Vascular endothelial growth factor receptor tyrosine kinase inhibitors associated hepatotoxicity: An Analysis of the FDA Adverse Event Reporting System

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Abstract

Vascular endothelial growth factor tyrosine kinase inhibitors (VEGFR-TKIs) are widely used in cancer. Despite the growing number of reported cases of hepatotoxicity resulting from the use of these drugs, there is a lack of information regarding the specific features and severity of hepatotoxicity associated with VEGFR-TKIs. We conducted disproportionality analyses using the Food and Drug Administration Adverse Event Reporting System (FAERS) to evaluate the potential association between hepatotoxicity and ten VEGFR-TKIs. The reporting odds ratios (ROR) and the information component (IC) were calculated to determine the presence of signals for severe liver injury. A total of 10,236 hepatotoxicity events cases with VEGF-TKIs as primary suspected drugs were collected. Apatinib, axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib and sunitinib generated significant signals for liver injury. Significant signals indicating severe liver injury were detected with sorafenib, regorafenib, pazopanib, sunitinib and lenvatinib. The prognosis of drug-related liver injury was poor, sometimes resulting in death.

Introduction

Angiogenesis plays a crucial role in tumorigenesis, progression, invasion, and metastasis. Inhibition of tumor angiogenesis has proven to be an effective approach in suppressing tumor growth.[1]. Vascular endothelial growth factor (VEGF) and its tyrosine receptors (VEGFRs) have emerged as promising targets for cancer treatment and have been extensively investigated in recent decades.[2,3]. Currently, drugs targeting the VEGF/VEGFR signaling pathway consist of monoclonal antibodies and small molecule VEGFR tyrosine kinase inhibitors (TKIs)[4]. The use of VEGFR inhibitors presents a novel therapeutic strategy that can serve as an alternative or adjunct to conventional treatments in various cancers, including non-small cell lung cancer, renal carcinoma, breast cancer, colorectal cancer, and liver cancer[5,6].

However, the application of VEGFR inhibitors may be limited due to the occurrence of adverse events. Hepatotoxicity has been identified as one of the serious safety concerns associated with several VEGFR-TKIs observed in clinical trials, and its incidence has also been gradually reported in clinical practice[7]. According to the preregistration or registration trials, as well as several case reports, sorafenib, pazopanib, sunitinib and regorafenib carry a boxed warning for the risk of severe and potentially fatal hepatotoxicity[8]. In 2015, a meta-analysis involving 52 randomized clinical trials evaluated the hepatotoxicity of VEGFR-TKIs approved by the Food and Drug Administration (FDA) as of December 2013[9]. However, it is important to acknowledge that patients enrolled in clinical trials undergo a rigorous selection process, often displaying adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, which may differ from patients in clinical practice. Moreover, several novel VEGFR-TKIs, such as lenvatinib and regorafenib, have been introduced to the market and have gained widespread usage in the treatment of cancer patients in the past decade[10]. These drugs have been reported to be associated with liver injury in various studies. Specifically, a decline in hepatic function has been observed in metastatic hepatocellular carcinoma (HCC) patients who received early treatment with lenvatinib [11,12]. *Sacré A et al* reported three cases of severe, icteric toxic liver injury caused

by regorafenib, one of which resulted in a fatality[13]. Additionally, a postmarketing drug surveillance study conducted in Japan collected case reports of regorafenib-induced liver injury, highlighting the challenge in predicting and identifying such cases [14].

These studies have raised attention to the hepatotoxicity induced by VEGF-TKIs. Therefore, it is important to regularly monitor liver function indicators, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels, when using these drugs.[15]. Patients with hepatic impairment, particularly those with moderate and severe liver insufficiency, to exercise caution and be extra vigilant when using these drugs. Due to the limited availability of patient-level data, the reporting of liver toxicity induced by VEGFR-TKIs relies mostly on case reports. It is crucial to establish a comprehensive evaluation of VEGFR-TKIs associated hepatotoxicity from adverse event reports. The United States FDA Adverse Event Reporting System (FAERS) database serves as a valuable resource, containing a vast collection of adverse event reports and medication error reports submitted by medical professionals and consumers worldwide[16,17]. The data collected from this large spontaneous system provides valuable insight into the occurrence of adverse drug events in real-world scenarios. In our research, we aimed to explore the relationship between hepatotoxicity and VEGFR-TKIs through a comprehensive assessment of adverse events submitted to the FAERS database.

Results

Descriptive Analysis

A total of 14,8647 cases were reported in the FAERS database. Of these, 1,459 cases were excluded due to the indication of “liver injury” indication. Consequently, 134,088 cases with VEGFR-TKIs as primary suspected drugs were included in the study. Among these cases, 10,236 cases were reported with hepatotoxicity events. The characteristics of these cases are shown in Table 1. The five drugs with the highest number of cases were sunitinib (2410 cases), sorafenib (2061 cases), pazopanib (1955 cases), cabozantinib (1168 cases), and regorafenib (946 cases). The ratio between males and females with drug-related hepatotoxicity was 1.50. Drug-induced liver injury was concentrated among patients aged 18 to 64 years. A majority of drug-related hepatotoxicity cases (71.28%) were reported by healthcare professionals. The top five drug-related hepatotoxicity reporting regions were North America (36.01%), followed by Asia (34.52%), Europe (21.66%), South America (4.45%), and Oceania (1.08%). We conducted an analysis of the outcomes of VEGFR-TKIs-associated hepatotoxicity events, revealing a fatality proportion of 23.09%. The details of the fatality proportion for VEGFR-TKIs-associated hepatotoxicity were presented in Fig. 1. In addition, VEGFR-TKIs associated hepatotoxicity events resulted in a larger proportion of hospitalization and other serious events. The proportions of hospitalizations and other serious events were 28.69% and 29.55%, respectively. Figure 2 provides the number of hepatotoxicity cases associated with VEGFR-TKIs submitted to the FAERS database from 2006 to 2022. Notably, the number of reports for sorafenib has shown a significant surge since 2009. However, it has experienced a sharp decline since 2013. On the other hand, the number of reports for axitinib, lenvatinib, and cabozantinib has steadily increased over the past five years.

Table 1
Characteristics of VEGFR-TKIs-related hepatotoxicity events and nonhepatotoxicity events submitted to the FAERS database.

	Hepatotoxicity cases		Non hepatotoxicity cases	
Characteristics	Number(n)	Proportion (%)	Number(n)	Proportion (%)
VEGF-TKIs				
Sunitinib	2410	23.54	32594	26.32
Sorafenib	2061	20.13	9365	7.56
Pazopanib	1955	19.10	21107	17.04
Cabozantinib	1168	11.41	20316	16.40
Regorafenib	946	9.24	6452	5.21
Apatinib	641	6.26	11154	9.01
Lenvatinib	505	4.93	9101	7.35
Axitinib	482	4.71	11910	9.62
Vandetanib	44	0.43	1151	0.93
Erdafitinib	24	0.23	702	0.57
Sex				
Female	3813	37.25	48481	39.14
Male	5703	55.72	65861	53.18
Unknown	720	7.03	9510	7.68
Age group				
18 year	47	0.46	606	0.49
18–64 year	4158	40.62	42731	34.50
≥ 65 year	3914	38.24	41470	33.48
Unknown	2117	20.68	39045	31.53
Reporter occupation				
Health professionals	7296	71.28	65776	53.11
Non-health professionals	2639	25.78	54191	43.75
Unknown	301	2.94	3885	3.14

VEGFR-TKIs, vascular endothelial growth factor tyrosine kinase inhibitors

	Hepatotoxicity cases		Non hepatotoxicity cases	
Reporter region (Top 5)				
North America	3686	36.01	77744	62.77
Asia	3533	34.52	18241	14.73
Europe	2217	21.66	17767	14.35
South America	456	4.45	5023	4.06
Oceania	111	1.08	1030	0.83
Outcomes				
Death	2363	23.09	27962	22.58
Disability	60	0.59	706	0.57
Hospitalization	2937	28.69	29627	23.92
Life threatening	362	3.54	2421	1.95
Other serious events	3025	29.55	22797	18.41
Required intervention	2	0.02	61	0.05
Unknown	1487	14.53	40278	32.52
VEGFR-TKIs, vascular endothelial growth factor tyrosine kinase inhibitors				

Signal Values

Ten VEGFR-TKI drugs were investigated for severe hepatotoxicity cases by narrow SMQ search in the FAERS database. The strongest significant signal was detected with sorafenib (ROR = 7.86, 95% CI 7.43–8.32; IC = 2.81, 95% CI 2.62–2.99), followed by regorafenib (ROR = 3.68, 95% CI 3.34–4.05; IC = 1.81, 95% CI 1.49–2.12), pazopanib (ROR = 2.20 95% CI 2.05–2.35; IC = 1.10, 95% CI 0.87–1.33) and sunitinib (ROR = 1.79 95% CI 1.69–1.91; IC = 0.82, 95% CI 0.62–1.02). The weakest signal was detected with lenvatinib (ROR = 1.59, 95% CI 1.40–2.80; IC = 0.65, 95% CI 0.24–1.06). No significant signal was detected with cabozantinib, axitinib, apatinib, vandetanib and erdafitinib (Table 2).

Table 2
Signal values of severe hepatotoxicity cases associated with VEGFR-TKIs by SMQ narrow search in FAERS

VEGF-TKIs	Hepatotoxicity cases (N)	ROR (95% CI)	IC (95% CI)
Sorafenib	1365	7.86 (7.43, 8.32)	2.81 (2.62, 2.99)
Sunitinib	1054	1.79 (1.69, 1.91)	0.82 (0.62, 1.02)
Pazopanib	845	2.20 (2.05, 2.35)	1.10 (0.87, 1.33)
Regorafenib	443	3.68 (3.34, 4.05)	1.81(1.49, 2.12)
Cabozantinib*	384	1.05 (0.95, 1.16)	0.07 (-0.27, 0.40)
Axitinib*	259	1.23 (1.09, 1.39)	0.29 (-0.11, 0.70)
Lenvatinib	257	1.59 (1.40, 1.80)	0.65 (0.24, 1.06)
Apatinib*	247	1.23 (1.09, 1.40)	0.30 (-0.12, 0.71)
Vandetanib*	18	0.88 (0.55, 1.41)	-0.18 (-1.68, 1.34)
Erdafitinib*	12	0.97 (0.55, 1.72)	-0.04 (-1.86,1.78)
VEGFR-TKIs, vascular endothelial growth factor tyrosine kinase inhibitors; ROR, reporting odds ratio; IC, information component; SMQ, Standardized medical dictionary for regulatory activities queries.			
*Signal was not detected			

The signal detection results of liver injury and three classifications (hepatic failure, cholestatic injury, and hepatocellular injury) were summarized in Table 3. In terms of liver injury, significant signals were detected for the other eight VEGFR-TKIs investigated in our study, except for vandetanib and erdafitinib. For hepatic failure detection, only sorafenib, sunitinib, regorafenib, pazopanib and lenvatinib were detected with significant signals. Compared with other drugs, the strongest signal was observed in sorafenib (ROR = 18.90, 95% CI 17.26–20.70; IC = 4.16, 95% CI 3.81–4.42), followed by regorafenib (ROR = 7.58, 95% CI 6.38-9.00; IC = 2.89, 95% CI 2.26–3.40). The weakest signal was detected for pazopanib (ROR = 1.89, 95% CI 1.56–2.29; IC = 0.91, 95% CI 0.26–1.54). For cholestatic injury, five drugs detected significant signals, including regorafenib (ROR = 9.48, 95% CI 8.54–10.52; IC = 3.17, 95% CI 2.80–3.49), sorafenib (ROR = 6.29, 95% CI 5.69–6.96; IC = 2.61, 95% CI 2.25–2.92), sunitinib (ROR = 5.73, 95% CI 5.39–6.08; IC = 2.47, 95% CI 2.26–2.66), apatinib (ROR = 4.20, 95% CI 3.72–4.74; IC = 2.04, 95% CI 1.63–2.42) and pazopanib (ROR = 3.82, 95% CI 3.49–4.18; IC = 1.91, 95% CI 1.60–2.20). For hepatocellular injury, significant signals were observed for eight VEGFR-TKIs (sorafenib, sunitinib, regorafenib, pazopanib, lenvatinib, cabozantinib, apatinib and axitinib).

Table 3
Signal values of liver injury and three classifications (hepatocellular injury, cholestatic injury, hepatic failure) associated with VEGFR-TKIs

VEGF-TKIs	Hepatotoxicity cases (N)	ROR (95% CI)	IC (95% CI)
Liver injury			
Sunitinib	2410	2.55 (2.44, 2.65)	1.28 (1.14, 1.42)
Sorafenib	2061	7.58 (7.23, 7.95)	2.67 (2.51 ,2.82)
Pazopanib	1955	3.19 (3.04, 3.34)	1.58 (1.43, 1.73)
Cabozantinib	1168	1.98 (1.86, 2.10)	0.94 (0.74, 1.14)
Regorafenib	946	5.04 (4.71,5.40)	2.17 (1.94, 2.39)
Apatinib	641	1.97 (1.82, 2.14)	0.94 (0.67, 1.20)
Lenvatinib	505	1.91 (1.74, 2.08)	0.89 (0.59, 1.19)
Axitinib	482	1.39 (1.27, 1.52)	0.46 (0.15, 0.76)
Vandetanib*	44	1.31 (0.97,1.77)	0.38 (-0.62, 1.36)
Erdafitinib*	24	1.17 (0.78, 1.76)	0.22 (-1.11, 1.54)
Hepatic failure			
Sorafenib	491	18.90 (17.26, 20.70)	4.16 (3.81, 4.42)
Sunitinib	179	2.14 (1.85, 2.48)	1.09 (0.60, 1.57)
Regorafenib	132	7.58 (6.38, 9.00)	2.89 (2.26, 3.40)
Pazopanib	104	1.89 (1.56, .29)	0.91 (0.26, 1.54)
Lenvatinib	48	2.09 (1.57, 2.78)	1.06 (0.09, 1.96)
Apatinib	36	1.27 (0.92, 1.77)	0.35 (-0.74, 1.41)
Cabozantinib*	34	0.66 (0.47, 0.92)	-0.60 (-1.69, 0.52)
Axitinib*	18	0.60 (0.38, 0.96)	-0.72 (-2.19 ,0.80)
Erdafitinib*	1	0.57 (0.08, 4.08)	-0.80 (-5.07, 4.15)
Vandetanib*	1	0.35 (0.05, 2.47)	-1.52 (-5.56, 3.66)
Cholestatic injury			
Sunitinib	1087	5.73 (5.39, 6.08)	2.47 (2.26, 2.66)

VEGFR-TKIs, vascular endothelial growth factor tyrosine kinase inhibitors

*Signal was not detected

VEGF-TKIs	Hepatotoxicity cases (N)	ROR (95% CI)	IC (95% CI)
Pazopanib	486	3.82 (3.49, 4.18)	1.91 (1.60, 2.20)
Sorafenib	391	6.29 (5.69, 6.96)	2.61 (2.25, 2.92)
Regorafenib	375	9.48 (8.54, 10.52)	3.17 (2.80, 3.49)
Apatinib	273	4.20 (3.72, 4.74)	2.04 (1.63, 2.42)
Cabozantinib*	155	1.29 (1.10, 1.51)	0.36 (-0.17, 0.88)
Lenvatinib*	73	1.35 (1.08, 1.71)	0.43 (-0.33, 1.19)
Axitinib*	70	1.00 (0.79, 1.27)	0.01 (-0.77, 0.78)
Vandetanib*	7	1.04 (0.50, 2.19)	0.06 (-2.26, 2.36)
Erdafitinib*	6	1.47 (0.66, 3.29)	0.56 (-2.01, 2.93)
Hepatocellular injury			
Pazopanib	1432	3.91 (3.71, 4.12)	1.89 (1.71, 2.07)
Sorafenib	1066	6.07 (5.70, 6.47)	2.48 (2.27, 2.68)
Sunitinib	1005	1.74 (1.64, 1.85)	0.78 (0.57, 0.99)
Cabozantinib	861	2.46 (2.30, 2.63)	1.26 (1.03, 1.49)
Regorafenib	551	4.74 (4.35, 5.17)	2.16 (1.86, 2.43)
Apatinib	412	2.13 (1.93, 2.35)	1.06 (0.73, 1.39)
Axitinib	328	1.60 (1.43, 1.79)	0.66 (0.30, 1.02)
Lenvatinib	313	1.98 (1.77, 2.22)	0.96 (0.58, 1.33)
Vandetanib*	26	1.31 (0.89, 1.93)	0.38 (-0.90, 1.63)
Erdafitinib*	17	1.41(0.87, 2.28)	0.49 (-1.10, 2.01)
VEGFR-TKIs, vascular endothelial growth factor tyrosine kinase inhibitors			
*Signal was not detected			

Discussion

The risk management of postmarketing drug assessment is crucial due to the limitation of adverse events studies in clinical trials before approval. In recent years, significant attention has been devoted to the reporting of adverse events following drug approval in the market. The FAERS database, which provides free access to pharmacovigilance information, has played a significant role in postmarketing

drug safety surveillance. To the best of our knowledge, this is the first analysis to evaluate the correlation between VEGFR-TKIs and hepatotoxicity using the real-world data available in the FAERS system.

Although VEGFR-TKIs have greatly altered the medical treatment of cancer, hepatotoxicity remains a major concern that may lead to treatment interruption[18]. Our findings revealed that sorafenib, sunitinib, regorafenib, pazopanib, and lenvatinib exhibited a significant association with severe hepatotoxicity. The outcomes of hepatotoxicity can be severe and, in some cases, result in fatality. The highest mortality rate (42.31%) was observed in patients treated with sorafenib, indicating a poor prognosis for hepatotoxicity. Furthermore, sorafenib demonstrated the strongest signals of hepatocellular injury and hepatic failure. In contrast, no positive findings were obtained for vandetanib and erdafitinib, possibly due to the rarity of hepatotoxicity reports.

The prediction of hepatotoxicity related to VEGFR-TKIs remains a challenge in clinical practice. Drug-induced acute liver injury can often be asymptomatic, with elevated levels observed solely in ALT, AST, alkaline phosphatase (ALT), and gamma-glutamyl transpeptidase (GGT)[19]. Early identification of the severity and prognosis of drug-induced liver injury (DILI) is vital in the diagnosis and treatment process. After observing cases of drug-induced liver toxicity, Zimmerman proposed the concept of Hy's Law[20]. In short, when the ALT or AST ≥ 3×the upper limit of normal (ULN) and the total bilirubin (TBIL) > 2×ULN in drug-induced liver injury, it usually indicates a poor prognosis[21]. The Hy's Law has been widely utilized as a convenient tool for predicting acute hepatotoxicity for many years. To enhance the accuracy of prediction, extensive efforts have been devoted to identifying predictive markers of drug-induced liver injury. One such approach involves the application of a new ratio value ((ALT or AST, whichever is highest/ULN)/ (alkaline phosphatase/ULN)) [22]. This alternative approach aims to strike a balance between sensitivity and specificity in predicting hepatotoxicity. In addition to Hy's Law, other commonly used prediction methods include the Robles-Diaz model and the DrILTox ALF Score [23,24]. As more research is focused on this area, it is anticipated that the future will bring forth more sensitive and specific signals that can be used to predict the severity and prognosis of drug-induced liver injury.

The exact mechanism underlying liver toxicity caused by VEGFR-TKIs remains complex and has not yet been fully elucidated at present. Reactive metabolites produced by VEGFR-TKIs can lead to hepatotoxicity, while also exerting indirect toxicity to the liver by affecting endogenous metabolism.[25,26]. The identified pathways serve as promising targets to prevent hepatotoxicity. In clinical practice, the management strategies for liver toxicity induced by VEGFR-TKIs involve dose adjustment and discontinuation, along with the administration of liver-protective medications [27,28]. Physicians play a crucial role in conducting a comprehensive assessment of patients prior to prescribing VEGF-TKIs. Given that several VEGF-TKIs are metabolized via the CYP3A4 pathway, it is essential to pay attention to potential drug interactions, particularly when co-administering CYP3A4 inhibitors or inducers.[29].

Several limitations existed in our research. First, given that the FAERS is a self-reporting system, reporting bias is inevitable. Further real-world studies or expert consultations may be necessary to verify the results.

Second, certain VEGFR-TKIs, such as sorafenib and lenvatinib, have been employed for the treatment of HCC. Differentiating between hepatotoxicity resulting from the cancer itself or the administered drug poses a significant challenge. Notably, the occurrence of hepatotoxicity can be influenced by various factors, including drug combinations and treatment duration, which pose difficulties in their assessment. Finally, it is important to acknowledge that all signal detection results merely indicate statistical correlation, and further pharmacological studies are required to elucidate the specific mechanism of liver toxicity.

Conclusion

In this retrospective analysis of a pharmacovigilance database, it was suggested that sorafenib, sunitinib, regorafenib, pazopanib and lenvatinib were significantly associated with severe hepatotoxicity. The prognosis for drug-related liver injury was generally poor, and in some cases, it led to fatal consequences. To enhance preventive measures and better understand the underlying mechanisms behind hepatotoxicity induced by these medications, additional research is warranted.

Method

Data source and study procedures

The current study was designed as a retrospective pharmacovigilance investigation, utilizing original data downloaded from the FAERS database. The data covered the period from January 2005 to December 2022. To maintain data integrity and accuracy, any duplicate adverse event reports and cases marked as "deleted" were carefully excluded from the analysis, following the guidelines provided in the FAERS specification documents. By the MedEx 1.3.8 software, different names for the same drug are converted into the *generic name* [30]. The study focused on investigating ten individual component VEGFR-TKIs, namely apatinib, axitinib, cabozantinib, erdafitinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, and vandetanib. Our study only included cases where VEGFR-TKIs were reported as the primary suspected (PS) drugs. The adverse events data used for analysis were obtained from the FAERS database, and these were compiled and categorized using the Medical Dictionary for Regulatory Activities (MedDRA). The adverse events were predominantly expressed in the format of "preferred terms" (PTs). [31]. Severe liver injury cases were identified by the Standardized MedDRA Queries (SMQs) narrow search (version 25.1, SMQ code: 20000007), which contained 133PTs. Additionally, three categories of liver injury were also analysed, including hepatocellular injury (26PTs), cholestatic injury (16PTs), and hepatic failure (6PTs) [32,33]. The details of the PTs were shown in Supplementary Table S1. We excluded cases with indications preferred terms of “liver injury” described above. The outcomes of each included cases were also analysed.

Statistical analysis

The signal related to hepatotoxicity was analysed by reporting the odds ratio (ROR, a frequency approach) and the information component (IC, a Bayesian approach). In terms of ROR, when the lower limit of the 95% confidence interval (CI) > 1 and the number of reported adverse event cases ≥ 3, a significant signal was considered to be detected. In terms of IC, when IC > 0 and the lower limit of 95% CI is > 0, a significant signal was considered to be detected. If the threshold values of both ROR and IC were met, the finally significant signal was detected, indicating a significant association between target drug and liver injury events. The analyses were performed by Microsoft Excel 2016 (Microsoft, Redmond, Washington, USA) and SPSS version 25.0 (IBM, Armonk, New York, USA).

Declarations

Supplementary Materials

Table S1. Preferred terms for the severe DILI cases by SMQ narrow search. Table S2. Preferred terms for hepatocellular injury, cholestatic injury and hepatic failure cases.

Author Contributions

H.Z. and B.W. contributed to conception and study design. Y.Z. and M.X. analyzed data, prepared all figures and tables, and took responsibility for the collection, integrity and accuracy of the data. H.Z. and K.Z. drafted the manuscript. F.W., FB.W., B.W. participated in data analyses and interpretation, and revisions of the manuscript. All authors read and approved the final manuscript.

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Ethics approval

Ethical approval was waived for this study due to FAERS is a database of anonymous information.

Data availability statement

The original data can be downloaded from the FDA Adverse Event Reporting System Public Dashboard at: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

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Conflict of interest

None.

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Figures

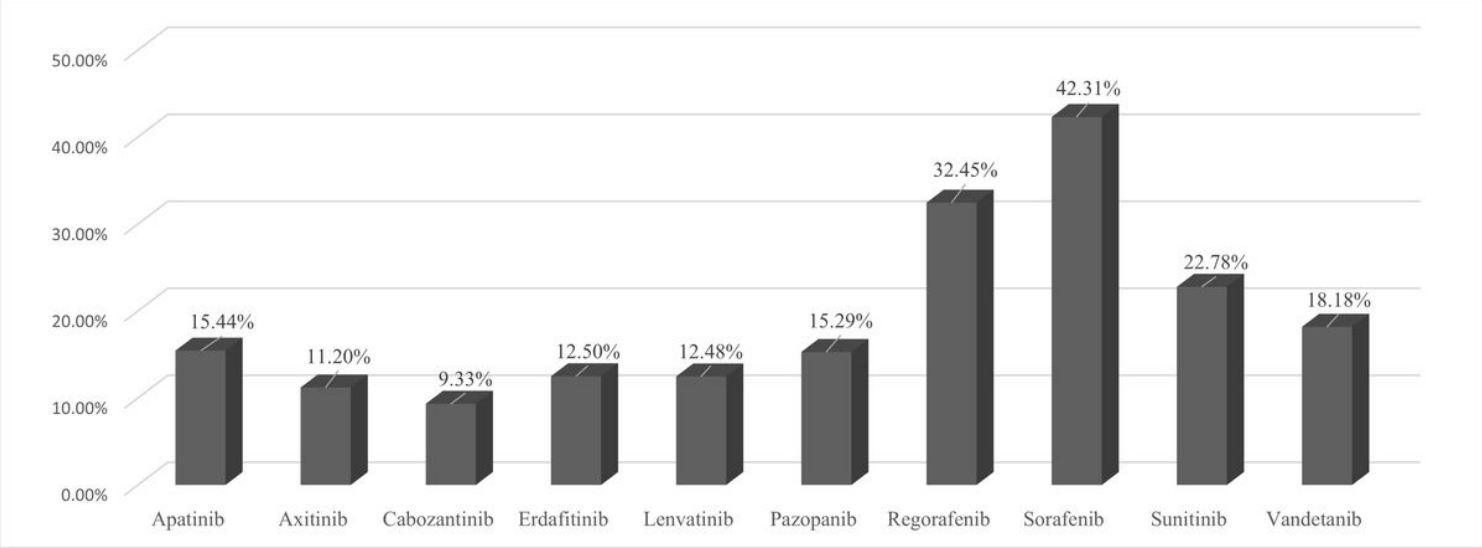

Figure 1

The fatality proportion for VEGFR-TKIs-associated hepatotoxicity cases.

VEGFR-TKIs, vascular endothelial growth factor tyrosine kinase inhibitors

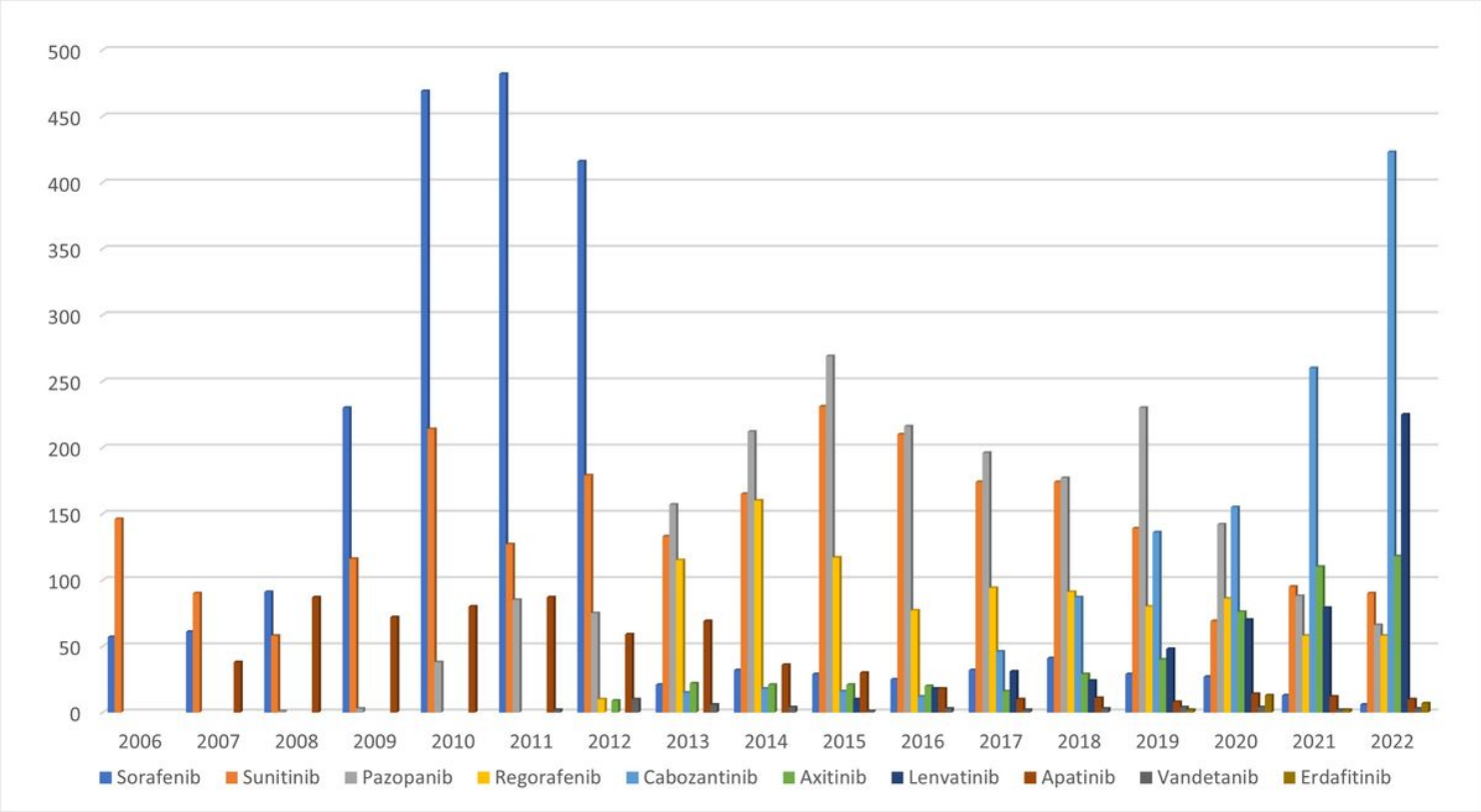

Figure 2

Number of hepatotoxicity cases associated with VEGFR-TKIs submitted to the FAERS database from 2006 to 2022.

VEGFR-TKIs, vascular endothelial growth factor tyrosine kinase inhibitors

Supplementary Files

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