Study in Japanese -Patients with AF, a prospective, single-arm, observational study.

The clinical outcomes of 9,578 patients who completed the 1-year follow-up were evaluated. Safety and effectiveness outcomes were compared between patients with and without prior ischemic stroke/TIA.

Among the patients, 2,153 (22.5%) had prior ischemic stroke/TIA. They were significantly older and had lower body weight, lower creatinine clearance, higher CHADS2, CHA2DS2-VASc, and modified HAS-BLED scores as compared to those without prior ischemic stroke/TIA. Any bleeding (9.1 vs. 7.2 events per 100 patient-years), major bleeding (2.3 vs. 1.6 events per 100 patient-years), and stroke/non-central nervous system systemic embolism/myocardial infarction (3.4 vs. 1.3 events per 100 patient-years) were more frequent in patients with prior ischemic stroke/TIA. Stepwise regression analysis suggested that body weight of ≤50 kg and diabetes mellitus were predictive of major bleeding in patients with prior ischemic stroke/TIA.

Safety and effectiveness event rates were higher in patients with prior ischemic stroke/TIA than those without. This might be explained by differences in several risk profiles including age, body weight, renal function, and risk scores such as CHADS2 between the groups. Clinicaltrials.gov: NCT01582737 [3)].

2018

In a multicenter registry based study (Novel-Oral-Anticoagulants-In-Stroke-Patients collaboration;NOACISP;ClinicalTrials.gov:NCT02353585) of patients with stroke while taking rivaroxaban, we compared Rivaroxaban plasma levels (RivLev) in patients with acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH). Seiffge et al. determined how many AIS-patients had RivLev≤100ng/ml, indicating possible eligibility for thrombolysis and how many ICH-patients had RivLev≥75ng/ml, possibly eligible for the use of specific reversal agents. We explored factors associated with RivLev (Spearman correlation; regression models) and studied the sensitivity and specificity of INR-thresholds to substitute RivLevs using cross tables and ROC curves.

Among 241 patients (median age 80 years[IQR73-84], median time-from-onset-to-admission 2 hours[IQR1-4.5hours], median RivLev 89ng/ml[31-194]), 190 had AIS and 51 had ICH. RivLev were similar in AIS-patients (82ng/ml[IQR30-202] and ICH-patients (102ng/ml[IQR 51-165]; p=0.24). Trough RivLev(≤137ng/ml) occurred in 126/190 (66.3%) AIS- and 34/51 (66.7%) ICH-patients. Among AIS-patients, 108/190 (56.8%) had RivLev≤100ng/ml. In ICH-patients 33/51(64.7%) had RivLev≥75ng/ml. RivLev were associated with rivaroxaban dosage, inversely with renal function and time-since-last-intake (each p<.05). INR≤1.0 had a specificity of 98.9% and a sensitivity of 25.7% to predict RivLev≤100ng/ml. INR≥1.4 had a sensitivity of 59.3% and specificity of 90.1% to predict RivLev≥75ng/ml.

RivLev did not differ between patients with AIS and ICH. Half of the patients with AIS under Rivaroxaban had RivLev low enough to consider thrombolysis. In ICH-patients, 2/3 had RivLev high

enough to meet the eligibility for the use of a specific reversal agent. INR-thresholds perform poor to inform treatment decisions in individual patients [4].

2015

A total of 70 patients with traumatic intracranial hemorrhage (tICH) after mild traumatic brain injury (TBI) were included in a retrospective analysis and were categorized into three groups: group A (no antithrombotics n=37), group B (antiplatelet medication n=22, VKA=5), and group C (rivaroxaban n=6). Medical charts were reviewed for baseline characteristics, laboratory values, intracranial haemorrhage, repeated computed tomography (CT) scans, re-haemorrhage, Glasgow Coma Scale (GCS) scores and in-Hospital mortality.

No significant differences were observed for baseline characteristics. The rate of re-haemorrhage was significantly higher in group C (50%) than in group A (11%) ($p<0.05$). Two patients died and both had been treated with rivaroxaban which resulted in a significantly higher mortality rate of 33% in group C compared with groups A (0%) and B (0%). No significant differences were observed for GCS at discharge and length of hospital stay between survivors of groups A-C.

Despite major limitations of retrospective design and small patient numbers, the results suggest that rivaroxaban may exacerbate intracranial hemorrhage in patients with mild TBI. Further studies are needed to characterize the risk profile of this drug in patients with tICH [5].

Case reports

2016

First case described in the literature of spontaneous intracranial epidural hematoma secondary to the use of Xareltor. Spontaneous intracranial epidural hematomas are rarely described in the literature. They are associated with infectious diseases of the skull, coagulation disorders, vascular malformations of the dura mater and metastasis to the skull. Long-term post-marketing monitoring and independent reports will probably detect the full spectrum of hemorrhagic complications of the use of rivaroxaban [6].

2015

The clinical and radiologic findings and follow-up of an 80-year-old male patient with intracerebral hemorrhage who uses rivaroxaban for anticoagulation are presented in the article of Çalışkan et al. [7].

2014

Ishihara et al. report an acute stroke patient taking rivaroxaban who received intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA). An 80-year-old man with a history of nonvalvular atrial fibrillation, who had been receiving 10 mg of rivaroxaban showed abrupt onset of aphasia and right hemiparesis. National Institutes of Health Stroke Scale score was 10. Onset

of neurologic deficits occurred 4 hours after the last dose of rivaroxaban. Clinical data on admission were as follows: blood pressure, 170/90 mm Hg; prothrombin time (PT), 22.6 seconds (control, 12.9 seconds); international normalized ratio, 2.03; activated partial thromboplastin time, 46 seconds (normal, 23-32 seconds); and creatinine level, 1.11 mg/dL. Magnetic resonance angiography revealed occlusion of the superior trunk of the left middle cerebral artery. Intravenous infusion of .6 mg/kg of rt-PA (total dose, 36 mg) was performed 6 hours after the last rivaroxaban administration with informed consent. The neurologic deficit improved during infusion of rt-PA. Repeat brain computed tomography showed left frontal cortical infarction without hemorrhagic changes. In the case of rivaroxaban, it is difficult to accurately determine the drug activity. As the anticoagulant activity of rivaroxaban can be estimated from its pharmacokinetics and PT, it is clinically important to obtain accurate information about the timing of medication and blood sampling [8].

Till 2015, only three published cases report the incidence of rivaroxaban-induced nontraumatic spinal subdural hematoma (SSDH) [9].

A 83-year-old woman had a medical history with ischemic stroke due to paroxysmal atrial fibrillation and was then administered 10 mg of rivaroxaban daily. Although she took rivaroxaban in the morning, ischemic stroke recurred at midnight of that day. Soon after transferring to the hospital, Kimura et al. confirmed right middle cerebral artery (MCA) occlusion in the patient and then initiated treatment with intravenous rt-PA. Although no hemorrhagic complication occurred, recovery of her symptoms was not seen, and endovascular thrombectomy was performed. Although the inferior branch of the MCA was recanalized, an infarct was seen in her left frontal lobe. Hemorrhagic transformation was not observed during or after these combined treatments [10].

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