Drugs in R&D (2023) 23:403–409
https://doi.org/10.1007/s40268-023-00439-1

ORIGINAL RESEARCH ARTICLE

Pharmacovigilance Study of Infigratinib: A Safety Analysis of the FDA Adverse Event Reporting System

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Accepted: 17 August 2023 / Published online: 12 September 2023

Abstract

Background Infigratinib is a fibroblast growth factor receptor (FGFR)-specifc tyrosine kinase inhibitor indicated for the treatment of patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma. However, few studies have been conducted to evaluated the safety of infigratinib in the real world. In this study, we conducted a pharmacovigilance study to evaluate the adverse events (AEs) of infigratinib by using the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods OpenVigil 2.1 was employed to extract the FAERS database. Descriptive analysis was used to describe the characteristics of infigratinib-associated AE reports. Disproportionality analysis was performed by calculating the proportional reporting ratio (PRR), reporting odds ratios (ROR), and Bayesian analysis confidence propagation neural network (BCPNN) to detect positive signals.

Results Our findings revealed 149 AE reports, among which 36 significant signals were identified. These significant AE signals were mainly observed in gastrointestinal disorders ($N = 26$, ROR = 26.03, PRR = 8.44, information component [IC] = 3.08) and skin and subcutaneous tissue disorders ($N = 21$, ROR = 92.13, PRR = 40.41, IC = 5.34). Notably, dehydration and skin exfoliation were unexpected AEs, but had relatively high signal intensities (ROR = 29.75, PRR = 26.64, IC = 4.74; ROR = 50.61, PRR = 45.24, IC = 5.50, respectively) despite not being listed on the drug label. Furthermore, our analysis showed that infigratinib dose differed statistically between severe and non-severe reports (113.82 ± 16.13 mg vs 125 ± 0.00 mg, $t = -4.28$; $p < 0.001$). However, there were no significant differences in sex, age, and types of AEs between the two groups ($p = 0.06$, $p = 0.86$, and $p = 0.93$, respectively).

Conclusions These findings suggest that gastrointestinal and skin toxicities are the most common adverse reactions for infigratinib. It is important to recognize skin exfoliation and dehydration in clinical practice, as they are unexpected AEs. Additionally, our study indicates that infigratinib dose may correlate with an increased risk of AE severity, highlighting the need for dose adjustment of infigratinib when exposure to the drug is increased due to internal or external factors.

Key Points

Gastrointestinal and skin toxicities are the most common adverse reactions for infigratinib.

Skin exfoliation and dehydration are unexpected adverse events (AEs) for infigratinib, which need to be close monitored in practice.

The infigratinib dose may correlate with an increased risk of AE severity.

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1 Introduction

The fibroblast growth factor receptor (FGFR) signaling pathway plays a crucial role in the proliferation and survival of malignant cancer cells, specifically cholangiocarcinoma [1, 2]. Previous studies have shown that FGFR2 fusions or rearrangements are present in 10–16% of patients with intrahepatic cholangiocarcinoma [3]. Consequently, FGFR becomes a key target for cholangiocarcinoma therapy. Infigratinib, an orally bioavailable inhibitor of FGFRs, has demonstrated selective binding and inhibition of FGFR1, FGFR2, and FGFR3 [4]. Through this mechanism, infigratinib reduces cell proliferation in tumors with activating FGFR amplifications, mutations, or fusions [5]. Several clinical trials have provided evidence of infigratinib's promising clinical activity and manageable safety profile in previously treated locally advanced or metastatic cholangiocarcinoma patients with FGFR2 gene fusions or rearrangements [6–8]. As a result, infigratinib received approval on May 28 2021 from the US Food and Drug Administration (FDA) for the treatment of previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement. However, it is important to acknowledge the potential adverse reactions associated with infigratinib [9, 10]. Retinal pigment epithelial detachment, hyperphosphatemia, soft tissue mineralization, and embryofetal toxicity are among the adverse effects observed in previous studies [7, 8]. Although most of the safety data comes from clinical trials, these studies are limited by strict inclusion criteria, small sample sizes, and reduced follow-up. Therefore, a post-marketing surveillance investigation is necessary to explore potential adverse events (AEs) further. The Food and Drug Adverse Event Reporting System (FAERS), a public database of spontaneously reported AEs, is widely utilized for post-marketing surveillance [11, 12]. The FAERS database compensates for the limitations of clinical trials by providing AE data for detection potential positive signals. Consequently, we conducted a real-world pharmacovigilance study to examine the safety of infigratinib using the FAERS database.

2 Material and Methods

2.1 Data Sources and Data Collection

Data collection for AEs related to infigratinib was conducted between May 28, 2021 and September 30, 2022. The FAERS database and OpenVigil 2.11 were utilized to retrieve AE records associated with both the generic name and brand name of the drug ('infigratinib' and 'Truseltiq'). In each FAERS AE report, reporters assigned role codes to reported drugs, designating them as primary suspect, secondary suspect, concomitant, or interacting. This study included primary and secondary suspect drugs that were responsible for AEs. Relevant information, such as individual safety reports (ISR), outcome, drug name, role code, dosage, indication, event, case ID, and clinical characteristics (sex, reporter country, age) of the patient, were gathered. To ensure data accuracy, duplicate and conflicting records were excluded, with only the latest case ID retained. In cases where the case ID was the same, the ISR with the largest number was selected. Preferred terms (PTs) associated with indication, off-label use, and product use issues were removed from the analysis to minimize confounding effects.

2.2 Definition of Adverse Events

The FAERS database codes AEs using Medical Dictionary for Regulatory Activities (MedDRA) terminology at a PT level. We used MedDRA version 26.0 to categorize AEs in each report into system organ class (SOC) levels.

2.3 Statistical Analysis

Descriptive analysis was employed to present the clinical characteristics of AE reports, including event, outcome, sex, age, and reporting country. Proportions were compared using Pearson's chi-squared (χ^2) or Fisher's exact test, while independent samples *t*-test and Kruskal-Wallis test were applied for continuous data and skewed distribution data, respectively. A statistical significance level of $p < 0.05$ was considered significant. To identify AE signals, disproportionality analysis was conducted through the calculation of reporting odds ratio (ROR), proportional reporting ratio (PRR), and Bayesian analysis confidence propagation neural network (BCPNN). The algorithm equations and criteria for the disproportionality analysis are provided in Tables 1 and 2. A signal was deemed significant only if it fulfilled all three algorithm criteria simultaneously. Furthermore, based on FDA classification, AE cases were categorized as serious or non-serious. AEs were considered 'serious' if they resulted in death, hospitalization (initial or prolonged), disability or permanent damage, life-threatening situations, or

Table 1 Disproportionality analysis algorithm

Item	Target AEs	Other AEs	Sums
Target drug	a	b	$a + b$
Other drugs	c	d	$c + d$
Sums	$a + c$	$b + d$	$a + b + c + d$

Table 2 The equations and criteria for the algorithm

Algorithms	Equation	Criteria
ROR	$ROR = (a \times d) / (b \times c)$ $95\%\ CI = e^{\ln(ROR) \pm 1.96\times (1/a + 1/b + 1/c + 1/d)\wedge 0.5}$	Lower limit of the 95% CI > 1 and $a \geq 3$
PRR	$PRR = [a \times (c + d)] / [c \times (a + b)]$ $\chi^2 = [(a \times d - b \times c)^2] \times (a + b + c + d) /[(a + b) \times (c + d) \times (a + c) \times (b + d)]$	PRR ≥2, χ^2 ≥4, and a ≥ 3
BCPNN	$IC = \log_2 {}^{a \times (a + b + c + d)/[(a + c) \times (a + b)]}$ $IC_{025} = e^{\ln(IC)-1.96\times (1/a + 1/b + 1/c + 1/d)\wedge 0.5}$	$IC_{025} > 0$

BCPNN Bayesian analysis confidence propagation neural network, *CI* confidence interval, *IC* information component, IC_{025} the lower limit of the 95% CI of the IC, *PRR* proportional reporting ratio, *ROR* reporting odds ratio, χ^2 chi-squared

other serious medical events. Sex distribution, types of AEs, infigratinib dosage, and age were compared between AEs with serious and non-serious outcomes. All data processing and statistical analyses were performed using Microsoft Excel version 2019 and SPSS 23.0 statistical software.

3 Results

3.1 Descriptive Analysis

A total of 149 AE reports were retrieved from the FAERS database using OpenVigil 2.1. After data cleaning, 113 records (75.84%) were removed, comprising 72 AE reports associated with other drugs and 41 duplicate records. This resulted in 36 AE reports (24.16%) remaining for inclusion in this study. In terms of age distribution, patients aged 45–64 years (22.22%) and 65–74 years (19.44%) accounted for a higher proportion compared with other age groups, with a median age of 62.00 years. Regarding sex, there were more female patients (58.33%) than male patients (30.56%). The majority of the reports were from the United States (75.00%), followed by China (8.33%), Spain (5.56%), Belgium (5.56%), Puerto Rico (2.78%), and Australia (2.78%). The most reported outcomes associated with infigratinib-related AEs were hospitalization (33.33%), followed by other outcomes (25.00%) and death (16.67%). The characteristics of AE reports for infigratinib are listed in Table 3.

Table 3 Characteristics of adverse event reports for infigratinib

Characteristics	*N* (%)
Age (year)	
< 18	2 (5.56)
18–44	2 (5.56)
45–64	8 (22.22)
65–74	7 (19.44)
≥ 75	3 (8.33)
Unknown	14 (38.89)
Median (IQR)	62.00 (49.50–70.50)
Sex	
Female	21 (58.33)
Male	11 (30.56)
Not specified	4 (11.11)
Reporter country	
United States	27 (75.00)
China	3 (8.33)
Spain	2 (5.56)
Belgium	2 (5.56)
Puerto Rico	1 (2.78)
Australia	1 (2.78)
Outcomes	
Hospitalization (initial or prolonged)	12 (33.33)
Other outcomes	9 (25.00)
Unknown	9 (25.00)
Death	6 (16.67)

3.2 Disproportionality Analysis

3.2.1 Preferred Term (PT) Analysis

A total of 133 AE signals related to infigratinib were extracted from the FAERS database, and 19 signals were considered significant according to the disproportionality analysis. In terms of signal intensity, blood phosphorus increased (ROR = 2095.95, PRR = 1812.85, IC = 10.78), hyperphosphatemia (ROR = 1476.99, PRR = 1357.32, IC = 10.37), onychomadesis (ROR = 1045.72, PRR = 932.78, IC = 9.84) had relatively strong signal intensities. As to the frequencies of AE reports, fatigue ($N = 10$), alopecia ($N = 6$), and stomatitis ($N = 6$) had relatively high frequencies. The significant AE signals of infigratinib at the PT level are listed in Table 4.

3.2.2 System Organ Class (SOC) Analysis

The significant AE signals of infigratinib were distributed into eight SOCs. Gastrointestinal disorders involved six PTs, skin and subcutaneous tissue disorders involved five

Table 4 Significant AE signals of infigratinib at the PT level

PTs	*N*	ROR (95% CI)	PRR (χ^2)	IC (95% CI)
Fatigue	10	10.19 (4.93–21.05)	7.705 (53.71)	2.95 (1.43–6.09)
Alopecia	6	25.16 (10.47–60.32)	21.24 (97.09)	4.41 (1.84–10.57)
Stomatitis	6	79.87 (33.31–191.52)	67.08 (33.65)	6.07 (2.53–14.55)
Blood phosphorus increased	5	2095.95 (805.43–5454.28)	1812.85 (7090.75)	10.78 (4.14–28.04)
Decreased appetite	5	16.70 (6.51–42.86)	14.58 (50.83)	3.87 (1.51–9.92)
Vomiting	5	9.90 (3.86–25.40)	8.70 (27.21)	3.12 (1.22–8.01)
Constipation	4	13.80 (4.89–38.95)	12.41 (31.61)	3.63 (1.29–10.26)
Dehydration	4	29.75 (10.54–84.00)	26.64 (75.01)	4.74 (1.68–13.37)
Diarrhea	4	4.51 (1.60–12.72)	4.13 (6.79)	2.05 (0.72–5.77)
Dry skin	4	33.23 (11.77–93.82)	29.74 (84.48)	4.89 (1.73–13.82)
Malignant neoplasm progression	4	23.49 (8.32–66.30)	21.05 (57.94)	4.40 (1.56–12.41)
Nausea	4	4.23 (1.50–11.95)	3.88 (6.09)	1.96 (0.69–5.53)
Onychomadesis	4	1045.72 (367.47–2975.84)	932.78 (2800.61)	9.84 (3.46–28.00)
Skin exfoliation	4	50.61 (17.92–142.90)	45.24 (131.85)	5.50 (1.95–15.53)
Arthralgia	3	4.74 (1.46–15.44)	4.44 (5.02)	2.15 (0.66–7.00)
Dry eye	3	40.25 (12.36–131.11)	37.07 (72.42)	5.21 (1.60–16.97)
Dry mouth	3	34.70 (10.65–113.01)	31.97 (61.81)	5.00 (1.53–16.28)
Hyperphosphatemia	3	1477.00 (447.40–4875.92)	1357.32 (2752.32)	10.37 (3.14–34.23)
Nail disorder	3	323.54 (99.07–1056.64)	297.39 (611.30)	8.21 (2.51–26.81)

AE adverse event, *CI* confidence interval, *IC* information component, *PRR* proportional reporting ratio, *PT* preferred term, *ROR* reporting odds ratio, χ^2 chi-squared

PTs, and metabolism and nutrition disorders involved three PTs. Each of the other five SOCs involved one PT. Investigation (ROR = 2095.95, PRR = 1812.85, IC = 10.78), skin and subcutaneous tissue disorders (ROR = 92.13, PRR = 40.41, IC = 5.34), eye disorders (ROR = 40.25, PRR = 37.07, IC = 5.21), metabolism and nutrition disorders (ROR = 35.37, PRR = 24.22, IC = 4.60), gastrointestinal disorders (ROR = 26.03, PRR = 8.44, IC = 3.08), and neoplasms benign, malignant and unspecified (including cysts and polyps) (ROR = 23.49, PRR = 21.05, IC = 4.40) had relatively strong signal intensities. The significant AE signals at the SOC level are listed in Table 5.

3.2.3 Serious Versus Non-Serious AEs

Infigratinib dose differed statistically between severe and non-severe AEs (113.82 ± 16.13 mg vs 125 ± 0.00 mg, respectively; $t = -4.28$; $p < 0.001$), as shown in Table 6. However, sex, age, and types of AEs did not differ significantly between the two groups ($p = 0.06$, $p = 0.86$, and $p = 0.93$, respectively).

4 Discussion

The study revealed that in the real world, the most common adverse reactions of infigratinib were gastrointestinal and skin toxicities. Furthermore, unexpected AEs including skin exfoliation and dehydration require more attention in clinical practice. Frequentist analysis and Bayes analysis are the two disproportionality analysis methods used to detect positive AE signals [13, 14]. The frequentist analysis, which includes ROR and PRR, is simple and sensitive [15]. However, its accuracy is excessively dependent on the number of AE reports, and a small number of AE reports in the database can easily result in false-positive signals [15]. On the other hand, Bayes analysis, which includes BCPNN and multi-item gamma poisson shrinker (MGPS), provides robust calculation results and a strong ability to predict adverse reactions [14]. Therefore, to minimize bias caused by using a single algorithm, both frequentist analysis and Bayes analysis were employed for signal detection.

Patients aged 45–64 years old and 65–74 years old accounted for a greater proportion compared with other age groups, which is consistent with the higher incidence rate of cholangiocarcinoma in these age groups [16]. The results also showed that AEs were more likely to occur in females, suggesting that significant attention should be paid to female patients. Additionally, most of the AE reports were from the United States, which may be attributed to the fact that infigratinib was first marketed in the United States [5].

The most common drug-related adverse reactions listed in the infigratinib label were nail toxicity, stomatitis, dry eye, fatigue, alopecia, arthralgia, dysgeusia, constipation, dry mouth, diarrhea, dry skin, decreased appetite, vomiting, and hyperphosphatemia [17]. These findings were

Table 5 Significant AE signals of infigratinib at the SOC level

SOC	PTs (N)	*N*	ROR (95% CI)	PRR (χ^2)	IC (95% CI)
Eye disorders	Dry eye (3)	3	40.25 (12.36–131.11)	37.07 (72.42)	5.21 (1.60–16.97)
Gastrointestinal disorders	Constipation (4) Diarrhea (4) Dry mouth (3) Nausea (4) Stomatitis (6) Vomiting (5)	26	26.03 (12.86–52.69)	8.44 (178.02)	3.08 (1.52–6.23)
General disorders and administration-site conditions	Fatigue (10)	10	10.19(4.93–21.05)	7.71 (53.71)	2.95 (1.43–6.09)
Investigations	Blood phosphorus increased (5)	5	2095.95 (805.43–5454.28)	1812.85 (7090.75)	10.78 (4.14–28.04)
Metabolism and nutrition disorders	Decreased appetite (5) Dehydration (4) Hyperphosphatemia (3)	12	35.37 (17.77–70.41)	24.22 (247.67)	4.60 (2.31–9.15)
Musculoskeletal and connective tissue disorders	Arthralgia (3)	3	4.74 (1.46–15.44)	4.44 (5.02)	2.15 (0.66–7.00)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Malignant neoplasm progression (4)	4	23.49 (8.32–66.30)	21.05 (57.94)	4.40 (1.56–12.41)
Skin and subcutaneous tissue disorders	Alopecia (6) Dry skin (4) Nail disorder (3) Onychomadesis (4) Skin exfoliation (4)	21	92.13 (48.07–176.57)	40.41 (778.50)	5.34 (2.78–10.23)

AE adverse event, *CI* confidence interval, *IC* information component, *PRR* proportional reporting ratio, *ROR* reporting odds ratio, *SOC* system organ class, χ^2 chi-squared

consistent with the results of AE signals analysis, indicating the credibility of this study. Although the number of AE reports associated with increased blood phosphorus, hyperphosphatemia, and onychomadesis was small, the signal intensities were high, indicating a strong relationship with infigratinib. Gastrointestinal disorders and skin and subcutaneous tissue disorders had the highest number of PT and AE reports among all SOCs, suggesting that gastrointestinal and skin toxicities are the most common adverse reactions for infigratinib. Therefore, close monitoring of gastrointestinal and skin toxicities is necessary during infigratinib treatment. Investigations had the highest signal intensity at the SOC level, including only one PT, namely nausea blood phosphorus. Thus, attention should be paid to blood phosphorus in patients receiving infigratinib treatment.

Unexpected AEs were defined as significant AEs that were not listed in the drug label. Dehydration (ROR = 29.75, PRR = 26.64, IC = 4.74) and skin exfoliation (ROR = 50.61, PRR = 45.24, IC = 5.50) were considered unexpected AEs as they were not included in the drug label. In the phase II study of infigratinib in patients with FGFR-altered advanced cholangiocarcinoma, four patients developed grade 1 or 2 dehydration, but none experienced grade 3 or 4 dehydration [7]. Hence, dehydration was found to be highly correlated with infigratinib, and caution should be exercised by clinicians regarding this AE. Moreover, the results also suggested that the FDA should consider adding dehydration to the drug label. As for skin exfoliation, there were no relevant reports on skin exfoliation induced by infigratinib. However, based on the disproportionality analysis, skin exfoliation showed a high correlation with infigratinib, indicating the need for caution in clinical practice.

The study further revealed that the infigratinib dose may correlate with an increased risk of AE severity. In a phase I trial, many AEs were found to be dose-dependent, with higher doses being more prone to developing serious AEs [8, 18]. Therefore, in order to reduce the toxicity of the drug, the infigratinib dose should be modified when the exposure of infigratinib is increased by some internal or external factors, such as patients with hepatic or renal impairment, co-administered with strong or moderate CYP3A inhibitors, or co-administered with food [17–19].

Despite the comprehensive analysis of AE signals of infigratinib based on real-world data, this study also has certain limitations that should be considered. Firstly, the FAERS database, being a spontaneous AE reporting system, cannot provide the total number of patients receiving infigratinib treatment, making it impossible to estimate the incidence of adverse reactions. Secondly, the data obtained from the FAERS database are random and incomplete, which may reduce the accuracy of analysis results. Thirdly, due to missing information, the causal relationship between AEs and

Table 6 Differences in clinical characteristics of severe and non-severe AEs

Characteristics	Serious cases	Non-serious cases	Statistic	*p*-value
Sex, *N* (%)				
Female	22 (61.11)	11 (37.93)	3.453[a]	0.06
Male	14 (38.89)	18 (62.07)		
Age, years				
Median (IQR)	66 (66, 71)	68 (68, 69)	0.17[b]	0.86
Infigratinib dose, mg				
Mean ± SD	113.82 ± 16.13	125 ± 0.00	− 4.28[c]	< 0.001
Types of AEs, *N* (%)				
Alopecia	2 (5.13)	2 (6.90)	11.76[d]	0.93
Arthralgia	1 (2.56)	0 (0.00)		
Blood phosphorus increased	2 (5.13)	2 (6.90)		
Constipation	3 (7.69)	1 (3.45)		
Decreased appetite	4 (10.26)	1 (3.45)		
Dehydration	3 (7.69)	1 (3.45)		
Diarrhea	3 (7.69)	1 (3.45)		
Dry eye	2 (5.13)	1 (3.45)		
Dry mouth	2 (5.13)	1 (3.45)		
Dry skin	3 (7.69)	1 (3.45)		
Fatigue	5 (12.82)	3 (10.34)		
Hyperphosphatemia	0 (0.00)	2 (6.90)		
Malignant neoplasm progression	1 (2.56)	3 (10.34)		
Nail disorder	1 (2.56)	2 (6.90)		
Nausea	1 (2.56)	1 (3.45)		
Onychomadesis	1 (2.56)	3 (10.34)		
Skin exfoliation	1 (2.56)	1 (3.45)		
Stomatitis	2 (5.13)	2 (6.90)		
Vomiting	2 (5.13)	1 (3.45)		

AE adverse event, *IQR* interquartile range, *SD* standard deviation

[a]Pearson's chi-squared (χ^2) test

[b]Kruskal-Wallis test

[c]Independent samples *t* test

[d]Fisher's exact test

drugs cannot be determined. Lastly, although disproportionality analysis is commonly used for AE mining, it lacks a gold standard for assessing the significance of suspected adverse drug reactions, potentially leading to false-positive signals. Nonetheless, the FAERS database remains one of the largest databases of adverse drug events in the world, providing valuable drug safety information and serving as an important tool for post-marketing safety assessments.

5 Conclusion

This study utilized the FAERS data to mine and analyze the AE signals of infigratinib. The findings indicated that gastrointestinal and skin toxicities were the most common infigratinib-related adverse reactions. Skin exfoliation and dehydration were identified as unexpected AEs, highlighting the importance for clinicians to be aware of these two AEs. Due to the potential risk of increased AE severity with infigratinib dose, dose adjustment is recommended when the infigratinib exposure is increased by some internal and external factors. Although this study has limitations, it provides valuable insights into the AEs of infigratinib in the real-world setting, warranting further clinical studies for validation.

Declarations

Funding No funding was received.

Availability of Data and Material Data are available on the FAERS database.

Competing Interests The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate Not applicable.

Patient Consent for Publication Not applicable.

Authors' Contributions DZ and XL conceived the study and performed the data analysis. DZ drafted the manuscript. DZ and JW revised the manuscript. All authors have read and approved the final manuscript.

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