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Analyzing the adverse events of NK-1 receptor antagonists: a pharmacovigilance study from the FAERS database

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Background NK-1 receptor antagonists (NK-1RAs) are proven to be successful in preventing chemotherapy-induced nausea and vomiting (CINV). The safety profile of NK-1RAs has not been systematically analyzed in the real world. This pharmacovigilance study investigated the differences in adverse events (AEs) between NK-1RAs.

Methods Adverse events (AEs) associated with NK-1RAs were gathered and standardized using data from the FAERS database spanning from the first quarter of 2009 to the fourth quarter of 2023. Various disproportionality techniques were employed for data analysis, such as the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinker (MGPS).

Results A total of 5434AE reports listing NK-1RAs as the primary suspected drugs were identified. The System Organ Classes (SOC) appeared as significant safety signals were found. Among NK-1RAs, the most frequently reported AEs were related to general disorders and administration site conditions. In terms of PT level, the strong signals were mainly injection site reactions associated with aprepitant and fosaprepitant. Moreover, toxic encephalopathy and encephalopathy of the aprepitant were all positive with four algorithms. A significant finding was the recognition of adverse events linked to endocrine disorders, which were not previously mentioned in the medication instructions.

Conclusion The safety profile of NK-1RAs has been reported to be variable.If intravenous formulations were used in the clinic, injection site reactions should be a concern. In addition, more attention should be paid to the management of encephalopathy toxicity in patients treated with aprepitant in combination with ifosfamide. Besides known AEs, we have identified several new high-risk AEs, such as inappropriate antidiuretic hormone secretion, adrenal insufficiency and hyponatraemia. Overall, clinicians should closely monitor the occurrence of NK-1RA-related AEs in clinical applications.

Keywords NK-1 receptor antagonists, Adverse events, FAERS database, Pharmacovigilance, Drug safety

Chemotherapy-induced nausea and vomiting (CINV) is a prevalent and distressing side effect of cancer therapy, impacting a substantial proportion of patients[1]. In 2022, the global incidence of malignant tumors reached nearly 20 million cases, resulting in approximately 9.7 million fatalities[2]. Concurrently, China reported nearly 4.82 million new cases of malignant tumors, leading to approximately 2.57 million deaths[3]. Chemotherapy continues to serve as the primary modality for treating tumors, with CINV representing a frequently encountered adverse reaction. CINV impacted a considerable number of patients receiving moderately or highly emetogenic chemotherapy, with up to 61% experiencing symptoms despite prophylactic measures[4]. The pathophysiology of CINV involves a complex interplay of various neurotransmitters and receptors[5]. In addition to causing electrolyte and nutritional imbalances, severe cases of CINV can result in esophageal mucosal lacerations, leading to decreased patient compliance with treatment regimens or even refusal of anti-neoplastic therapies. Severe cases of CINV may result in decreased or postponed delivery of chemotherapeutic medications, potentially diminishing the efficacy of treatment and shortening patients' survival duration[6].

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Commonly used medications for treating CINV consist of 5-HT_3 receptor antagonists, neurokinin-1 receptor antagonists (NK-1RAs), dexamethasone, atypical antipsychotics, and dopamine receptor blockers. NK-1RAs are a pharmacological class of agents with diverse therapeutic properties, including antiemetic, antidepressant, anxiolytic, and antipruritic effects. By attaching to NK-1 receptors in both the central nervous system and periphery, these agents work to prevent the release of substance P (SP), thus exerting their effects[7]. Aprepitant (APR) was the first NK-1RA approved by the US Food and Drug Administration (FDA) for treating nausea and vomiting caused by chemotherapy[8]. Fosaprepitant (FAP), a prodrug of APR designed for patients with challenges in oral intake, was subsequently approved by the FDA in 2008. Rolapitant (RP), which was granted approval by the FDA in September 2015, is an oral, long-acting, highly selective NK-1RA with a half-life of up to 180 h. The combination of NK-1RAs with standard anti-emetic therapy had been documented in literature as an efficacious treatment for preventing CINV and was widely used in clinical practice[9]. The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database, a valuable tool for collecting and analyzing drug-related adverse events, especially with the widespread use of three medications and increasing awareness of their side effects. It helps evaluate the safety and effectiveness of these drugs and address issues like incomplete and delayed reporting[10]. This study aimed to use data mining methods to identify and evaluate adverse event signals associated with common NK-1RAs medications after they have been released to the market, in order to improve understanding of the adverse event profiles related to NK-1RAs.

Materials and methods

Data source and collection

In order to thoroughly investigate the various adverse events associated with NK-1RAs, a retrospective pharmacovigilance study was conducted utilizing the FAERS database. The NK-1RAs examined in this study include aprepitant (APR), fosaprepitant (FAP), and rolapitant (RP). Data from reports submitted between the first quarter of 2009 (2009 Q1) and the fourth quarter of 2023 (2023 Q4) for APR and FAP, and between the third quarter of 2015 (2015 Q3) and the fourth quarter of 2023 (2023 Q4) for RP were included. A PubMed search was conducted using MeSH terms and keywords "aprepitant", "fosaprepitant", and "rolapitant" to identify all the relevant terms. The ultimate target terms for these NK-1RAs were determined as follows: for APR, the terms included "Aprepitant", "MK0869", "MK0517", and "Emend"; for FAP, the terms included "Fosaprepitant" and "Fosaprepitant dimeglumine"; for RP, the terms included "Rolapitant" and "Varubi". In accordance with recommendations from the FDA, data extraction was performed, with duplicate reports being removed.

Data mining

AEs in the FAERS database were categorized and normalized using utilizing the Medical Dictionary for Regulatory Activities (MedDRA version 26.1). Within the FAERS, each AE report underwent coding and description based on the Preferred Term (PT) and subsequent classification by System Organ Class (SOC). To assess potential AEs associated with NK-1RAs, disproportionality methods such as Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN) and Multi-item Gamma Poisson Shrinker(MGPS) were employed for data analysis[11]. Each of four methods has its own advantages.ROR can adjust for bias when the number of AE reports is small.Compared to ROR, PRR has higher specificity because it is less affected by missing of AEs.BCPNN and MGPS are Bayesian algorithms. BCPNN is excellent for integration of data from multiple sources and cross-validation, while MGPS has the advantage that it can detect signals from rare events.Therefore, by combining the four algorithms, this study mitigates the risk of false-positive signals, expands the detection range and enhances the credibility of the study's objectives[12].

The number of reports of NK-1RA related AEs was not less than three and the vaule of the 95% CI of the ROR should be greater than one.The BCPNN method further categorised ADR signals into four groups (no, weak, medium, and strong signals) based on the vaule of IC_{025}[13].Higher values indicated the strength of stronger signal, which suggested a more reliable association between the target drug and the adverse event.The calculation formulas and threshold values for these four methods were provided in Tables S1 and S2 in the supplementary materials. The data analyses were carried out using R 4.2.3.

Results

Basic information

From the first quarter of 2009 to the fourth quarter of 2023, a total of 5434 AE reports identified NK-1RAs as the primary suspected drugs. Among these AE reports, 3596 cases were associated with APR, 989 cases were related to FAP and 849 cases were linked to RP. The basic characteristics of these adverse reports were presented in Table 1. Adverse events were more commonly reported in females than in males for these three drugs. The 18 to 64.9 age group had the highest proportion in APR at 41.0% and in FAP at 49.9%, whereas the missing age group made up the majority in RP at 68.1%. The majority of AEs were reported by consumers and doctors, with a significant proportion originating from the United States (APR 50.3%, FAP 42.0%, RP 98.5%). In addition to unspecified serious AEs, the primary serious outcome of RP AEs was death (29.4%), while hospitalization or prolonged hospitalization was the main outcome for the other two NK-1RAs (APR 22.5%, FAP 21.9%) (Fig. 1a). Despite a lack of information on AE occurrences and medication dates, it was evident that APR and FAP had higher occurrences within 0–7 days compared to other time periods, whereas RP had higher occurrences at 8–30 days (Fig. 1b).

Categories	APR, %	FAP, %	RP, %
Cases	3596	989	849
Gender			
Female	1893 (52.6)	498 (50.4)	377 (44.4)
Male	1192 (33.1)	372 (37.6)	254 (29.9)
Missing	511 (14.2)	119 (12.0)	218 (25.7)
Age, years			
< 18	98 (2.7)	20 (2.0)	1 (0.1)
18-64.9	1475 (41.0)	494 (49.9)	151 (17.8)
65–85	745 (20.7)	239 (24.2)	117 (13.8)
> 85	13 (0.4)	4 (0.4)	2 (0.2)
Missing	1265 (35.2)	232 (23.5)	578 (68.1)
Weight, kg			
< 50	135 (3.8)	62 (6.3)	8 (0.9)
50–100	908 (25.3)	399 (40.3)	96 (11.3)
> 100	83 (2.3)	39 (3.9)	12 (1.4)
Reporters			
Consumer	1075 (29.9)	193 (19.5)	400 (47.1)
Health Professional	129 (3.6)	52 (5.3)	16 (1.9)
Doctor	1051 (29.2)	421 (42.6)	97 (11.4)
Pharmacist	615 (17.1)	206 (20.8)	103 (12.1)
Others	673 (18.7)	102 (10.3)	230 (27.1)
Report countries			
United States	1810 (50.3)	416 (42.0)	836 (98.5)
France	478 (13.3)	3 (0.3)	1 (0.1)
Korean	349 (9.7)	339 (34.3)	NA
Japan	294 (8.2)	125 (12.6)	NA
Serious outcomes			
Death	338 (9.4)	65 (6.5)	250 (29.4)
Hospitalization-initial or prolonged	810 (22.5)	217 (21.9)	129 (15.1)
Life-threatening	214 (5.9)	63 (6.3)	10 (1.1)
Disability	35 (0.9)	9 (0.9)	0
Other serious outcomes	888 (24.7)	334 (33.8)	265 (22.8)

Table 1. Basic characteristics of NK-1RAs in FAERS.

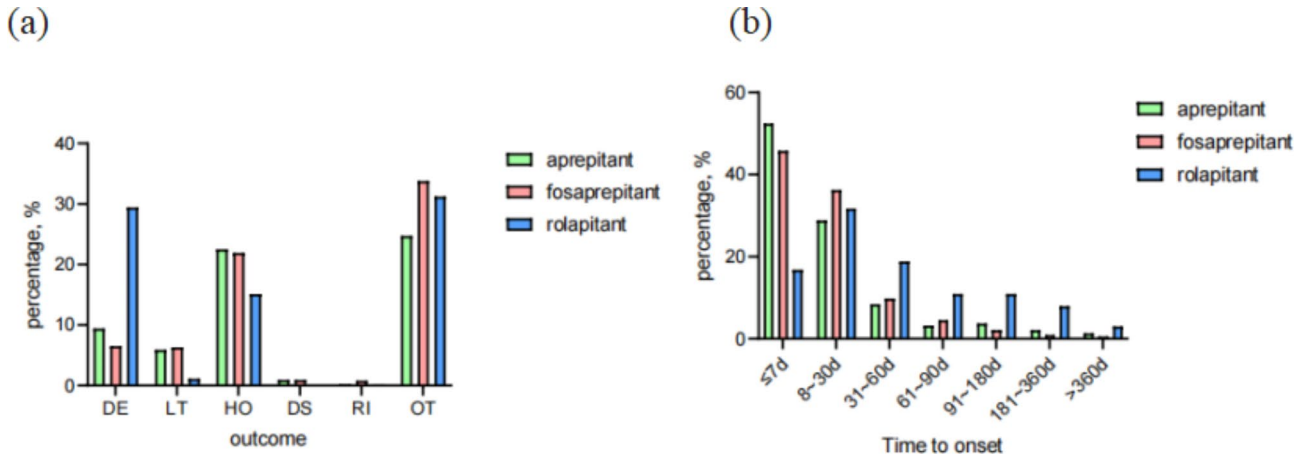

Fig. 1. Basic characteristics of NK-1RAs. **a** Serious outcomes. DE for death. LT for Life-threatening. HO for hospitalization-initial or prolonged. DS for disability. RI for required intervention to prevent permanent impairment/damage. OT for other serious outcomes. **b** Adverse event occurrence time-medication date (days).

Signal mining results

This study presented an analysis of the top ten most frequently reported AEs associated with NK-1RAs at SOC level, as depicted in Fig. 2. The whole findings indicated that APR encompassed 27 SOCs, with 9 positive signals identified (Table S3). The most commonly reported AEs related to APR were general disorders and administration site conditions ($n=2209$), gastrointestinal disorders ($n=1258$), and respiratory, thoracic and mediastinal disorders ($n=867$). The three most significant signals were immune system disorders (ROR = 3.20), vascular disorders (ROR = 2.44), and blood and lymphatic system disorders (ROR = 2.01). The analysis of AEs of FAP revealed that out of 26 SOCs, 7 exhibited positive signals, all the information was shown in Table S3. The general disorders and administration site conditions had the highest number of AEs ($n=733$), followed by gastrointestinal disorders($n=442$), and respiratory, thoracic and mediastinal disorders($n=351$). Vascular disorders exhibited the strongest signal with an ROR of 2.98, followed by immune system disorders (ROR = 2.80) and blood and lymphatic system disorders (ROR = 2.78). Given that FAP was the injectable prodrug of AP, it was not surprising that they share many similar AEs. In comparison, RP involved 25 SOCs, with 8 positive signals identified (Table S3). Similarly to the two medications previously discussed, the highest number of AEs related to RP was general disorders and administration site conditions ($n=522$), followed by gastrointestinal disorders ($n=272$) and investigations ($n=258$). Vascular disorders (ROR = 3.07), surgical and medical procedures (ROR = 2.56), and investigations (ROR = 2.18) were the three strongest signals identified.

In terms of the PT level, we utilized four algorithms to analyze the AEs linked to NK-1RAs and evaluate their conformity with the diverse screening criteria. From the positive signals given by four algorithms, the top ten most frequently reported AEs of NK-IRAs were shown in Table 2. For the most common clinical symptoms associated with AEs, the most frequently reported AE of APR was dyspnea($n=378$). The same was true for FAP ($n=139$) and the most frequently reported AE of RP was flushing ($n=92$). The signal profiles of the top

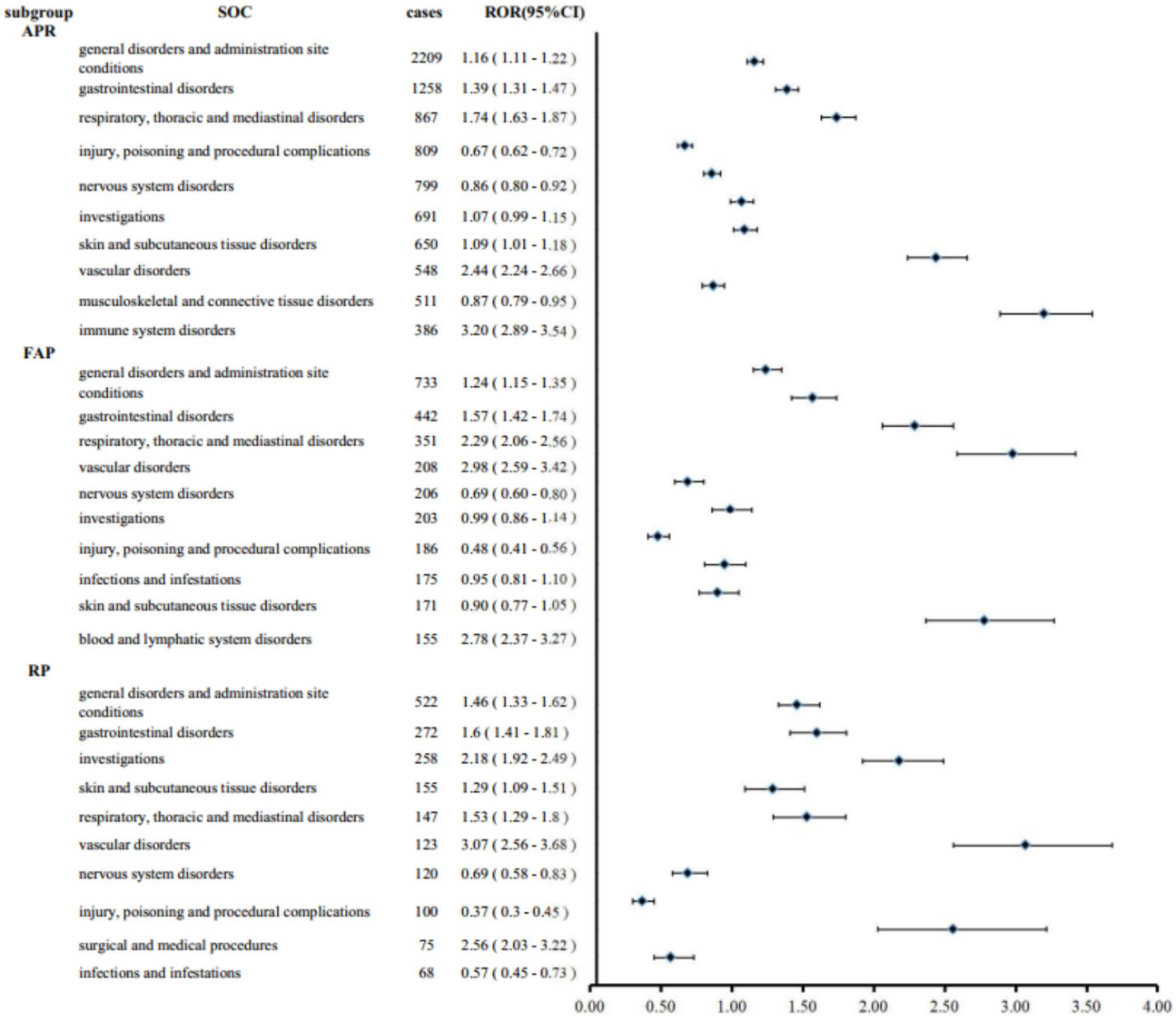

Fig. 2. Top ten most frequently reported AEs of NK-1RAs at the SOC level.

Rank	APR						FAP						RP					
	PTs	*n*	ROR (95%CI lower limit)	χ^2	IC (IC_{025})	EBGM ($EBGM_{05}$)	PTs	*n*	ROR(95%CI lower limit)	χ^2	IC (IC_{025})	EBGM ($EBGM_{05}$)	PTs	*n*	ROR (95%CI lower limit)	χ^2	IC (IC_{025})	EBGM ($EBGM_{05}$)
1	Dyspnoea	378	3.46	763.93	0.23	3.43	Dyspnoea	139	3.80	363.06	0.46	3.78	Death	241	7.59	1453.00	1.30	6.99
2	Flushing	267	12.64	3205.79	2.13	12.57	Flushing	112	15.85	1859.81	2.54	15.82	Flushing	92	29.53	3026.10	3.45	29.23
3	Erythema	180	4.06	515.54	0.55	4.10	Pyrexia	87	3.70	237.47	0.50	3.76	Dyspnoea	73	3.06	150.11	0.25	3.10
4	Back pain	163	3.31	340.28	0.27	3.35	Infusion related reaction	75	17.52	1470.91	2.76	17.79	Infusion related reaction	64	22.51	1668.18	3.14	22.74
5	Hypersensitivity	138	3.52	327.42	0.38	3.58	Erythema	54	3.42	143.21	0.48	3.53	Erythema	56	5.64	299.48	1.18	5.76
6	Infusion related reaction	119	9.10	1056.00	1.76	9.26	Neutropenia	54	5.59	289.65	1.18	5.76	Feeling hot	47	18.73	1058.15	2.94	19.19
7	Chest discomfort	114	5.40	523.22	1.02	5.51	Chest discomfort	54	7.49	419.97	1.61	7.71	Hospitalisation	35	4.04	131.52	0.81	4.21
8	Adverse event	113	5.70	559.55	1.10	5.82	Back pain	52	2.97	110.87	0.28	3.07	Back pain	32	2.79	69.71	0.30	2.92
9	Anaphylactic reaction	108	10.12	1100.57	1.93	10.32	Constipation	49	3.18	118.77	0.40	3.30	Chest discomfort	30	6.29	211.02	1.49	6.59
10	Infusion site pain	79	28.68	2632.54	3.47	29.29	Febrile neutropenia	44	9.24	456.65	1.95	9.58	Abdominal discomfort	29	3.14	78.67	0.50	3.30

Table 2. Top ten most frequently reported AEs of NK-1RAs at the PT level.

8 induced by NK-1RAs in the SOC of general disorders and administration site conditions, nervous system disorders, endocrine disorders and musculoskeletal and connective tissue disorders were listed in Table 3. The strong signals were mainly injection site reactions associated with APR and FAP. Interestingly, we found that toxic encephalopathy and encephalopathy of APR were both positive with four algorithms. Furthermore, we discovered new and valuable AE signals that were not explicitly identified in the prescribing information, such as adrenal insufficiency, inappropriate antidiuretic hormone secretion, and hypothyroidism in the SOC for endocrine disorders, which should be taken into account in clinical practice.

Discussion

CINV can occur at various points during chemotherapy. Acute CINV happens within the first 24 h of receiving chemotherapy, with vomiting primarily caused by 5-HT_3. On the other hand, delayed CINV occurs between 24 and 120 h after chemotherapy and is mainly mediated by substance P (SP) binding to NK-1R in the central nervous system[14]. As reported in the literature[15,16], the prophylactic use of NK-1RAs can significantly reduce CINV. This study compared and analyzed the similarities and differences of NK-1RAs from the FAERS database in the real world. Four main discoveries were explored: (1) NK-1RAs associated AEs were linked to multiple SOCs, such as gastrointestinal disorders, general disorders and administration site conditions, vascular disorders, immune system disorders, and respiratory, thoracic and mediastinal disorders; (2) although the reporters of injection site reactions linked to RP were low, but the ROR of it was the highest of the three drugs;3) the likelihood of encephalopathy toxicity associated with APR was greater than the other two medications; 4) in addition to established AEs, novel AEs were identified, such as inappropriate antidiuretic hormone secretion, adrenal insufficiency, hypothyroidism and hyperthyroidism.

Table 1 indicated that females experienced a greater number of adverse events than males. Consistent with previous reports, women were at a higher risk for CINV[1,16,17]. Apart from the missing age, the age group of 18-64.9 had a higher proportion of AE reporters, suggesting that there may be widespread use of NK-1RAs in

SOC	APR			FAP			RP		
	PTs	n	Intensity	PTs	n	Intensity	PTs	n	Intensity
General disorders and administration site conditions	Injection site vasculitis	13	+++	Injection site vasculitis	12	+++	Feeling hot	47	++
	Injection site phlebitis	29	+++	Injection site phlebitis	26	+++	Chest discomfort	30	+
	Infusion site phlebitis	6	+++	Infusion site irritation	8	+++	Death	241	+
	Infusion site irritation	18	+++	Infusion site reaction	8	+++	Chest pain	28	+
	Infusion site urticaria	8	+++	Infusion site discomfort	3	+++	Disease progression	17	+
	Infusion site rash	11	+++	Infusion site pain	32	+++	Chills	8	—
	Therapeutic producteffective for unapproved indication	3	+++	Infusion site induration	3	+++	Adverse drug reaction	6	—
	Infusion site reaction	17	+++	Injection site atrophy	4	+++	Illness	6	—
Nervous system disorders	Tonic clonic movements	4	++	Seizure like phenomena	3	+++	Unresponsive to stimuli	3	+
	Encephalopathy	69	++	Unresponsive to stimuli	11	+	Cerebral haemorrhage	4	+
	Seizure like phenomena	4	++	Presyncope	6	+	Dizziness	45	—
	Toxic encephalopathy	8	++	Sensory disturbance	3	+	Loss of consciousness	10	—
	Clonus	4	+	Depressed level of consciousness	6	—	Hypoaesthesia	9	—
	Muscle contractions involuntary	4	+	Loss of consciousness	15	—	Neuropathy peripheral	6	—
	Peripheral sensory neuropathy	6	+	Paraesthesia	17	—	Seizure	8	—
	Unresponsive to stimuli	20	+	Aphasia	3	—	Burning sensation	3	—
Endocrine disorders	Inappropriate antidiuretic hormone secretion	15	++	Inappropriate antidiuretic hormone secretion	3	+			
	Adrenal insufficiency	5	—	Adrenal insufficiency	3	+			
	Hypothyroidism	3	—						
Musculoskeletal and connective tissue disorders	Joint deposit	3	+++	Back pain	52	+	Back pain	32	+
	Facet joint syndrome	4	++	Muscle twitching	4	—	Bone pain	3	—
	Rheumatic fever	5	++	Musculoskeletal pain	6	—	Muscle spasms	5	—
	Hand deformity	12	+	Neck pain	4	—	Arthralgia	4	—
	Back pain	163	+	Muscle spasms	10	—			
	Synovitis	11	+	Pain in extremity	14	—			
	Joint range of motion decreased	6	—	Myalgia	7	—			
	Flank pain	4	—	Arthralgia	8	—			

Table 3. The top 8 signal strength of AEs refered to four SOCs. Strong signal(+++)IC_{025}>3,Medium signal(++)1.5< IC_{025} ≤ 3,Weak signal(+)0< IC_{025} ≤ 1.5,No signal(—)IC_{025} ≤ 0. IC_{025} the lower limit of the 95% confidence interval of IC.

this age group. This finding was consistent with the existing literature, which reported the highest tumor risk in people over 50[18].

In this study, injection site vasculitis and phlebitis showed strong signals for APR and FAP. Injection site reactions (ISRs) were a prevalent type of side effect associated with NK-1RAs, and may lead to adjustment, pauses, or discontinuation. Furthermore, several studies have indicated a correlation between the use of FAP and ISRs[19–21], with reported rates varying from 7% to as high as 67% reported in retrospective studies. These ISRs included injection site vasculitis, phlebitis, irritation, infusion-related hypersensitivity reaction and other conditions.A study comparing the use of APR and FAP in the treatment of gynecological tumors showed that intravenous administration of FAP and age less than 65 years were risk factors for ISRs[22]. Furthermore, ISRs tended toward a higher incidence with shorter infusion times(less than 15 min)and higher concentration(0.6 mg/L,1.0 mg/L,1.5 mg/L)[23].Among breast cancer patients undergoing doxorubicin-/cyclophosphamide chemotherapy, the occurrence of infusion site reactions linked to FAP was 34.7%, significantly higher than the 2.3% seen with APR ISRs[20]. In addition, the simultaneous administration of anthracycline-based regimens increased the risk of FAP-related ISRs by around six times[21]. Currently, the RP-related ISRs were less commonly reported, but the ROR of them in our study was the highest of the three drugs, suggesting that we still need to be vigilant in clinical therapy. A previous study found that out of 60 patients who used RP to prevent CINV prophylactically, there were 6 cases of ISRs with intravenous RP[24]. This incidence was higher than the 2.8% reported in its Phase I clinical trial[25]. In January 2018, the U.S. FDA issued a Health Care Provider Letter noting that anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions were associated with the use of RP Injectable Emulsion in the post-marketing setting[24]. In order to reduce the incidence of ISRs, infusion of FAP via a central venous catheter had been reported in previous literature[26], diluting the concentration to 0.6 mg/ml and infusing over 30 min[27].

This study found that several PTs in nervous system disorders had positive signals, particularly in relation to APR, such as encephalopathy, tonic clonic movements, seizure like phenomena and so on. Sano T et al.[28]. reported a case of ifosfamide-induced encephalopathy(IIE) in a patient treated with a combination of APR and ifosfamide (IFO). Furthermore, Shimada K et al.. believed that APR might be associated with a higher risk of IIE[29] and the incidence was as high as 26%[30]. The mechanisms of APR and IIE were that APR may interfere with the metabolism of IFO via CYP3A4 inhibition, resulting in an increased concentration of IFO in the blood and its metabolites, such as 2-chloroacetaldehyde and acrolein. Both of these substance can cross the blood-brain barrier and induce encephalopathy[31]. However, the results of a systematic review indicated a positive enhanced trend between neurotoxicity and concomitant use of IFO and APR or FAP, but the association was not statistically significant[32]. Baseline albumin < 3.5 g/dl[33] ,age ≥ 60 years and IFO dose $\geq 2000 mg/m^2$[29] were risk factors for IIE. The association of NK-1RAs with IIE was not clear, but vigilance was required for IIE when combined with IFO, which can be reduced by prolonged titration or administration of methylene blue[34] .

Furthermore, our study revealed novel AEs related to endocrine disorders, including inappropriate antidiuretic hormone secretion, adrenal insufficiency, hypothyroidism and hyperthyroidism in both APR and FAP. Despite no new adverse events regarding endocrine disorders being found with RP, hyponatremia induced by RP was still considered to be connected to either inappropriate antidiuretic hormone secretion or adrenal insufficiency.Studies had indicated that the NK-1R was present in the nervous system and peripheral tissues, participating in endocrine and paracrine processes. SP was also related to various physiological and pathological processes in the human body[35]. Additionally, a prospective clinical trial found that APR decreased aldosterone production by approximately 30% in healthy male participants by inhibiting the vasorelaxant effect of SP, leading to a decrease in adrenal blood flow[36].Isorna and colleagues had found that both SP and NK-1R were expressed in normal thyroid tissue and thyroid cancer[37].In summary, we speculated that the endocrine disorders were related to the antagonism of NK-1R to SP, however, the more precise mechanisms still require further research and exploration.The signal strength of back pain linked to all three medications found to be high at the PT level (APR: $N=163$, ROR 3.86; FAP: $N=52$, ROR 3.91; RP: $N=32$, ROR 3.96), indicating the need for further attention.Furthermore, continuous exposure to SP could be associated with the development of tendinopathy[38]. Therefore, it was suggested[39] that the NK-1RA showed promise in treating tendinopathy, rheumatoid arthritis and osteoarthritis. However, in our study, apart from the commonly reported AEs, we found some new AEs in musculoskeletal and connective tissue disorders, such as musculoskeletal stiffness, osteoarthritis, systemic lupus erythematosus and so on. The mechanism was considered to possibly involve the SP-NK1R pathway in inflammatory processes, as suggested by the aberrant expression of this pathway in various inflammatory diseases[40].

This research offers trustworthy scientific data for evaluating the safety of NK-1RAs from various angles. Nevertheless, the FAERS database is not without its drawbacks, given its reliance on voluntary reporting that could introduce bias anf result in incomplete data. Some reports were submitted by consumers, which may lack the reliability and depth of analysis seen in reports from medical professors. Moreover, the database's incomplete nature means that a definitive causal relationship between product exposure and NK-1RA-related AEs cannot be proven. More cases and clinical trials are necessary in the future to establish scientific conclusions.

Conclusion

This study not only confirms the known AEs of NK-1RAs listed on the drug label but also identifies several new high-risk AEs, such as inappropriate antidiuretic hormone secretion, adrenal insufficiency and hyponatremia. In addition, our study also shows that the number of reactions at the site of infection associated with NK-1RAs was high. Furthermore, the encephalopathy toxicity associated with APR was higher than with the other two drugs. The analysis of AEs associated with NK-1RAs in the real world suggests the need to be vigilant for the occurrence of ISRs when using intravenous NK-1RAs.Secondly, it suggests the need for further research into new AEs and potential drug interactions to provide safety recommendations for clinical medication.

Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.The datasets supporting the conclusions of this study are publicly accessible. All data we used in this study is available on the website:https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html

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Author contributions

LS designed the study. XS and JQW download and clean the data. LS and YGJ analyzed the data and generated the figures. LS, PH, and JQW wrote the manuscript. XS and YGJ supervised the details of the study. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

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