VEGF inhibitors: arterial aneurysm and dissection

● Cases of arterial aneurysm or dissection have been reported with VEGF inhibitors, such as *bevacizumab*, used to treat cancer. Systemic administration and hypertension, a known adverse effect of these anti-angiogenic drugs, are risk factors.

● In practice, monitoring is warranted for patients treated with VEGF inhibitors, especially those with cardiovascular risk factors.

Drugs that target vascular endothelial growth factor (VEGF) inhibit angiogenesis and are mainly used to treat diseases involving vascular proliferation, in particular cancer and certain eye conditions (by intravitreal administration). They can provoke cardiovascular disorders such as hypertension, heart failure and arterial or venous thromboembolic events (1).

In 2019, the European Pharmacovigilance Risk Assessment Committee (PRAC) reported arterial dissections or aneurysms linked to the use of VEGF inhibitors (2).

Hundreds of cases, sometimes fatal. In late 2018, the European pharmacovigilance database contained several hundred cases of arterial dissection or aneurysm, recorded since the market introduction of the various VEGF inhibitors: 256 cases were reported with *bevacizumab*, 249 with *ranibizumab*, 79 with *sunitinib* and 43 with *sorafenib.* Fewer cases were described with other VEGF inhibitors (2).

A PRAC report published in late 2018 mentioned 26 fatal cases of aortic dissection or aneurysm attributed to *sunitinib* (3).

Our literature search identified about 15 case reports of arterial aneurysm, pseudoaneurysm or dissection in patients treated with a VEGF inhibitor. They occurred at various sites: the coeliac trunk, inferior pancreaticoduodenal artery, aorta or cervical artery (4-13). In most cases, the VEGF inhibitor had been used to treat cancer. Some patients had no history of cardiovascular disease, but at least two patients had hypertension before exposure to the VEGF inhibitor. The time to diagnosis of the disorders ranged from about 20 days to several months after starting VEGF inhibitor therapy; in several cases, the disorders resolved after discontinuing the VEGF inhibitor (4-11).

20-fold risk of aortic dissection. In a study based on data from a Japanese pharmacovigilance database, 91 055 patients were identified as having undergone treatment for cancer; 16 441 of these patients had been treated with at least one VEGF inhibitor, and 74 614 of them had not been exposed to this type of drug. The risk of aortic dissection was about 20 times greater (95% confidence interval: 10-41) in patients exposed to VEGF inhibitors (49 cases) than in unexposed patients (10 cases). The median time to onset was 105 days (range: 4 days to 1363 days) (7).

A retrospective study conducted in Latin America in 1173 patients treated with intravitreal *bevacizumab* for eye disorders identified 2 iliac artery aneurysms (5).

Disruption of vessel remodelling. VEGF induces the formation of new blood vessels by stimulating endothelial cell proliferation. VEGF inhibitors on the other hand contribute to endothelial cell apoptosis (genetically programmed cell death). VEGF inhibitors can therefore alter the structure of vascular endothelium, exposing patients to the risk of haemorrhagic and thrombotic complications (6).

Hypertension, which can be caused by VEGF inhibitors, is another major risk factor for aortic dissection (7,8,10).

In practice VEGF inhibitors can cause arterial aneurysm and dissection. This risk should be taken into account and warrants careful monitoring of exposed patients, especially those with other cardiovascular risk factors. Urgent investigation is required when a patient receiving a VEGF inhibitor develops abdominal or chest pain or signs of ischaemia.

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Literature search up to 20 January 2020

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