Post-Marketing Safety of Vemurafenib: A Real-World Pharmacovigilance Study of the FDA Adverse Event Reporting System

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ABSTRACT-Purpose: Vemurafenib received approval for treatment of BRAF V600 variation metastatic melanoma in August 2011. This study analyzed Vemurafenib-related adverse events (AEs) to detect and characterize relevant safety signals using the real-word-data through the Food and Drug Administration Adverse Event Reporting System (FAERS). **Methods:** Disproportionality analyses, including the reporting odds ratio (ROR), the healthcare products regulatory agency (MHRA), the Bayesian confidence propagation neural network (BCPNN), and the multiitem gamma Poisson shrinker (MGPS) algorithms, were applied to quantify the signals of vemurafenib-related AEs. **Results:** Out of 8,042,244 reports gathered from the FAERS, 9554 reports of vemurafenib as the 'primary suspected (PS)' AEs were recognized. Vemurafenib-induced AEs occurrence targeted 23 system organ class (SOC). A total of 138 significant disproportionality PTs was simultaneously reserved according to the four algorithms. Unexpected significant AEs such as sarcoidosis and kidney fibrosis might also occur. The median onset time of vemurafenib-related AEs was 26 days (interquartile range [IQR] 8-97 days), and most of the cases occurred within the first one and two months after vemurafenib initiation. **Conclusion:** Our study detected potential new AEs signals and might provide powerful support for clinical monitoring and risk identification of vemurafenib.

INTRODUCTION

Melanoma is the most aggressive form of skin cancer with rising incidence and morbidity. Despite advances in treatment, the 10-yr survival for patients with metastatic disease is less than 10%. BRAF inhibitor vemurafenib is the first officially approved medical treatment for metastatic melanoma (1,2). It has marked antitumor effects against melanoma cell lines with the BRAF V600E mutation but not against cells with wild-type BRAF (3). Phase 1 and 2 clinical trials of vemurafenib have shown response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation (4,5). A validated test is required to determine if patients carry the mutation, and BRAF positivity must be confirmed in order for the treatment to be warranted (6). Although ten years have passed since its launch in August 2011, vemurafenib remains indispensable in treating BRAF V600 mutation-positive unresectable or metastatic melanoma. In recent years, the indications of vemurafenib have also been continuously updated, including Erdheim-Chester with BRAF V600 mutation (7). In addition, several clinical studies have demonstrated that vemurafenib could be used in BRAF V600-mutant refractory non-small cell lung cancer and glioma (8,9).

In the clinical phase Ⅰ-III studies of vemurafenib, the most common adverse drug reactions (ADRs) included arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous-cell carcinoma, photosensitivity, nausea, and diarrhea, which were manageable in the clinical trial setting. 38% of patients required dose modification because of toxic effects (1,5,10). In recent years, the ADRs in the instructions of vemurafenib are still being updated continuously, including malignant tumor progression related to RAS mutation, drug rash with eosinophilia and systemic symptoms (DRESS), drug-induced liver injury, pancreatitis, etc. Some ADRs are still controversial, and some studies are ongoing. Long-term efficacy and safety data of

treatment of vemurafenib have only been reported in clinical trials or previous case reports. And ADRs are mostly focused on a single or several systems due to strict diagnosis standards, selection criteria, relatively small sample sizes, and limited duration of follow-ups. In addition, prolonged treatment with targeted agents may result in the occurrences of previously unidentified or serious safety issues (11). Currently, data on the large sample and real-world comprehensive safety of vemurafenib are lacking. Therefore, it is necessary to employ data mining algorithms to seek out the potential ADRs signals of vemurafenib by post-marketing monitoring.

The FAERS database is used for post-marketing surveillance of drug safety, which is one of the largest pharmacovigilance databases in the world (12). Three FAERS analyses related to vemurafenib focused on the risk of cardiovascular events, DRESS (13-15). Data are lacking regarding the real-world comprehensive safety of vemurafenib. We assessed the AEs of vemurafenib by mining FAERS. In the present study, we retrospectively analyzed the AEs reported from the first quarter of 2016 to the third quarter of 2021 with vemurafenib.

METHODS

Data source and collection

Our study aimed to assess the safety of vemurafenib in the post-marketing setting. FAERS contains drug adverse event reports, product quality complaints, and medication error reports. It supports the FDA's post-marketing surveillance for drugs and therapeutic biologic products. Data from the FAERS database were innominate according to regulatory authorities. The FDA publishes FAERS files every quarter. FAERS data files encompass seven datasets, including demographic and administrative information (DEMO), drug information (DRUG), adverse drug reaction information (REAC), patient outcome information (OUTC), information on report sources (RPSR), drug therapy starts dates and end dates (THER), and indications for use/diagnosis (INDI) (11). Depending on FDA's recommendation, we chose the latest FDA_DT with the same CASEID or selected the higher PRIMARYID when the CASEID and FDA_DT were the same to recognize and remove repetitive reports (12).

AEs in FAERS reports are coded using the Medical Dictionary for Regulatory Activities (MedDRA) of Preferred Terms (PTs). All individual AEs based on MedDRA SOC, and PT level recorded on vemurafenib reports were identified to describe the spectrum of toxicities. Code for the drug's reported role in the event include PS, secondary suspect drug (SS), concomitant (C), and interacting (I). FAERS permits the reporting of arbitrary drug names, therefore, drug names were classified into the generic name (vemurafenib), including trade name (Zelboraf), and select the ROLE_COD as PS. Severe outcomes included life-threatening events or those causing hospitalization, disability, or death.

Statistical analysis

Our study analyzed AEs caused by investigating drugs but not by disease state. Currently, the signal detection applied to spontaneous reporting system databases that are mainly used can be summarized as frequency count methods and Bayesian methods around the world. The former mainly have proportional reporting ratio (PRR), ROR and MHRA. And MHRA combines PRR values, absolute reporting numbers and Pierson chi-square or corrected chi-square values to assess the strength of association of the signal (16-18). The latter includes the BCPNN applied by the WHO Upshara Global Drug Monitoring Center and the MGPS adopted by the FDA (19-20). MHRA is based on the PRR, which integrates several indicators and uses the specified threshold as the signal generation condition. The method is more rigorous, and the results are more stable. Therefore, our study did not apply the PRR algorithms. The ROR, MHRA, BCPNN, and MGPS algorithms were applied to quantify the signals of vemurafenib-associated AEs (11, 21). The equations and standards for the four algorithms are shown in Supplementary Table S1. The extraction rules of the four algorithms were used to discover signals and compute scores to measure connections between drugs and AEs. The AEs could be discovered when at least one of the four algorithms met the criteria. In general, the higher the values of the four parameters, the stronger the signal appeared to be. In our study, we chose AE signals that simultaneously met the four algorithm criteria for research. The novelty/unexpected signals are defined as any significant AEs discovered which were not listed in the FDA drug instructions (22-23).

The time-to-onset of AEs was calculated according to the following formula: (Time-to-onset = Adverse event onset date - Start date of vemurafenib use). Reports with input errors (EVENT_DT earlier than START_DT) or incorrect date entries were ruled out. The median and interquartile ranges were used to depict the time-to-onset. All data processing and statistical analyses were executed using MYSQL

8.0, Navicat Premium 15, and Microsoft EXCEL 2019.

RESULTS

General characteristics

During the study period, 8,042,244 reports were gathered from the FAERS. Totally, 9554 reports on vemurafenib were reported. The clinical characteristics of events with vemurafenib are described in Table 1. Among all AEs, males (52.02%) accounted for a more significant proportion than females (39.27%). 28.69% of the AEs occurred in people aged 18-60 years. Malignant melanoma was the most reported indication (27.19%). Serious outcomes accounted for a relatively high proportion (54.24%), with other serious medical events being the most reported outcome (25.47%), followed by hospitalization (17.46%). Death or life-threatening events were reported in 413 (9.11%) and 79 (1.74%) cases, respectively. The country that reported the most was America (66.04%). Most reports were submitted by health-care professionals, including pharmacist (38.99%), other health professionals (12.61%), and physician (6.28%). Interestingly, consumers represented the main reporter of reports accounting for 39.51%. From 2016 to 2021, with the exception of 4.12% reported in the third quarter of 2021, the most reported year was 2016 (53.25%).

Signal detection

The signal strengths of reports of vemurafenib at the System Organ Class (SOC) level are depicted in Table 2. Surprisingly, we found that vemurafenib-induced AEs occurrence targeted 23 SOCs. However, MedDRA contains only 27 SOCs in total. The significant SOCs that at least one of the four indices met the criteria were skin and subcutaneous tissue disorders (SOC: 10040785, 2860), general disorders and administration site conditions (SOC: 10018065, 1594), gastrointestinal disorders (SOC: 10017947, 1211), musculoskeletal and connective tissue disorders (SOC: 10028395, 889), neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC: 10029104, 685), investigations (SOC: 10022891, 550), metabolism and nutrition disorders (SOC: 10027433, 408), eye disorders (SOC: 10015919, 341), hepatobiliary disorders (SOC: 10019805, 122), social circumstances (SOC: 10041244, 49).

A total of 138 significant disproportionality PTs conforming to the four algorithms simultaneously are shown in Table 3. Cutaneous events, gastrointestinal events, musculoskeletal events, and neoplasms benign, malignant, and unspecified events included in the label are usually reported in patients with vemurafenib. In our research, rash (PT: 10037844), arthralgia (PT: 10003239), fatigue (PT: 10016256), nausea (PT: 10028813), diarrhoea (PT: 10012735), alopecia (PT: 10001760), decreased appetite (PT: 10061428) were presented, which were consistent with findings from clinical practice. Notably, unexpected significant AEs were uncovered in the label, including aphthous ulcer (PT: 10002959), retinal detachment (PT: 10038848), hypophysitis (PT: 10062767), sarcoidosis (PT: 10039486), nipple pain (PT: 10029421) and kidney fibrosis (PT: 10023421). However, vitiligo (PT: 10047642), cough (PT: 10011224), and cardiac disorders containing cardiac tamponade (PT: 10007610), pericarditis (PT: 10034484), atrial fibrillation (PT: 10003658) and vasculitis (PT: 10047115), which are listed in drug instructions, did not meet the criteria for at least one of the four algorithms.

Onset time of events

Apart from unreported onset time reports, a total of 1354 AEs reported onset time and the median onset time was 26 days (interquartile range [IQR] 8-97 days). As shown in Figure 1, our results suggested that the onsets of vemurafenib were changeable, most of the cases occurred within the first 1 (n = 747, 55.17%) and 2 months (n = 175, 12.92%) after vemurafenib beginning. Of note, AEs might still occur after 1 year of vemurafenib treatment with the percentage of 8.20% as illustrated in our data.

DISCUSSION

We collected and evaluated the safety of nearly six years of vemurafenib in terms of pharmacovigilance on the basis of the largest samples of real-world data. The AEs of vemurafenib occurred more commonly in males (52.02%) than in females (39.27%), which was consistent with epidemiology studies of melanoma that age and sex were strongly related to its development (24). Males are approximately 1.5-times more likely to develop melanoma than females, while the different prevalence in both sexes must be analyzed in relation to age: the rate is greater in females than males until they reach the age of 40 years, however, by 75 years of age, the incidence is almost 3-times as high in males versus females (24). Our study illustrated a higher AEs proportion in middle-aged patients (28.7%)

Table 1. Clinical characteristics of reports with vemurafenib from the FAERS.

Characteristics	Case number, n	Case proportion, %
Number of events Gender	4535	
Female	1781	39.27%
Male	2359	52.02%
Unknow	395	8.71%
Age		
<18	85	1.87%
18≤and≤65	1301	28.69%
>65	730	16.10%
Unknow	2419	53.34%
Indications (TOP five)		
Malignant melanoma	1233	27.19%
Metastatic malignant melanoma	782	17.24%
Neoplasm malignant	90	1.98%
Colon cancer	79	1.74%
Hairy cell leukaemia	61	1.35%
Serious Outcome		
Death	413	9.11%
Life-threatening	79	1.74%
Hospitalization	792	17.46%
Disability	21	0.46%
Other serious medical events	1155	25.47%
Reported Countries (TOP five)		
America	2995	66.04%
France	373	8.22%
Germany	151	3.33%
Italy	126	2.78%
Britain	122	2.69%
Reported Person health profession		
pharmacist	1768	38.99%
other health-professional	572	12.61%
physician	285	6.28%
Health-professional	94	2.07%
non-healthcare professional		
consumer	1792	39.51%
Unknow	24	0.53%
Reporting year		
2021 Q3	187	4.12%
2020	384	8.47%
2019	467	10.30%
2018	556	12.26%
2017	526	11.60%
2016	2415	53.25%

*The third quarter of 2021.

18≤and≤65 years) rather than in elderly patients (16.10%>65 years). It is different from the age distribution of most cancer patients (25), maybe due to more than half of the patients whose age was unknown in our findings (53.34%). In terms of reporting time, the number of reports increased significantly in 2016. It may be due to increased public awareness of AEs with vemurafenib.

Rash was among the most commonly reported adverse effects of vemurafenib therapy. At a dosing of 960 mg of vemurafenib twice daily orally, 25%, 52%, and 18% of patients experienced a rash in phase I-III clinical trials, respectively, with 3%, 7%, and 8% experiencing grade 3 symptoms (1,5,26). It is consistent with our findings. Additionally, a follicularly centered eruption has been described in sundry case reports, with beginning as early as 5 days after starting vemurafenib (20, 21). This is similar to our findings: 55.17% of patients experienced adverse events within the first 30 days of starting treatment.

Table 2. Signal strength of reports of vemurafenib at the System Organ Class (SOC) level in FAERS.

System Organ Class (SOC)	Vemurafenib Cases Reporting SOC	ROR (95% two-sided CI)	PRR (χ2)	IC (95% two-sided CI)	EBGM (EBGM 05)
Skin and subcutaneous tissue disorders	2860	8.48(8.12-8.86)*	6.24(13195.76)*	2.64(2.57,2.70)*	6.23(5.96)*
General disorders and administration site conditions	1594	1.54(1.46-1.62)*	1.45(249.61)	0.53(0.46,0.61)*	1.17(1.11)
Gastrointestinal disorders	1211	2.56(2.41-2.72)*	2.36(1005.93)*	1.24(1.15,1.33)*	1.91(1.80)
Musculoskeletal and connective tissue disorders	889	2.73(2.55-2.92)*	2.57(883.02)*	1.36(1.26,1.46)*	2.08(1.94)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	685	3.40(3.14-3.67)*	3.23(1074.26)*	1.69(1.57,1.80)*	2.61(2.41)*
Investigations	550	1.74(1.60-1.90)*	1.70(164.28)	0.77(0.63,0.89)*	1.38(1.26)
Injury, poisoning and procedural complications	490	0.58(0.53-0.63)	0.60(143.26)	-0.74(-0.87,-0.61)	0.49(0.44)
Metabolism and nutrition disorders	408	2.07(1.87-2.28)*	2.02(215.35)*	1.02(0.86,1.15)*	1.64(1.48)
Eye disorders	341	2.90(2.61-3.23)*	2.84(409.92)*	1.50(1.33,1.65)*	2.30(2.06)*
Nervous system disorders	137	0.22(0.19-0.26)	0.23(375.67)	-2.12(-2.37,-1.87)	0.19(0.16)
Hepatobiliary disorders	122	1.65(1.38-1.98)*	1.65(31.18)	0.72(0.44,0.96)*	1.33(1.12)
Infections and infestations	58	0.18(0.14-0.23)	0.18(215.96)	-2.44(-2.82,-2.06)	0.15(0.12)
Psychiatric disorders	49	0.13(0.10-0.17)	0.14(279.9)	-2.88(-3.3,-2.47)	0.11(0.08)
Social circumstances	49	1.48(1.12-1.96)*	1.47(7.52)	0.56(0.10,0.93)*	1.19(0.90)
Cardiac disorders	24	0.07(0.05-0.11)	0.08(282.07)	-3.73(-4.33,-3.15)	0.06(0.04)
Respiratory, thoracic, and mediastinal disorders	20	0.05(0.03-0.07)	0.05(382.28)	-4.34(-4.99,-3.70)	0.04(0.03)
Blood and lymphatic system disorders	15	0.11(0.06-0.18)	0.11(110.8)	-3.2(-3.95,-2.46)	0.09(0.05)
Endocrine disorders	13	0.18(0.10-0.30)	0.18(49.69)	-2.49(-3.31,-1.71)	0.14(0.08)
Immune system disorders	11	0.04(0.02-0.07)	0.04(256.64)	-4.62(-5.5, -3.76)	0.03(0.02)
Vascular disorders	10	0.02(0.01-0.04)	0.02(435.31)	-5.44(-6.36,-4.53)	0.02(0.01)
Reproductive system and breast disorders	9	0.07(0.04-0.14)	0.08(102.85)	-3.72(-4.7,-2.77)	0.06(0.03)
Ear and labyrinth disorders	5	0.14(0.06-0.33)	0.14(27.22)	-2.86(-4.19,-1.61)	0.11(0.05)
Renal and urinary disorders	4	0.02(0.01-0.05)	0.02(187.59)	-5.58(-7.03,-4.15)	0.02(0.01)

* indicate statistically significant signals in algorithm. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; EBGM, empirical Bayesian geometric mean.

Table 3. Signal strength of reports of vemurafenib at the Preferred Term (PT) level in FAERS database.

SOC	Preferred Terms (PTs)	Vemurafenib Cases Reporting PT	ROR (95% two-sided CI)	PRR(χ2)	IC (95% two-sided CI)	EBGM (EBGM 05)
Skin and subcutaneous tissue disorders	Rash	818	9.08(8.46,9.74)	8.63(5530.55)	3.09(2.99,3.19)	8.60(8.01)
	Alopecia	372	7.00(6.31,7.76)	6.85(1857.70)	2.74(2.59,2.90)	6.83(6.16)
	Pruritus	206	2.74(2.39,3.15)	2.72(224.83)	1.42(1.22,1.63)	2.72(2.37)
	Photosensitivity reaction	167	48.96(41.95,57.14)	48.42(7558.00)	5.20(4.97,5.43)	47.2(40.44)
	Erythema	142	2.76(2.34,3.25)	2.74(157.38)	1.43(1.18,1.67)	2.74(2.32)
	Blister*	91	8.32(6.77,10.23)	8.27(579.81)	2.92(2.61,3.22)	8.24(6.70)
	Hyperkeratosis	91	84.96(68.81,104.89)	84.44(7173.59)	5.42(5.11,5.73)	80.77(65.42)
	Dry skin	86	2.30(1.86,2.85)	2.29(62.87)	1.16(0.85,1.47)	2.29(1.85)
	Rash maculo-papular	71	16.66(13.18,21.06)	16.58(1030.75)	3.74(3.39,4.08)	16.44(13.01)
	Skin exfoliation*	70	3.19(2.52,4.04)	3.18(104.66)	1.60(1.26,1.95)	3.18(2.51)
	Drug reaction with eosinophilia and systemic symptoms	59	9.63(7.45,12.44)	9.59(451.93)	3.04(2.66,3.42)	9.55(7.39)
	Skin toxicity	55	53.38(40.81,69.83)	53.19(2737.30)	4.74(4.34,5.13)	51.72(39.54)
	Skin mass*	45	29.68(22.10,39.87)	29.60(1223.70)	4.14(3.71,4.58)	29.14(21.70)
	Rash erythematous	43	5.27(3.90,7.11)	5.25(147.78)	2.22(1.78,2.67)	5.24(3.88)
	Dermatitis acneiform	35	29.38(21.03,41.05)	29.32(942.33)	3.98(3.49,4.48)	28.87(20.67)
	Stevens-Johnson syndrome	34	10.27(7.33,14.39)	10.25(282.20)	2.97(2.47,3.47)	10.20(7.28)

Tables 3. continues…

	Rash pruritic	31	3.12(2.19,4.44)	3.12(44.50)	1.50(0.98,2.02)	3.11(2.19)
	Palmar-plantar erythrodysaesthesia syndrome	30	6.00(4.19,8.59)	5.99(124.37)	2.32(1.79,2.85)	5.97(4.17)
	Skin disorder	28	4.31(2.98,6.25)	4.31(70.98)	1.90(1.35,2.44)	4.30(2.97)
	Toxic skin eruption	27	13.83(9.47,20.21)	13.81(318.46)	3.19(2.63,3.74)	13.71(9.39)
	Erythema multiforme	26	16.11(10.94,23.70)	16.08(364.51)	3.31(2.74,3.87)	15.95(10.84)
	Rash papular	23	4.23(2.81,6.37)	4.23(56.55)	1.83(1.23,2.44)	4.22(2.80)
	Skin discolouration*	23	2.27(1.51,3.42)	2.27(16.33)	1.05(0.44,1.65)	2.27(1.51)
	Skin lesion	20	3.68(2.37,5.71)	3.68(38.95)	1.63(0.99,2.28)	3.67(2.37)
	Dermatitis	19	4.07(2.59,6.39)	4.07(43.85)	1.74(1.08,2.41)	4.06(2.59)
	Drug eruption	19	6.23(3.97,9.78)	6.23(83.12)	2.23(1.56,2.89)	6.21(3.96)
	Skin reaction	18	5.70(3.59,9.05)	5.69(69.44)	2.11(1.43,2.79)	5.68(3.57)
	Skin ulcer*	17	3.06(1.90,4.92)	3.05(23.44)	1.37(0.67,2.07)	3.05(1.89)
	Panniculitis	16	29.88(18.23,48.97)	29.85(438.93)	3.37(2.65,4.10)	29.38(17.92)
	Keratosis pilaris	15	339.9(195.88,589.82)	339.56(4272.28)	3.83(3.03,4.63)	286.66(165.19)
	Purpura*	11	7.03(3.89,12.71)	7.02(56.61)	2.10(1.22,2.97)	7.00(3.87)
	Actinic keratosis	10	16.94(9.09,31.58)	16.93(148.53)	2.65(1.73,3.56)	16.79(9.00)
	Erythema nodosum	10	16.85(9.04,31.41)	16.84(147.62)	2.64(1.73,3.56)	16.69(8.95)
	Neutrophilic panniculitis	9	569.4(269.49,1203.06)	569.05(3894.78)	3.14(2.07,4.21)	434.51(205.65)
	Palmoplantar keratoderma	9	110.82(56.54,217.22)	110.76(923.13)	3.05(2.06,4.04)	104.50(53.32)
	Rash morbilliform	9	16.41(8.51,31.64)	16.40(129.04)	2.53(1.57,3.50)	16.27(8.44)
	Scab*	9	3.45(1.80,6.64)	3.45(15.65)	1.32(0.35,2.28)	3.45(1.79)
	Solar dermatitis	9	131.05(66.63,257.76)	130.97(1083.44)	3.07(2.07,4.06)	122.31(62.18)
	Dermatitis bullous	7	5.09(2.42,10.69)	5.09(22.93)	1.56(0.46,2.65)	5.08(2.42)
	Dermatitis exfoliative generalised	7	7.89(3.75,16.57)	7.88(41.90)	1.89(0.79,2.98)	7.85(3.74)
	Neutrophilic dermatosis*	6	56.44(25.04,127.2)	56.42(316.87)	2.43(1.24,3.63)	54.76(24.30)
	Rash follicular*	5	173.04(69.16,432.95)	172.98(781.24)	2.28(0.93,3.62)	158.16(63.21)
	Rash vesicular*	5	5.22(2.17,12.56)	5.22(17.00)	1.35(0.06,2.64)	5.21(2.16)
	Skin hypertrophy*	5	9.97(4.14,24.01)	9.97(40.11)	1.73(0.44,3.03)	9.92(4.12)
	Milia*	4	84.33(30.95,229.78)	84.30(314.79)	1.93(0.46,3.40)	80.64(29.60)
General disorders and administration site conditions	Fatigue	555	3.39(3.11,3.69)	3.30(899.00)	1.71(1.59,1.84)	3.30(3.03)
	Pyrexia	279	4.21(3.74,4.74)	4.15(668.29)	2.03(1.85,2.20)	4.14(3.68)
	Mass	165	52.2(44.68,60.98)	51.63(7969.42)	5.27(5.04,5.50)	50.24(43.00)
	Peripheral swelling	111	2.7(2.24,3.26)	2.69(117.84)	1.39(1.12,1.67)	2.69(2.23)
	Disease progression	83	4.23(3.41,5.25)	4.21(203.26)	2.00(1.68,2.32)	4.21(3.39)
	Swelling	67	3.26(2.56,4.14)	3.25(104.15)	1.63(1.28,1.98)	3.24(2.55)
	Chills	65	2.95(2.31,3.77)	2.95(83.49)	1.49(1.13,1.85)	2.94(2.31)
	Swelling face*	37	2.88(2.08,3.98)	2.87(45.17)	1.41(0.94,1.89)	2.87(2.08)
	Decreased activity	35	17.61(12.62,24.58)	17.57(541.93)	3.54(3.05,4.03)	17.42(12.48)
	Mucosal inflammation*	28	5.31(3.66,7.70)	5.30(97.54)	2.15(1.61,2.70)	5.29(3.65)
	Face oedema*	15	5.1(3.07,8.47)	5.10(49.25)	1.92(1.18,2.67)	5.08(3.06)
	Nodule	8	2.97(1.48,5.94)	2.97(10.43)	1.11(0.09,2.13)	2.97(1.48)
	Hyperthermia	7	4.56(2.17,9.57)	4.55(19.37)	1.46(0.37,2.55)	4.55(2.16)
	Performance status decreased	6	7.43(3.33,16.56)	7.42(33.22)	1.73(0.55,2.91)	7.4(3.32)
	Xerosis	6	31.09(13.87,69.68)	31.08(171.75)	2.33(1.14,3.51)	30.58(13.64)
Gastrointestinal disorders	Nausea	387	2.48(2.24,2.74)	2.44(331.99)	1.28(1.13,1.43)	2.44(2.20)
	Diarrhoea	376	2.76(2.49,3.05)	2.71(409.74)	1.43(1.28,1.58)	2.71(2.45)
	Dysphagia	91	5.00(4.07,6.15)	4.98(288.97)	2.24(1.93,2.54)	4.97(4.04)
	Aphthous ulcer*	9	4.69(2.44,9.02)	4.69(26.04)	1.62(0.66,2.59)	4.68(2.43)
	Oral mucosal blistering*	9	5.95(3.09,11.46)	5.95(36.96)	1.84(0.87,2.80)	5.94(3.08)
	Lip blister*	7	12.3(5.85,25.87)	12.29(72.15)	2.15(1.06,3.25)	12.22(5.81)

Tables 3. continues…

	Cheilitis	5	5.74(2.38,13.80)	5.73(19.48)	1.42(0.12,2.71)	5.72(2.38)
Musculoskeletal and connective tissue disorders	Arthralgia	582	7.48(6.88,8.12)	7.22(3125.06)	2.83(2.71,2.95)	7.20(6.62)
	Myalgia	205	6.15(5.36,7.06)	6.08(869.51)	2.56(2.36,2.76)	6.06(5.28)
	Limb mass*	16	21.16(12.92,34.64)	21.14(303.46)	3.18(2.45,3.91)	20.91(12.77)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin papilloma	130	162.25(135.52,194.25)	160.84(18986.24)	6.11(5.85,6.38)	147.95(123.58)
	Squamous cell carcinoma	123	60.57(50.58,72.54)	60.08(6919.99)	5.3(5.04,5.57)	58.2(48.60)
	Metastases to central nervous system*	101	41.74(34.25,50.88)	41.47(3901.13)	4.86(4.56,5.15)	40.57(33.29)
	Melanocytic naevus*	74	78.73(62.35,99.41)	78.34(5419.07)	5.22(4.88,5.56)	75.17(59.54)
	Squamous cell carcinoma of skin	33	26.41(18.72,37.25)	26.35(793.60)	3.86(3.36,4.37)	26.00(18.43)
	Malignant melanoma	32	9.60(6.78,13.60)	9.58(244.82)	2.88(2.37,3.39)	9.54(6.74)
	Keratoacanthoma	31	276.51(189.48,403.49)	275.93(7381.32)	4.78(4.23,5.33)	239.97(164.45)
	Acrochordon*	29	115.32(79.21,167.88)	115.1(3086.39)	4.52(3.96,5.07)	108.36(74.43)
	Neoplasm	22	9.90(6.51,15.06)	9.89(174.83)	2.77(2.15,3.38)	9.84(6.47)
	Basal cell carcinoma	19	5.38(3.43,8.44)	5.37(67.46)	2.06(1.40,2.73)	5.36(3.42)
	Seborrhoeic keratosis	14	58.13(34.14,98.99)	58.08(761.24)	3.49(2.70,4.27)	56.33(33.08)
	Brain neoplasm*	11	5.88(3.25,10.64)	5.88(44.42)	1.94(1.06,2.81)	5.86(3.24)
	Metastasis	10	7.66(4.12,14.26)	7.66(57.63)	2.11(1.20,3.03)	7.63(4.10)
	Metastatic malignant melanoma	9	16.95(8.79,32.69)	16.94(133.79)	2.55(1.58,3.52)	16.8(8.71)
	Malignant melanoma in situ	6	14.29(6.4,31.92)	14.29(73.58)	2.08(0.89,3.26)	14.19(6.35)
	Benign neoplasm of skin	5	61.55(25.24,150.08)	61.53(288.07)	2.21(0.89,3.52)	59.57(24.43)
	Tumour haemorrhage*	5	7.80(3.24,18.79)	7.80(29.53)	1.61(0.31,2.90)	7.77(3.23)
	Melanoma recurrent	4	41.45(15.38,111.68)	41.44(154.36)	1.86(0.41,3.32)	40.54(15.05)
Investigations	Blood lactate dehydrogenase increased*	81	31.89(25.59,39.75)	31.72(2369.47)	4.49(4.17,4.82)	31.2(25.03)
	Hepatic enzyme increased	56	4.43(3.41,5.76)	4.42(147.96)	2.03(1.65,2.42)	4.41(3.39)
	Blood creatinine increased	51	4.20(3.19,5.53)	4.19(123.60)	1.95(1.54,2.36)	4.18(3.17)
	Electrocardiogram QT prolonged	49	6.03(4.55,7.98)	6.01(204.10)	2.42(2.00,2.83)	5.99(4.53)
	Aspartate aminotransferase increased	39	4.80(3.51,6.58)	4.79(116.76)	2.09(1.63,2.55)	4.78(3.49)
	Blood bilirubin increased	39	8.44(6.16,11.57)	8.42(254.08)	2.79(2.32,3.25)	8.39(6.12)
	Alanine aminotransferase increased	33	3.27(2.32,4.60)	3.26(51.67)	1.57(1.06,2.07)	3.26(2.31)
	Blood creatine phosphokinase increased*	29	6.67(4.63,9.61)	6.66(139.13)	2.43(1.90,2.97)	6.64(4.61)
	Liver function test increased	25	3.86(2.60,5.71)	3.85(52.72)	1.74(1.16,2.32)	3.85(2.60)
	Gamma-glutamyltransferase increased	22	5.89(3.87,8.95)	5.88(88.88)	2.21(1.59,2.83)	5.87(3.86)
	Blood alkaline phosphatase increased	20	5.18(3.34,8.03)	5.17(67.09)	2.04(1.39,2.68)	5.16(3.32)
	Ejection fraction decreased*	18	5.70(3.59,9.06)	5.70(69.49)	2.11(1.43,2.79)	5.68(3.58)
	Transaminases increased	18	3.59(2.26,5.70)	3.59(33.51)	1.58(0.90,2.26)	3.58(2.25)
	Lipase increased	11	8.16(4.51,14.76)	8.16(68.77)	2.22(1.35,3.10)	8.12(4.49)
Injury, poisoning and procedural complications	Sunburn	251	174.46(153.13,198.76)	171.54(38919.24)	6.59(6.40,6.78)	156.95(137.76)
	Thermal burn	9	7.01(3.64,13.50)	7.01(46.21)	1.98(1.01,2.94)	6.99(3.63)
	Radiation skin injury	8	34.61(17.20,69.68)	34.60(256.17)	2.69(1.67,3.72)	33.97(16.88)
	Recall phenomenon	6	40.46(18.02,90.88)	40.45(225.85)	2.38(1.19,3.57)	39.6(17.63)
Metabolism and nutrition disorders	Decreased appetite	285	5.95(5.29,6.69)	5.85(1146.37)	2.52(2.34,2.69)	5.84(5.19)
	Hypokalaemia*	31	3.49(2.46,4.97)	3.49(54.99)	1.65(1.13,2.17)	3.48(2.45)
	Hypercholesterolaemia*	9	7.81(4.06,15.03)	7.80(53.16)	2.06(1.10,3.02)	7.77(4.04)
	Hypophosphataemia*	9	6.28(3.26,12.09)	6.28(39.80)	1.88(0.92,2.85)	6.26(3.25)
	Hypertriglyceridaemia*	7	6.32(3.01,13.27)	6.32(31.22)	1.73(0.64,2.82)	6.30(3.00)
Eye disorders	Vision blurred	74	2.86(2.28,3.60)	2.85(89.15)	1.46(1.12,1.79)	2.85(2.27)
	Uveitis	47	18.13(13.6,24.17)	18.07(750.84)	3.7(3.27,4.12)	17.91(13.43)
	Ocular hyperaemia*	37	3.97(2.87,5.48)	3.96(81.86)	1.84(1.36,2.31)	3.96(2.86)
	Chorioretinopathy*	20	49.29(31.6,76.87)	49.22(920.22)	3.82(3.17,4.47)	47.96(30.75)

Tables 3. continues…

	Retinal detachment*	18	10.57(6.65,16.8)	10.56(154.88)	2.73(2.05,3.41)	10.50(6.61)
	Serous retinal detachment*	14	88.30(51.63,150.99)	88.22(1151.77)	3.59(2.80,4.37)	84.21(49.25)
	Iridocyclitis	11	17.72(9.78,32.10)	17.71(171.76)	2.76(1.88,3.63)	17.55(9.69)
	Retinopathy	10	14.11(7.57,26.30)	14.10(120.83)	2.54(1.63,3.46)	14.00(7.52)
	Retinal oedema	4	13.71(5.13,36.68)	13.71(46.78)	1.63(0.18,3.08)	13.61(5.09)
Nervous system disorders	Dysgeusia	81	6.36(5.11,7.91)	6.33(362.57)	2.55(2.23,2.87)	6.31(5.07)
	Facial paralysis*	18	6.17(3.89,9.81)	6.17(77.70)	2.20(1.52,2.88)	6.15(3.87)
	Guillain-Barre syndrome*	9	10.44(5.42,20.11)	10.44(76.37)	2.27(1.30,3.23)	10.38(5.39)
	Hyperaesthesia	8	4.71(2.35,9.42)	4.70(23.28)	1.56(0.54,2.59)	4.70(2.35)
Hepatobiliary disorders	Hepatotoxicity	21	4.52(2.94,6.93)	4.51(57.25)	1.89(1.26,2.52)	4.50(2.93)
	Cholestasis*	20	5.18(3.34,8.04)	5.18(67.20)	2.04(1.39,2.68)	5.16(3.33)
	Hypertransaminasaemia	5	4.91(2.04,11.8)	4.91(15.51)	1.31(0.01,2.60)	4.89(2.03)
Infections and infestations	Conjunctivitis*	13	3.60(2.09,6.20)	3.60(24.32)	1.49(0.69,2.29)	3.59(2.08)
	Folliculitis	12	10.9(6.18,19.23)	10.89(107.19)	2.51(1.67,3.35)	10.83(6.14)
	Rash pustular*	10	6.85(3.68,12.75)	6.85(49.77)	2.02(1.11,2.94)	6.83(3.67)
	Furuncle*	7	4.20(2.00,8.82)	4.20(17.02)	1.39(0.3,2.48)	4.19(2.00)
Psychiatric disorders	Poor quality sleep	49	11.25(8.49,14.91)	11.22(453.42)	3.18(2.77,3.60)	11.16(8.42)
Social circumstances	Impaired work ability	46	10.42(7.8,13.93)	10.39(388.4)	3.08(2.65,3.50)	10.34(7.73)
Cardiac disorders	Cardiotoxicity	9	5.02(2.61,9.65)	5.01(28.84)	1.68(0.72,2.65)	5.00(2.60)
Endocrine disorders	Hypophysitis*	5	8.52(3.54,20.50)	8.51(33.00)	1.65(0.36,2.95)	8.48(3.52)
Immune system disorders	Sarcoidosis*	11	11.36(6.28,20.56)	11.36(103.26)	2.48(1.61,3.35)	11.29(6.24)
Reproductive system and breast disorders	Nipple pain*	6	16.07(7.19,35.89)	16.06(84.01)	2.12(0.94,3.31)	15.93(7.13)
Renal and urinary disorders	Kidney fibrosis*	4	12.09(4.52,32.31)	12.08(40.40)	1.59(0.14,3.03)	12.01(4.49)

*Emerging findings of vemurafenib associated AEs from FAERS database. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; $\chi 2$, chi-squared; IC, information component; EBGM, empirical Bayesian geometric mean.

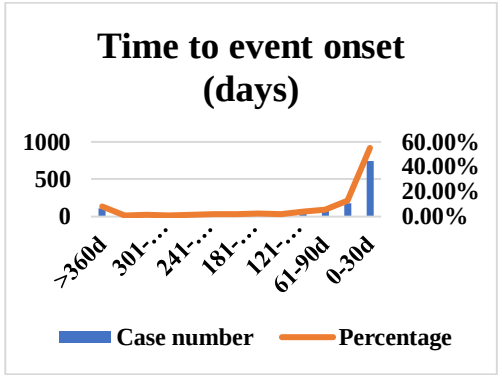

Figure 1. Time to onset of vemurafenib-related AEs.

With vemurafenib, a frequent rash is likely a hypersensitivity reaction that, however, does not preclude rechallenge in most cases. Most patients with rash were able to sustain full dose intensity or continue therapy after one dose-level reduction. An unprompted recovery rate of approximately 50% for grade 1and 2 rash without dose decrease was noted (27). Even so, clinicians should be aware of these AEs to educate better and manage their patients, as well as minimize the impact on patient quality of life. In addition, photosensitivity reactions were reported in 52% of vemurafenib-treated patients in phase II clinical trials (19). Broad spectrum sunscreens with a sun protection factor of at least 30 have shown validity in preventing photosensitivity skin reactions in patients during vemurafenib therapy; thus, their daily use should be proposed, regardless of sunlight intensity or season (20, 23). In addition to benign cutaneous adverse events, vemurafenib may also cause malignant cutaneous adverse events, most typically cutaneous squamous cell carcinoma (cuSCC). In our study, one of the most commonly reported grade 3 AEs associated with vemurafenib treatment was cuSCC with significant signal strength being 26.41 (18.72,37.25), 26.35 (793.6), 3.86 (3.36,4.37), and 26.00 (18.43), respectively. Risk factors for vemurafenib-associated cuSCC are similar to those for sporadic cases, including long-range sun exposure, and lesions develop more frequently in sun-exposed areas.1 The mechanism of cuSCC induced by vemurafenib could be attributed to the ability of vemurafenib to paradoxically activate the MAPK pathway in cells devoid of a BRAF mutation (24, 25). On the other hand, some reports demonstrated a high frequency of RAS, TGF-β-receptor or p53 oncogenic mutation in skin tumors among patients treated with BRAF inhibitors (26-28). Similarly, cutaneous papillomas and keratoacanthomas were detected in our research, with significant signal strength. There are also some reports of adverse events in malignant melanoma with vemurafenib in our study. Although malignant melanoma has been included in the instructions of vemurafenib, it cannot be ruled out the failure of one prior systemic therapy. And metastatic melanoma patients may still have tumor metastasis and tumor progression when the efficacy of vemurafenib is imperfect. However, due to the characteristics of local invasion and distant metastasis of malignant tumors, it might be illogical to determine whether tumor metastasis and tumor progression are caused by vemurafenib only by ADR signals.

It is noteworthy that the long-term use of vemurafenib is associated with a risk of eye disorders AEs, and the most common is uveitis (28). The pathogenesis of uveitis is unclear. At present, it has some predictions. One is direct vemurafenib action on subclinical metastatic cells within the uveal tract. The second possible mechanism is that the uveitis is caused by an inflammatory response to antigens shared by melanocytes in the melanoma and the choroid. The study showed that among the 568 patients treated with vemurafenib, ocular adverse effects developed in 22% (28). Vemurafenib should be discontinued if patients experience intolerable adverse events. However, it can be continued while the ocular symptoms are being managed. In some cases, the patients were treated with steroids (oral, periocular, or intravitreal) and mydriatic; and responded favorably (29). In addition, research has shown that exclude the possibility that prior therapies, especially immunotherapies, could increase the risk for uveitis from vemurafenib treatment.30 Although many of the ocular adverse events seen are not usually severe, uveitis is potentially blinding. Therefore, it deserves enough attention from doctors in clinical practice. In addition to uveitis, the ophthalmic AEs listed in the instruction of vemurafenib include vision blurred, iritis, photophobia, and retinal vein occlusion (23). Similarly, our study detected the novelty ophthalmic AEs of chorioretinopathy, retinal detachment and serous retinal detachment that were strongly associated with vemurafenib. The signal strength of serous retinal detachment is the most significant that was 88.30(51.63,150.99), 88.22(1151.77), 3.59(2.80,4.37), 84.21(49.25). According to recent literature reports (30), 901 patients of BRAF inhibitors treatment, 14 (1.6%) patients experienced an ophthalmic AE. The most common AE was uveitis in 7 (50%) patients, followed by dry eye in 4 (29%) patients, and central serous chorioretinopathy in 2 (14%) patients, with singular cases of cranial nerve VI palsy and conjunctival edema. It is speculated that chorioretinopathy and retinal detachment may be one of the causes of blurred vision caused by vemurafenib, but further research was needed to test this hypothesis. It is necessary for clinicians to pay more attention to the ocular AEs caused by vemurafenib.

Except for ophthalmic AEs, unexpected and significant safety signals such as aphthous ulcer, hypophysitis, sarcoidosis, nipple pain, kidney fibrosis, metastases to central nervous system,

hypercholesterolaemia and hypertriglyceridaemia were detected in our analysis. Surprisingly, as reported by Teuma et al., who found that biopsy from a woman aged 39 years after 7 months of vemurafenib treatment: X100 with Masson's trichrome staining showing chronic interstitial fibrosis with some dilated tubules in clinical (31). And it also prompted us to think that the significant risk factor for developing Acute Kidney Injury observed was male gender. The pathophysiology of vemurafenib nephrotoxicity is not completely understood. They speculate that extracellular signal-regulated kinase could play a role in the pathophysiology of renal diseases (31). Dam et al. reported vemurafenib-induced emergence of diffuse pulmonary micronodules with miliary lung on melanoma on his back patient, whose condition improved with surgical lung biopsy, and treatment with vemurafenib was continued (32). Another similar patient is reported in this case report. A 68-year-old patient with widely metastatic melanoma presented with the appearance of purplish skin lesions consistent with those of nodular dermatitis on the elbows next to the blood puncture site and on previous scars on the chest after taking vemurafenib in clinical. Biopsy of a skin lesion found a granulomatous infiltrate consistent with sarcoidosis (32). Meanwhile, a case report of a patient who had metastatic melanoma and was subsequently treated with anti-CTLA-4 (cytotoxic T lymphocyte-associated antigen-4, CTLA-4) monoclonal antibody and a selective BRAF inhibitor hinted at a possible deterioration of pre-existing sarcoidosis (33). Physicians managing such patients should be aware of this adverse event, as obfuscating pulmonary or lymph node sarcoidosis might be mistakenly interpreted as a progression of the metastatic disease. All of these events were qualified as AEs related to vemurafenib treatment. However, the exact mechanism of kidney fibrosis and sarcoidosis remained unclear and future research is still needed to confirm our findings. Although we cannot rule out that the significant signal of metastases to central nervous system is caused by uncontrolled tumors, as the study confirmed intracranial partial response to vemurafenib was 16%, with intracranial disease stabilization observed in 68% of patients (34). However, there are still studies reporting that one year after the beginning of the vemurafenib plus cobimetinib treatment, she developed a sub-acutemotor neuropathy with predominant cranial nerve involvement (35). This AE is more associated with vemurafenib use, and a combination of cobimetinib may increase vemurafenib AEs. Therefore, we still need to be particularly vigilant about the neurological adverse events of vemurafenib, and it can be treated with steroids medication if necessary. Marco et al. reported vemurafenib could be related to an increased hazard of dyslipidemia (36). In this study, children treated with vemurafenib showed a worsening in their lipid profiles, with a significant increase in triglycerides, low-density lipoprotein, and total cholesterol over time. On the other hand, in a phase I study that researched the pharmacokinetics, efficacy, and tolerability of vemurafenib (960 mg twice daily) in 42 Chinese patients (median age: 42, 19–69) with BRAFV600-mutation-positive unresectable or metastatic melanoma, dyslipidemia was a common AE, contrasted with the BRIM-3 study in Caucasians (cholesterol-level increase in 59% vs. <1%, hypertriglyceridemia in 22% vs. <1%) (34). To sum up, an accurate screening strategy in new clinical tests, and a multidisciplinary team, are demanded the optimal management of novelty AEs, including dyslipidemia. In addition, we did not find relevant literature reports about other significant new signals, like hypophysitis and nipple pain. Accordingly, further clinical studies are necessary to understand the pathogenesis of these AEs. Clinicians should be aware of these new and unexpected complications, and FDA could revise and give warnings on the label, if necessary, especially as novel multi-target kinase inhibitors are now being more widely used in cancer patients.

Results of this study indicated that the median onset time was 26 days, and most of the cases occurred within the first 1 (n = 747, 55.17%) and 2 months (n = 175, 12.92%) after vemurafenib initiation, which was consistent with that median time to the first incidence of grade 3 and 4 adverse events was 1.7 months reported by a previous study from clinical trials (31). With the increasing clinical application of vemurafenib in metastatic melanoma treatment, it is necessary for clinicians to be vigilant about the AEs associated with vemurafenib. Early recognition of AEs caused by vemurafenib therapy is essential because these AEs can be life-threatening.

Although the data mining techniques used in this study has many superiorities, unavoidable there are several limitations (37). Firstly, due to the voluntary of FAERS database, there are inaccurate, incomplete, false, and missing reports, all of which can result in reporting bias. Secondly, the voluntary reporting system is only used for qualitative study. Due to the lack of information on the completeness

of the reports in FAERS, it is hard to control confounders, such as age, dose, weight, comorbidities, drug combinations, or other factors that may influence AEs. Thirdly, the four algorithms have their limitations. ROR and MHRA are susceptible to target AEs of the target drug leading to biased results. BCPNN has the disadvantages of a large network construction workload, complex parameter settings, and relatively low sensitivity (38). The MGPS, which considers variables at different levels to reduce the influence of confounding factors in demographic data, can effectively avoid false positives and is more robust (39). Therefore, we apply four algorithms at the same time. Fourth, although data mining techniques can provide an outline of AEs for all drugs through signal detection, it is often not enough to prove a causal relationship between the target drug and AEs, and signal strength only indicates their strong statistical correlation. Since FAERS only added up reports of AEs with vemurafenib and did not include all reports using vemurafenib, it was impossible to define the incidence denominators in the disproportionality analysis. Therefore, we cannot verify the precise incidence of each AEs throughout the patient cohort. Despite these limitations in pharmacovigilance studies using FAERS, an exhaustive characterization of the AE signals from vemurafenib and the identification of new serious and unexpected AE signals may provide proof for further clinical research of vemurafenib.

CONCLUSION

Our pharmacovigilance analysis of FAERS comprehensively and systematically revealed the safety signals and time to AEs onsets in metastatic melanoma with the BRAF V600E mutation treatment with vemurafenib. Unexpected and new significant AEs such as sarcoidosis and kidney fibrosis might also occur. AEs of common skin, gastrointestinal, musculoskeletal and second primary cancer should be highly concern. Close guardianship and risk identification of these AEs is recommended in all populations. Cohort studies and long-term clinical research are still needed to determine these findings and to further understand the safety of vemurafenib.

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CONFLICTS OF INTERESTS. The authors declare that they have no conflicts of interest related to the subject matter discussed in this article.

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Supplementary Table 1. Four major algorithms used for signal detection.

Algorithms	Equation	Criteria
ROR	ROR=ad/b/c 95%CI=$e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	lower limit of 95% CI>1, N≥3
MHRA	PRR=a(c+d)/c/(a+b) χ^2=[(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]	PRR≥2, χ^2≥4, N≥3
BCPNN	IC=$\log_2$a(a+b+c+d)(a+c)(a+b) 95%CI= E(IC) ± 2V(IC)^0.5	IC025>0
MGPS	EBGM=a(a+b+c+d)/(a+c)/(a+b) 95%CI=$e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	EBGM05>2

Equation: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions. 95%CI, 95% confidence interval; *N*, the number of reports; χ^2, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; E(IC), the IC expectations; V(IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.