


SHORT REPORT

Tyrosine kinase inhibitors targeting vascular endothelial growth factor and the risk of aortic dissection—A pharmacovigilance analysis

Michael Dörks¹  | Kathrin Jobski¹  | Stefan Herget-Rosenthal² | Falk Hoffmann¹ | Antonios Douros^{3,4,5} 

¹Department of Health Services Research, Carl von Ossietzky University Oldenburg, Oldenburg, Germany

²Department of Medicine, Rotes Kreuz Hospital, Bremen, Germany

³Departments of Medicine and Epidemiology, McGill University, Montreal, QC, Canada

⁴Centre for Clinical Epidemiology, Lady Davis Institute - Jewish General Hospital, Montreal, QC, Canada

⁵Institute of Clinical Pharmacology and Toxicology, Charité-Universitätsmedizin Berlin, Berlin, Germany

Correspondence

Michael Dörks, Department of Health Services Research, Carl von Ossietzky University Oldenburg, Ammerländer Heerstr. 140 V04, D - 26129 Oldenburg, Germany.
Email: michael.doerks@uni-oldenburg.de

Funding information

There was no funding for this study.

Abstract

There are concerns by the United States Food and Drug Administration (FDA) regarding a potential link between tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF-TKIs) and the risk of aortic dissection. Elevation of blood pressure induced by VEGF-TKIs has been discussed as part of the pathomechanism. To address this important safety issue, we conducted a large pharmacovigilance study assessing the risk of aortic dissection reporting associated with the use of VEGF-TKIs, thereby exploring the role of blood pressure. We queried the FDA Adverse Event Reporting System from 2004 to 2019 for reports including VEGF-TKIs and aortic dissection and estimated reporting odds ratios (RORs) and 95% confidence intervals (CIs) of aortic dissection associated with the use of VEGF-TKIs. Secondary analyses stratified by the strength of blood pressure elevation (≥ 10 mmHg vs. < 10 mmHg increased systolic or diastolic bloods pressure) and pre-existing arterial hypertension. There were 81 reports of aortic dissection related to VEGF-TKIs during the study period. VEGF-TKIs were associated with an increased risk of aortic dissection reporting (ROR, 4.31; 95% CI, 3.43 to 5.42). The risk was higher among compounds strongly increasing blood pressure (ROR, 5.33; 95% CI, 3.88 to 7.32) than among compounds moderately increasing blood pressure (ROR, 2.79; 95% CI, 1.83 to 4.27). Pre-existing arterial hypertension did not modify the association. Overall, our study showed an increased risk of aortic dissection reporting associated with the use of VEGF-TKIs. Blood pressure elevation seems to play a role in the pathophysiology of this adverse effect.

KEYWORDS

cardiovascular toxicity, drug safety, tyrosine kinase inhibitors

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.

1 | INTRODUCTION

Tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF-TKIs) suppress angiogenesis in several cancers and have shown high efficacy in randomized controlled trials.¹ However, there are ongoing concerns by regulatory agencies such as the United States (US) Food and Drug Administration (FDA) with respect to their cardiovascular safety and particularly the potential risk of aortic dissection.² Indeed, multiple case reports have linked the use of VEGF-TKIs to this often-fatal adverse effect.^{3,4} The hypothesized pathomechanism involves an elevation of blood pressure caused by VEGF-TKIs with accompanying vascular rarefaction, endothelial dysfunction, and vasoconstriction.^{1,3}

To date, there has been only one observational study in the area.⁵ This study was based on Japanese pharmacovigilance data and assessed the risk of aortic dissection reporting associated with the use of VEGF pathway inhibitors overall (also including VEGF receptor antibodies such as bevacizumab) and not specifically VEGF-TKIs.⁵ Moreover, the elevation of blood pressure induced by VEGF-TKIs was not considered in the analyses, which precluded inferences about its potential role in the pathophysiology of the adverse effect. Given the scarcity of available clinical evidence, we conducted a large pharmacovigilance analysis to assess the risk of aortic dissection reporting associated with the use of VEGF-TKIs, with a specific focus on blood pressure elevation.

2 | MATERIALS AND METHODS

For the present study, we used the US FDA Adverse Event Reporting System (FAERS) database. The FAERS is a database that contains adverse event reports, medication error reports, and product quality complaints resulting in adverse events that were submitted to the FDA. It is based on voluntary reporting by health-care professionals and patients as well as mandatory reporting by pharmaceutical companies.⁶ The FAERS was queried from the third quarter of 2004 (when the first report with a VEGF-TKI was submitted to the FAERS) to the third quarter of 2019 (most recent data available at the time of the analysis) for reports including VEGF-TKIs (i.e., axitinib, cabozantinib, lenvatinib, nintedanib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, and vandetanib) documented as a “primary suspect” drug. To define the study outcome, we used the Medical Dictionary for Regulatory Activities terms “aortic dissection” and “aortic dissection rupture”.

In the primary analysis, we estimated crude as well as age- and sex-adjusted RORs and accompanying 95% CIs of aortic dissection associated with the use of VEGF-TKIs, as compared to all other drugs in the FAERS. The crude ROR is calculated using the formula $(a/b) / (c/d)$, where *a* is the number of cases using VEGF-TKIs and developing aortic dissection, *b* is the number of cases using VEGF-TKIs and developing adverse events other than aortic dissection, *c* is the number of cases using drugs other than VEGF-TKIs and developing aortic dissection, and *d* is the number of cases using drugs other

what is already known about this subject

- There are concerns by regulatory agencies regarding a potential link between tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF-TKIs) and the risk of aortic dissection.
- The hypothesized pathomechanism of this adverse effect involves an elevation of blood pressure caused by VEGF-TKIs.

what this study adds

- Our large pharmacovigilance study showed that VEGF-TKIs are associated with an almost 4-fold increase in the risk of aortic dissection reporting.
- The risk was higher among compounds strongly increasing blood pressure than among compounds moderately increasing blood pressure.

than VEGF-TKIs and developing adverse events other than aortic dissection.⁷

In secondary analyses, we examined the role of blood pressure elevation given its potential role in the pathophysiology of the adverse effect. First, leveraging recently published data about the effects of several VEGF-TKIs (i.e., axitinib, cabozantinib, pazopanib, sorafenib, and sunitinib) on blood pressure,¹ we stratified the respective compounds by strength of blood pressure elevation (“strong” vs. “moderate”; see below). The average increase in blood pressure due to VEGF-TKIs is 8.5 mmHg for systolic blood pressure and 6.7 mmHg for diastolic blood pressure.¹ Thus, we chose an elevation of 10 mmHg in systolic or diastolic blood pressure, a clinically significant change, as the “cut-off” for the stratification. The two groups were: (i) compounds strongly elevating blood pressure (defined as ≥ 10 mmHg increase in systolic or diastolic blood pressure) including axitinib and sunitinib, and (ii) compounds moderately elevating blood pressure (defined as < 10 mmHg increase in systolic and diastolic blood pressure) including cabozantinib, pazopanib, and sorafenib.¹ Other compounds were not considered in this secondary analysis due to the lack of respective data on blood pressure. Second, we stratified our analyses by pre-existing arterial hypertension using information from the comorbidity section of the case reports. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina, USA). RORs were obtained using the SAS procedure `proc logistic`.

3 | RESULTS

Overall, there were 6,395,662 cases with valid information on age and sex submitted to the FAERS during the study period (overall 11,014,871 cases). Among those, 1186 cases referred to aortic dissection and 71,717 cases involved the use of VEGF-TKIs. Specifically,

there were 81 reports of aortic dissection that involved VEGF-TKIs, with the most commonly documented compounds being sunitinib ($n = 34$), sorafenib ($n = 19$), and lenvatinib ($n = 9$). In these 81 reports, the median time-to-onset was 89.5 days (interquartile range: 15 to 393 days).

Compared to all other drugs in the FAERS, the use of VEGF-TKIs was associated with an increase in the risk of aortic dissection reporting (ROR, 4.31; 95% CI, 3.43 to 5.42) (Table 1). The risk of aortic dissection reporting was higher among VEGF-TKIs strongly increasing blood pressure (ROR, 5.33; 95% CI, 3.88 to 7.32) than among VEGF-TKIs moderately increasing blood pressure (ROR, 2.79; 95% CI, 1.83 to 4.27). Moreover, the risk was similar between patients with pre-existing arterial hypertension (ROR, 5.21; 95% CI, 2.88 to 9.41) and those without pre-existing arterial hypertension (ROR, 4.27; 95% CI, 3.34 to 5.47) (Table 1).

4 | DISCUSSION

Our large pharmacovigilance analysis identified a more than 4-fold increase in the risk of aortic dissection reporting associated with the use of VEGF-TKIs. Importantly, the risk was even more pronounced among compounds strongly increasing blood pressure, concordant with previous observations showing a “dose-response” relation between blood pressure elevation and aortic aneurysms.⁸ Pre-existing arterial hypertension, however, did not seem to modify

the association. Thus, we hypothesize that a de novo elevation of blood pressure due to the use of VEGF-TKIs rather than pre-existing hypertensive disease could be involved in the development of aortic dissection.

The risk of aortic dissection reporting associated with the use of VEGF-TKIs observed in our study was lower than what was previously shown by Oshima et al (ROR [95% CI] 19.4 [10.2 to 40.8]).⁵ However, directly comparing the results of the two studies is challenging given the several differences in design and analysis. First, Oshima et al. considered all VEGF pathway inhibitors and did not focus on VEGF-TKIs. Second, they restricted their study population to patients with a cancer diagnosis. Third, they adjusted only for arterial hypertension, while we adjusted for age and sex. That being said, we think that our results corroborate the results by Oshima et al, since they provide further evidence of a link between the use of VEGF-TKIs and the development of aortic dissection.

Our study has the following strengths. First, the large sample size of the FAERS allowed us to quantify the risk of reporting of aortic dissection, which is a rare adverse effect. Moreover, we assessed this risk in clinically important subgroups. Second, taking into account the role of blood pressure, we were able to provide useful mechanistic insights. Expectedly, the main limitation of our study is underreporting and other reporting biases inherent to the utilized data source. Moreover, while we adjusted for age and sex, we were not able to adjust for other potential confounders such as smoking or infections, since respective data are not available in the FAERS.

TABLE 1 Crude and adjusted RORs for the association between the use of VEGF-TKIs and the risk of aortic dissection reporting

| | Cases with aortic dissection | Crude ROR ³ (95% CI) | Adjusted ⁴ ROR (95% CI) |
|---|------------------------------|---------------------------------|------------------------------------|
| Primary analysis | | | |
| VEGF-TKIs overall | 81 | 6.47 (5.16 to 8.11) | 4.31 (3.43 to 5.42) |
| Secondary analyses | | | |
| VEGF-TKIs strongly increasing blood pressure ¹ | 40 | 8.10 (5.91 to 11.11) | 5.34 (3.88 to 7.32) |
| VEGF-TKIs moderately increasing blood pressure ² | 22 | 4.24 (2.78 to 6.46) | 2.79 (1.83 to 4.27) |
| VEGF-TKIs in patients with arterial hypertension | 12 | 6.85 (3.81 to 12.32) | 5.20 (2.88 to 9.41) |
| VEGF-TKIs in patients without arterial hypertension | 69 | 6.46 (5.06 to 8.25) | 4.27 (3.34 to 5.47) |

Abbreviations: CI, confidence interval; ROR, reporting odds ratio.

¹Includes axitinib and sunitinib. Defined as an increase of ≥ 10 mmHg in systolic or diastolic blood pressure.¹

²Includes cabozantinib, pazopanib and sorafenib. Defined as an increase of < 10 mmHg in systolic and diastolic blood pressure.¹

³The crude reporting odds ratio is calculated using the formula $(a/b) / (c/d)$, where a is the number of cases using VEGF-TKIs and developing aortic dissection, b is the number of cases using VEGF-TKIs and developing adverse events other than aortic dissection, c is the number of cases using drugs other than VEGF-TKIs and developing aortic dissection, and d is the number of cases using drugs other than VEGF-TKIs and developing adverse events other than aortic dissection.

⁴Adjusted for age and sex.

Overall, our pharmacovigilance study showed an increase in the risk of aortic dissection reporting associated with the use of VEGF-TKIs, albeit the adverse event was rare. Moreover, it provided data that support the role of blood pressure elevation in the pathophysiology of this adverse effect. Observational studies using large electronic health-care databases are needed to confirm this association.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

ACKNOWLEDGMENTS

Dr. Douros is the recipient of Chercheur-Boursier Junior 1 Award from the Fonds de recherche du Québec – santé (FRQS).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available online on the website of the United States Food and Drug Administration: <https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>.

ORCID

Michael Dörks  <https://orcid.org/0000-0002-9462-8661>

Kathrin Jobski  <https://orcid.org/0000-0002-3957-9721>

Antonios Douros  <https://orcid.org/0000-0002-6005-4006>

REFERENCES

1. Waliany S, Sainani KL, Park LS, Zhang CA, Srinivas S, Witteles RM. Increase in blood pressure associated with tyrosine kinase inhibitors targeting vascular endothelial growth factor. *JACC CardioOncology*. 2019;1:24-36.
2. FDA - October - December 2018: Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS). In, 2018.
3. Takada M, Yasui T, Oka T, et al. Aortic dissection and cardiac dysfunction emerged coincidentally during the long-term treatment with angiogenesis inhibitors for metastatic renal cell carcinoma. *Intern Heart J*. 2018;59:1174-1179.
4. Hatem R, Bebawi E, Schampaert E. Potential sunitinib-induced coronary artery and aortic dissections. *Can J Cardiol*. 2017;33(830):e17-30.e18.
5. Oshima Y, Tanimoto T, Yuji K, Tojo A. Association between aortic dissection and systemic exposure of vascular endothelial growth factor pathway inhibitors in the Japanese adverse drug event report database. *Circulation*. 2017;135:815-817.
6. FDA - Questions and Answers on FDA's Adverse Event Reporting System (FAERS). In, 2018.
7. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf*. 2009;18:427-436.
8. Kobeissi E, Hibino M, Pan H, Aune D. Blood pressure, hypertension and the risk of abdominal aortic aneurysms: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol*. 2019;34:547-555.

How to cite this article: Dörks M, Jobski K, Herget-Rosenthal S, Hoffmann F, Douros A. Tyrosine kinase inhibitors targeting vascular endothelial growth factor and the risk of aortic dissection—A pharmacovigilance analysis. *Pharmacol Res Perspect*. 2021;9:e00707. <https://doi.org/10.1002/prp2.707>