BMC Pharmacology and Toxicology

RESEARCH Open Access

Post-marketing safety of elacestrant in breast cancer: a pharmacovigilance investigation using the FDA adverse event reporting system

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Abstract

Background Recently, the US Food and Drug Administration approved a new oral selective estrogen receptor downregulator for breast cancer, namely, elacestrant (Orserdu). This study aimed to analyze the signals of adverse events (AEs) within the introduction of elacestrant to the market using the FDA Adverse Event Reporting System (FAERS) database.

Methods Reports on the AEs of elacestrant after its marketing were obtained from the FAERS database. Disproportionality was analyzed using the reporting odds ratio to calculate the magnitude of the risk of the target drug and the AE combination, and the proportional reporting ratio to quantify the strength of the association between the drug and the AEs.

Results A total of 3132 reports on elacestrant-related AEs were obtained, with disease progression, drug ineffectiveness, product dose omission, arthralgia, asthenia, increased tumor marker levels, and bone pain (Number of reported cases (a) ≥ 3 and lower limit of 95% confidence interval >1) being the high-frequency events not mentioned on the drug label. The top three total frequencies at the system organ class level comprised general disorders and administration site conditions, gastrointestinal disorders, and musculoskeletal and connective tissue disorders.

Conclusions FAERS data analyses were conducted to evaluate the safety of post-marketing clinical use of elacestrant and to ensure that physicians identify the risk factors for the AEs of this drug.

Keywords Elacestrant, Orserdu, Pharmacovigilance, FAERS, Breast cancer

Background

Selective estrogen receptor downregulators (SERD) are known to be effective in treating patients with hormone receptor-positive breast cancer owing to their ability to bind to the estrogen receptor to form DIMER, inactivating its function. For metastatic cancer, the standard-of-care first-line therapy commonly comprises endocrine therapy drugs combined with CDK4/6 inhibitors [1]. Fulvestrant is widely used as an intramuscular SERD for the treatment of late-stage breast cancer; however, it has limited bioavailability [2, 3]. In preclinical studies, elacestrant demonstrated an antitumor activity by affecting

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ER-related signaling. The tissue size in a patient-derived xenotransplantation (PDX) model receiving elacestrant monotherapy or in combination with other antitumor agents (palbociclib or everolimus) was significantly smaller than that of controls. In, elacestrant was effective in overcoming CDK4/6 resistance in an in vitro model, thereby limiting tumor growth [4, 5]. The activation of missense mutations in tumor ESR1 was a common cause of acquired tumor resistance to endocrine therapy drugs, particularly aromatase inhibitors (AIs). Tumor ESR1 mutations occur in 20–40% of patients after AI exposure. The EMERALD trial showed that elacestrant was superior to fulvestrant and other endocrine monotherapies in the backline treatment of breast cancer and that patients with ESR1-mutant breast cancer demonstrating endocrine therapy drug resistance achieved a high progression-free survival (PFS) [6]. In 2023, the Food and Drug Administration (FDA) approved elacestrant for patients with advanced or metastatic breast cancer with ESR1 mutation.

Elacestrant represents a significant treatment alternative for patients with advanced breast cancer owing to its unique mechanism of action, efficacy, and lower resistance. Healthy postmenopausal women can tolerate up to 1000 mg of elacestrant in a single dose and 500 mg in multiple doses [7]. No dose-limiting toxicities occurred in patients with metastatic breast cancer (ER+/HER2–) after receiving multiple lines of therapy, and no differences were observed in the incidence of gastrointestinal reactions among those who had been treated with different drugs [8]. In the EMERALD trial, serious AEs occurred in 12% of the patients in the experimental group. Other AEs included abnormal laboratory test markers, pain in different parts of the body, and gastrointestinal symptoms; the occurrence of AEs resulted in dosage adjustment or drug discontinuation [6].

To date, few retrospective cohort studies are available on elcestrant, and the safety of this drug still requires further investigation. Moreover, the AEs reported in clinical trials do not fully reflect real-world medication safety issues. The FDA Adverse Event Reporting System (FAERS) database collects safety data for FDA-approved drugs after they are marketed. It has more comprehensive and extensive data than clinical trials and is currently used widely in research on the safety of clinical drugs [9, 10]. This study aimed to assess the safety profile of elacestrant by analyzing the AEs reported in FAERS.

Methods

Data source and processing

The FAERS database records the AEs of drugs reported by consumers and healthcare providers worldwide. Owing to its wide coverage and extensive information, it is widely used for the early detection of AEs. We searched the FAERS database using "elacestrant" as the keyword and Orserdu as the brand name from the first to the fourth quarter of 2023 (detailed information is available at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers). We deduplicated and cleaned the AE reports obtained to ensure the accuracy and robustness of the results (Fig. 1). First, we used the case ID and primary ID as filtering points during the deduplication process. For reports with the same case ID, the report with larger primary ID was

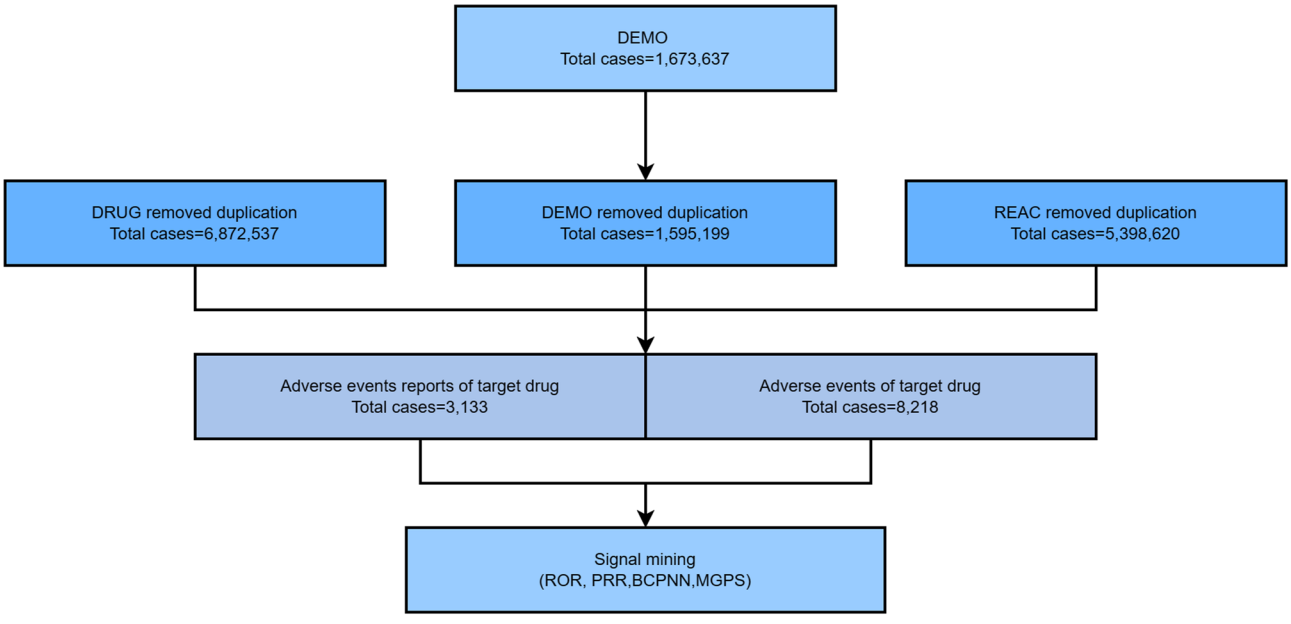

Fig. 1 Flow chart of the data analysis

prioritized. Second, reports with incomplete data and that did not meet the selection criteria were excluded. AE reports involving patients aged ≥18 years as well as reports in which elacestrant was the primarily suspected cause of AEs were retained. The Common Terminology Criteria for Adverse Events (CTCAE, please visit for detailed information https://bioportal.bioontology.org/ontologies/CTCAE) were published by the National Institutes of Health and the National Cancer Institute in the United States of America (USA). For reporting AEs in tumor clinical trials, severity levels were assigned for each AE. We used MedDRA data to map the data obtained from the FAERS database to different levels of the CTCAE dictionary's logical structure, including preferred terms (PT), advanced terms (HLTs), advanced group terms (HLGT), and system organ class (SOC). After the data deduplication and cleaning, the final AE data obtained were analyzed further.

Signal mining

Disproportionality analysis is a statistical method that is widely employed to detect the safety signals of marketed drugs and evaluate the association between AEs and the drugs. In this study, multiple algorithms were used to assess the AEs significantly associated with elacestrant, these included the reporting odds ratio (ROR), proportional reporting ratio (PRR), and Empirical Bayes Geometric Mean (EBGM) (Supplementary File 1). In addition, a four-grid table of AEs was constructed to facilitate the calculation of the above algorithm (a represents the total number of AEs of elacestrant) (Supplementary File 1). AEs were considered to be significantly related to elacestrant if they met one of the following criteria: (1) the lower limit of the 95% confidence interval (CI) of ROR was >1 and a > 3, the lower limit of the 95% CI of PRR was >1 and a > 3, and ROR and PRR are commonly used as signal detection indicators, with a 95% CI lower limit >1 indicating a statistically significant association between the AEs and the drugs. Number of reported cases (a) > The setting of 3 is to ensure the stability and reliability of the signal and to avoid false-positive results caused by a small number of cases, (2) EBGM05 >2. Significant AE reports were screened for further analysis. EBGM is a signal detection metric based on Bayesian methods, and EBGM05 >2 indicates a strong correlation between the AEs and the drug. This threshold was set to further improve the specificity of the signal and reduce the noise interference.

Statistical analysis

For subsequent analysis, the AEs of elacestrant were categorized into fatal and nonfatal. A descriptive analysis was conducted to present the clinical characteristics after filtering the data, including age, gender, reporter type, reporter country, outcome, and received time. Categorical variables were expressed as percentages (%). In addition, the induction time of AEs was defined as the interval between the treatment and event start times. Cumulative distribution curves were used to present the induction times of the two groups, and the differences between the groups were compared using the Wilcoxon test. Notably, some of the reports involved the combined use of elacestrant and other antitumor drugs. These antitumor drugs were classified into endocrine therapy, targeted therapy, and chemotherapy drugs. Univariate logistic regression analysis was employed to calculate the odds ratio (OR) of AEs based on age and exposure to other oncology drugs. $P < 0.05$ was considered to be statistically significant, and all statistical analyses and visualizations were performed using the R software (version 4.2.2).

Results

Descriptive analysis

In 2023, a total of 3132 reports related to elacestrant were recorded in the FAERS database, along with 8218 AE reports. The clinical data characteristics are presented in Fig. 2. Among the reported breast cancer cases, nine were men. Of the patients, 43.06% were aged <65 years, 32.07% were aged 65–74 years, and 24.88% were aged >75 years (median age, 67 years). The majority of cases were from the USA. Approximately 45.45% of the AEs had an onset time of 29 days, with the median time to onset (TTO) of events being day 39. On the SOC level, the median TTO for benign, malignant, and unspecified neoplasms was 60.5 days, whereas gastrointestinal disorders had a median TTO of 17 days (Fig. 3).

AE signals and SOCs involved in elacestrant

The most commonly reported elacestrant-related AEs were nausea ($n = 703$), fatigue ($n = 494$), disease progression ($n = 332$), vomiting ($n = 306$), diarrhea ($n = 319$) (Fig. 4), increased tumor marker level ($n = 82$), gastroesophageal reflux disease ($n = 42$), dehydration ($n = 46$), dysphagia ($n = 40$), and ascites ($n = 13$). The most strongly correlated SOC was gastrointestinal disorders. The remaining SOCs included general disorders and administration site conditions, gastrointestinal disorders, various musculoskeletal and connective tissue disorders, investigations, various surgical and medical procedures, metabolism and nutrition disorders, as well as benign, malignant, and unspecified tumors, including cystic and polypoid (Fig. 5).

The cumulative distribution curve of the TTO showed that the TTO of fatal AEs was earlier than that of nonfatal AEs after the drug administration. The median TTO for all AEs was 39 days (median TTO for fatal AEs, 18 days; median TTO for nonfatal AEs, 49 days) (Fig. 6).

Clinical characteristics	Fatal	Non-Fatal	P value
Number	1032	2100	
Age (%)			<0.001
<65	481 (46.6)	813 (38.7)	
65-74	290 (28.1)	673 (32.0)	
>=75	229 (22.2)	517 (24.6)	
Missing	32 (3.1)	97 (4.6)	
Gender (%)			0.896
Female	1014 (98.3)	2060 (98.1)	
Male	9 (0.9)	18 (0.9)	
Missing	9 (0.9)	22 (1.0)	
Reportertype (%)			0.023
CN	880 (85.3)	1841 (87.7)	
HP	122 (11.8)	191 (9.1)	
MD	17 (1.6)	54 (2.6)	
PH	7 (0.7)	9 (0.4)	
Missing	6 (0.6)	5 (0.2)	
Country (%)			0.153
US	1026 (99.4)	2089 (99.5)	
FR	0 (0.0)	5 (0.2)	
IL	0 (0.0)	1 (0.0)	
Not specified	6 (0.6)	5 (0.2)	
Outcome (%)			<0.001
DE	143 (13.9)	6 (0.3)	
HO	43 (4.2)	146 (7.0)	
LT	0 (0.0)	2 (0.1)	
OT	75 (7.3)	228 (10.9)	
Missing	771 (74.7)	1718 (81.8)	
Received time (%)			0.111
2023Q1	4 (0.4)	3 (0.1)	
2023Q2	123 (11.9)	203 (9.7)	
2023Q3	418 (40.5)	854 (40.7)	
2023Q4	487 (47.2)	1040 (49.5)	

Fig. 2 Characteristics of the reports of elacestrant-related adverse events (AEs) obtained from the FAERS database

Factors influencing severe elacestrant-related AEs

In the EMERALD trial, 237 patients receiving elacestrant were analyzed for age distribution: 40% of the patients were aged <65 years, 43% were aged 65–74.9 years, and 17% were aged ≥75 years. The *U*-test analysis revealed no differences between the two groups (comparison of the AEs in the EMERALD trial). When elacestrant was used in combination with endocrine therapy or chemotherapy, it reduced the risk of fatal AEs. However, when used in combination with targeted therapy drugs, it exerted an opposite effect.

The treatment for cancer patients usually includes multiple medications. This study analyzed the drugs used in each report, with 1585 cases treated with a single drug and others with commonly used combination drugs, including digestive and cardiovascular system drugs as well as analgesics (Fig. 7). The number of reported drug-related AEs at the SOC level during combination therapy varied (Fig. 8), demonstrating the potential impact of elacestrant combination therapy on multiorgan systems and providing a reference for optimizing clinical medication regimens.

Discussion

Elacestrant has demonstrated strong antitumor activity in preclinical studies. In different patient-derived xenotransplantation (PDX) models, it significantly reduced the tumor volume when used alone or in combination with other antineoplastic agents, such as palbociclib or everolimus. Furthermore, elacestrant can effectively overcome the drug resistance of CDK4/6 inhibitors, making it a novel effective treatment alternative for breast cancer. The results of the EMERALD trial indicated that elacestrant demonstrated better efficacy than traditional therapies, such as fulvestrant, in these specific patients, particularly in controlling tumor progression and prolonging PFS. Fulvestrant also has limited bioavailability and is often administered via injection, thereby affecting

PT	SOC	Cases number	ROR (95%CI)	PRR (95%CI)	EBGM (EBGM05)	IC (IC025)
NAUSEA	GASTROINTESTINAL DISORDERS	703	8.42 (7.79, 9.1)	7.78 (7.71, 7.85)	7.7 (7.22)	2.95 (1.28)
FATIGUE	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	537	4.94 (4.52, 5.39)	4.68 (4.6, 4.76)	4.66 (4.33)	2.22 (0.55)
DISEASE PROGRESSION	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	332	18.89 (16.9, 21.12)	18.17 (18.06, 18.28)	17.71 (16.13)	4.15 (2.48)
VOMITING	GASTROINTESTINAL DISORDERS	306	5.94 (5.29, 6.66)	5.75 (5.64, 5.86)	5.71 (5.19)	2.51 (0.85)
DIARRHOEA	GASTROINTESTINAL DISORDERS	245	2.83 (2.49, 3.21)	2.77 (2.65, 2.9)	2.77 (2.49)	1.47 (-0.2)
DEATH	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	228	2.24 (1.96, 2.56)	2.21 (2.08, 2.34)	2.2 (1.97)	1.14 (-0.53)
DRUG INEFFECTIVE	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	198	1.17 (1.02, 1.35)	1.17 (1.03, 1.31)	1.17 (1.04)	0.22 (-1.44)
PRODUCT DOSE OMISSION ISSUE	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	195	2.41 (2.09, 2.77)	2.37 (2.23, 2.51)	2.37 (2.1)	1.24 (-0.42)
CONSTIPATION	GASTROINTESTINAL DISORDERS	164	5.68 (4.87, 6.64)	5.59 (5.44, 5.74)	5.55 (4.87)	2.47 (0.81)
PAIN	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	163	2.01 (1.72, 2.35)	1.99 (1.84, 2.14)	1.99 (1.74)	0.99 (-0.68)
DECREASED APPETITE	METABOLISM AND NUTRITION DISORDERS	160	5.11 (4.37, 5.98)	5.03 (4.88, 5.19)	5 (4.39)	2.32 (0.66)
ARTHRALGIA	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	149	2.11 (1.79, 2.48)	2.09 (1.93, 2.25)	2.09 (1.82)	1.06 (-0.61)
HEADACHE	NERVOUS SYSTEM DISORDERS	103	1.33 (1.1, 1.62)	1.33 (1.14, 1.52)	1.33 (1.13)	0.41 (-1.26)
ASTHENIA	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	97	2.13 (1.74, 2.6)	2.12 (1.92, 2.32)	2.11 (1.79)	1.08 (-0.59)
MYALGIA	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	96	5.09 (4.16, 6.23)	5.04 (4.84, 5.24)	5.01 (4.23)	2.33 (0.66)
HOSPITALISATION	SURGICAL AND MEDICAL PROCEDURES	96	4.12 (3.37, 5.04)	4.09 (3.89, 4.28)	4.07 (3.43)	2.02 (0.36)
DYSPEPSIA	GASTROINTESTINAL DISORDERS	91	8.22 (6.68, 10.12)	8.14 (7.93, 8.35)	8.05 (6.77)	3.01 (1.34)
ABDOMINAL DISCOMFORT	GASTROINTESTINAL DISORDERS	83	3.46 (2.78, 4.3)	3.43 (3.22, 3.65)	3.42 (2.85)	1.77 (0.11)
TUMOUR MARKER INCREASED	INVESTIGATIONS	82	81.08 (64.4, 102.08)	80.28 (80.05, 80.51)	71.63 (59.08)	6.16 (4.49)
HOT FLUSH	VASCULAR DISORDERS	77	6.92 (5.52, 8.67)	6.86 (6.64, 7.08)	6.8 (5.63)	2.77 (1.1)

Fig. 3 Top 20 preferred terms (PT) associated with elacestrant for signal strength

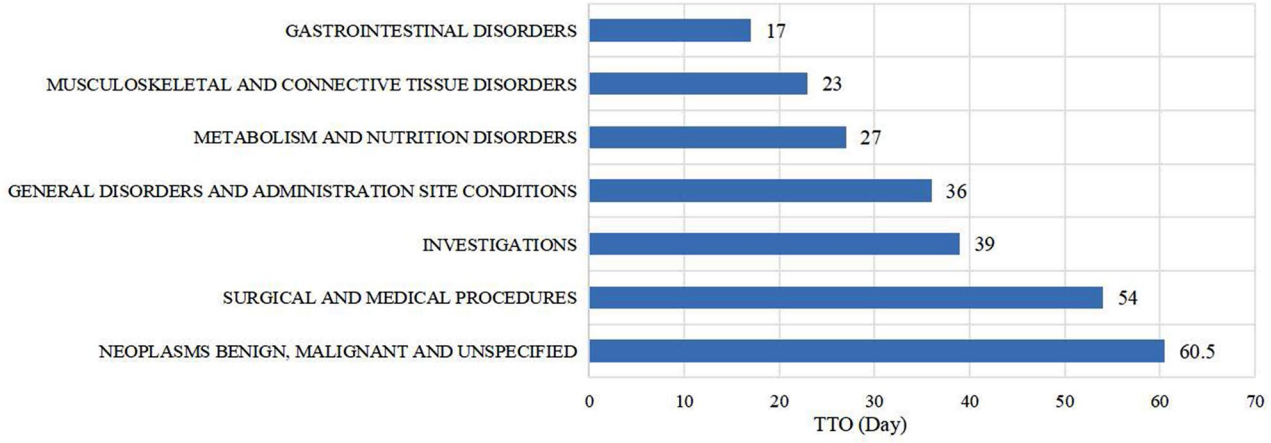

Fig. 4 Median TTO of elacestrant-related AEs on the SOC level

patient compliance. In addition, fulvestrant and other endocrine therapies have relatively poor efficacy in treating patients with drug-resistant ESR1 mutations. Therefore, elacestrant is a feasible treatment alternative for patients exhibiting endocrine therapy drug resistance owing to the drug's oral administration route and unique mechanism of action.

The FDA has approved elacestrant for the treatment of patients with HR+/HER2− breast cancer who have received at least one prior hormonal therapy and carry ESR1 mutations. It has also approved Guardant360 CDx for the detection of ctDNA ESR1 missense mutations as a companion diagnostic for elacestrant. However, it has not approved elacestrant for patients with ESR1 unmutated ER+, HER2−, advanced, or metastatic breast cancer owing to increased risk of gastrointestinal toxicity and dyslipidemia. Elacestrant was excreted via CYP3A4 in the liver and interacted with strong CYP3A4 inhibitors and inducers. However, its safety in patients with severe hepatic and renal insufficiency requires further studies. Elacestrant exhibited a mixed dose response in clinical trials of its ability to reduce hot flashes in postmenopausal women, improving vasodilatory symptoms only at the lowest dose [11].

According to a previous report, male breast cancer patients in the USA accounted for only about 1% of the total cases in 2022 [12]. In this study we reported nine cases of male breast cancer patients. The *P*-value

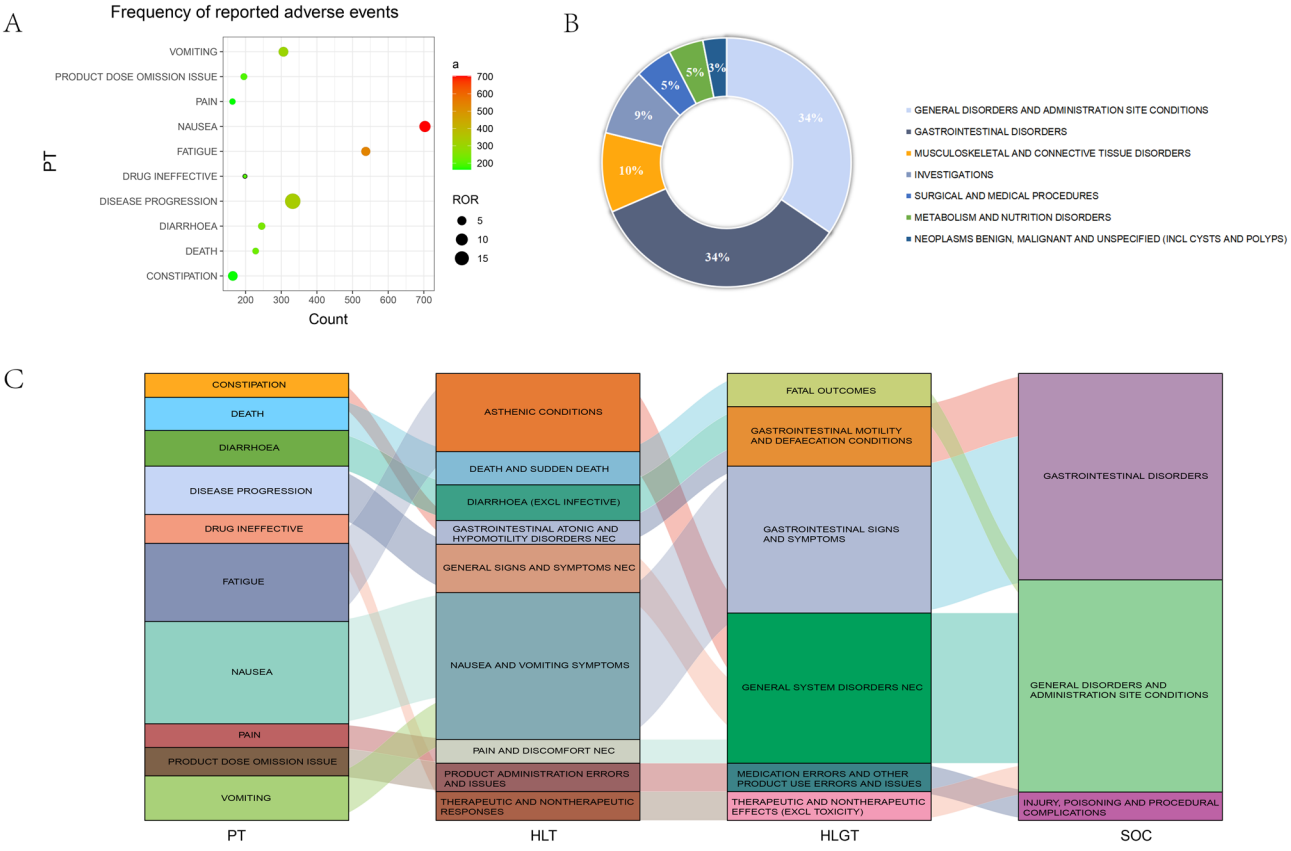

Fig. 5 Scanning for elacestrant-related AEs based on the FAERS database. A The bubble chart shows the ROR of the top 10 PT AEs, with the colors indicating the number of reported cases and the bubble size representing the magnitude of the ROR values. B The pie chart illustrates the proportion of drug-related AEs at different SOC levels. C Sankey diagram depicting the hierarchical relationship of PTs for 10 categories of elacestrant-related AEs in MedDRA. NES indicates not classified elsewhere; PT, preferred term; HLT, high-level term; HLGT, high-level group term; and SOC, system organ class

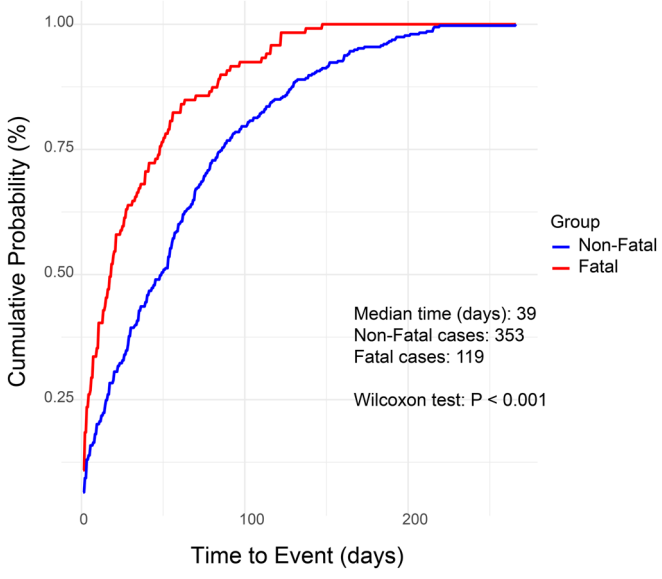

Fig. 6 The cumulative distribution curves show the onset time of elacestrant-related fatal AEs after drug administration. Statistical tests were conducted using the nonparametric Wilcoxon rank-sum test

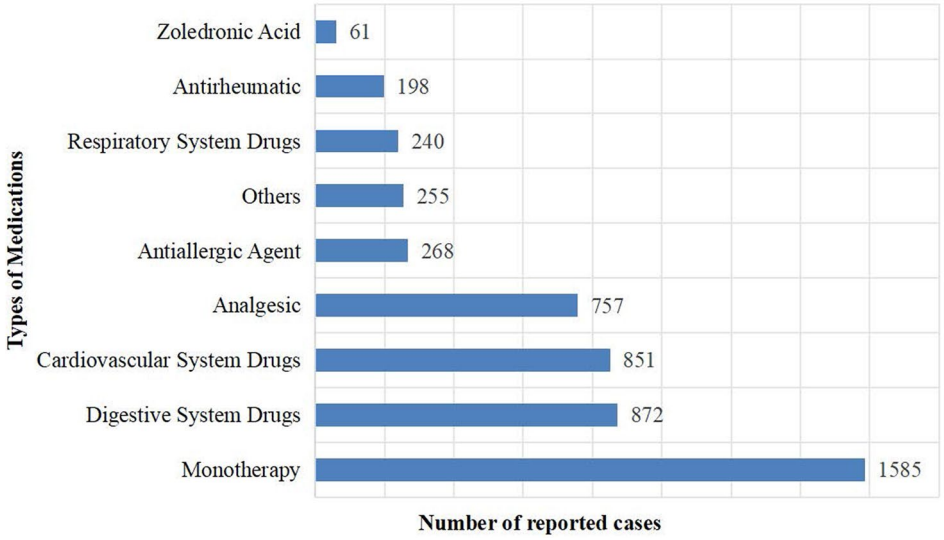

Fig. 7 Reported number of AEs associated with the combined use of elacestrant with different drug types

Types of Medications / AEs at the SOC	Analgesic	Zoledronic Acid	Antiallergic Agent	Respiratory System Drugs	Digestive System Drugs	Cardiovascular System Drugs	Antirheumatic
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3	2	0	0	5	5	2
CARDIAC DISORDERS	5	1	1	1	5	8	2
EAR AND LABYRINTH DISORDERS	3	0	2	2	5	4	3
ENDOCRINE DISORDERS	1	0	0	0	2	2	0
EYE DISORDERS	4	1	1	0	4	6	0
GASTROINTESTINAL DISORDERS	518	43	174	125	709	556	123
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	452	38	164	129	497	501	129
HEPATOBILIARY DISORDERS	3	0	1	0	4	3	3
IMMUNE SYSTEM DISORDERS	3	1	0	0	3	2	0
INFECTIONS AND INFESTATIONS	72	4	24	29	81	86	20
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	85	11	30	22	108	94	18
INVESTIGATIONS	96	12	34	25	96	109	28
METABOLISM AND NUTRITION DISORDERS	75	4	24	20	68	66	14
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	178	15	70	50	182	156	58
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	27	2	9	9	34	30	5
NERVOUS SYSTEM DISORDERS	97	3	21	15	109	105	24
PRODUCT ISSUES	7	1	2	3	7	5	2
PSYCHIATRIC DISORDERS	32	1	12	10	34	31	10
RENAL AND URINARY DISORDERS	17	1	8	8	18	16	3
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	12	1	2	1	11	11	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	56	2	20	27	61	63	23
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	56	6	29	15	72	79	11
SOCIAL CIRCUMSTANCES	1	1	2	0	3	3	0
SURGICAL AND MEDICAL PROCEDURES	48	5	17	13	44	47	14
VASCULAR DISORDERS	38	0	14	10	36	40	7

Fig. 8 Frequency of SOC-level AEs of elacestrant in combination with different types of drugs

obtained from the proportion test was 0.7726, which is greater than 0.05, indicating that there are no significant differences in the gender ratio of breast cancer in this study and in other reports.

Preclinical trials indicated that Eli's group does not affect cardiac rhythm at high doses [7]. Only three cases of heart rate irregularities were reported as AEs in this study, with a positive signal for irregular heart rate (ROR

>1, EBGM 95% ≥2). No other cardiac events showed drug-related AEs.

In the EMERALD trial, the elacestrant-related AEs (>10%) that occurred in patients with breast cancer were musculoskeletal pain, nausea, vomiting, diarrhea, constipation, abdominal pain, indigestion, fatigue, decreased appetite, headache, and hot flashes. In addition, 12% of the patients experienced serious AEs. These data indicate that the safety profile of elacestrant in clinical trials is similar to that of other endocrine therapy drugs but with a higher incidence of gastrointestinal reactions. FDA data analysis revealed that the most commonly reported elacestrant-related AEs were nausea, fatigue, disease progression, vomiting, diarrhea, death, drug ineffectiveness, product dose omission, constipation, and pain. Hot flashes were reported in 77 cases (ROR = 6.92), whereas dyspepsia was reported in 91 (ROR = 8.22). The incidence of these AEs was ≥3, and the lower 95% CI was >1. The occurrence and analyses of AEs can help clinicians identify and manage the safety risks in patients when receiving elacestrant.

The cumulative distribution curve of TTO indicates that fatal AEs occur earlier than nonfatal AEs. Furthermore, the median TTO for fatal AEs was also earlier than that for nonfatal AEs, suggesting that early occurrences of AEs require closer clinical monitoring.

The elderly patients belong to a special population for administration of medication. The phenomenon of polypharmacy (generally defined as the intake of ≥5 medications per day) among elderly patients with cancer increases their risk for AEs [13, 14] due to underlying diseases, liver and kidney function, and concomitant medication. In this study, logistic regression analysis was conducted to examine the impact of age on the occurrence of AEs. The results indicated that compared with patients aged <65 years, those aged 65–74.9 years and >75 years demonstrated 27% and 25% decreases in the risk of fatal AEs, respectively. Similarly, a previous study has indicated that advanced age (60–74 years) may reduce the risk of serious AEs related to fulvestrant administration [15]. This could be attributed to the clinical characteristics of and treatment alternatives for pre- and postmenopausal patients with breast cancer [16, 17]. Compared with postmenopausal breast cancer patients, premenopausal breast cancer patients have high recurrence risk, poor prognosis, and high mortality [18–20]. Due to the limited clinical data available for elacestrant post-marketing, clinicians may prefer combination therapy for elderly patients to reduce the incidence of AEs. However, these findings still require further validation through real-world studies.

At present, the 5-year survival rate for patients with early-stage breast cancer is as high as 90%, which relies on the development of various treatment methods and drugs [21]. Of the 3132 relevant reports, 1548 involved the use of multiple medications. The FDA has approved elacestrant for use in postmenopausal women or adult men with advanced or metastatic breast cancer demonstrating ER+, HER2−, and ESR1 mutations who have received at least one line of endocrine therapy and experienced disease progression. It has been reported that approximately 20–30% of patients with early-stage breast cancer are likely to experience distant metastasis. However, only 50% of the reports ($n = 1585$) involved the use of elacestrant as a single medication, which may be related to the partial or missing information in the reports; however, does not exclude the influence of doctors' proactive treatment strategies. Relevant studies have demonstrated that Orserdu is more effective than fulvestrant in these patients.

Conventional treatment alternatives for breast cancer include cytotoxic chemotherapy, endocrine therapy, and targeted therapy drugs. The FDA reported drug usage is as follows: combined use of hormonal drugs, 168 cases; combination of hormonal and chemotherapy drugs, 63; targeted therapy drugs, 61; and combination of chemotherapy drugs, 22. Logistic regression analysis revealed that compared with elacestrant alone, elacestrant combined with endocrine therapy or chemotherapy drugs decreased the risk of fatal AEs by 20%. However, elacestrant used in combination with targeted therapy drugs increased this risk by 5%. Nevertheless, the combined use of targeted and endocrine therapy drugs decreased the risk by 13%.

Studies show that depression can promote breast cancer recurrence, increasing the patients' mortality risk. The use of antidepressant and antianxiety medications can improve the prognosis of patients with breast cancer [22, 23]. Such drug usage was observed in 700 reported cases. The use of elacestrant in combination with other drugs is illustrated in Fig. 3. No significant differences were observed in the occurrence of AEs at the PT level when used in combination with other drugs.

This study analyzed reports on elacestrant-related AEs in the FAERS database. Elacestrant was found to be associated with AEs involving multiple organ systems, such as the gastrointestinal, hematologic, and urinary systems. Moreover, age differences and variations in treatment strategies for different drugs were observed for some AEs. In addition, potential AEs that have not been reported in the drug label or literature have been identified. In conclusion, elacestrant, as a new SERD, is clinically significant in the treatment of ER+/HER2− breast cancer demonstrating the ESR1 mutation. Its safety features have been mainly validated in clinical trials and post-market monitoring;

however, further research is still warranted to optimize its clinical application.

Limitations

(1) Limited data sources: This study mainly relied on data obtained from the FAERS database. Although this database provides extensive information on drug safety, the data sources are subject to certain biases, primarily consisting of self-reports from consumers and healthcare professionals. Such self-reported data may be affected by issues of underreporting or incompleteness, which may impact the true incidence of AEs. (2) Lack of auxiliary examination data: The FAERS database does not include detailed auxiliary examinations or laboratory data, thereby hindering a more in-depth analysis of AEs. This limits our understanding of the mechanisms of AEs hinder the accurate assessment of their occurrence in different patient populations. (3) Insufficient racial and regional representativeness: The data used in this study were mainly from the USA, resulting in a lack of analysis of different racial and regional patient groups, which may restrict the global applicability of the study findings. Failure to account for racial differences may impact the effectiveness and AEs. (4) Lack of comparisons for specific treatment strategies: While this study investigated the safety of and AEs associated with elacestrant, it did not comprehensively analyze the impact of different treatment strategies, such as monotherapy versus combination therapy, on the occurrence of AEs. The absence of corresponding controlled studies prevents the adequate investigation of the differences in safety between various treatment regimens. (5) Inability to provide explanations of potential biological mechanisms: The descriptive statistics and analysis presented in this study failed to reveal potential biological mechanisms associated with elacestrant-related AEs, and the lack of mechanistic explanations may affect the in-depth understanding of the study conclusions. (6) Limitations of observational studies: This study adopted an observational research approach. Observational studies cannot establish causal relationships and may be influenced by various confounding factors, leading to an unclear relationship between AEs and elacestrant. Despite these limitations, this study can aid healthcare professionals to consider to elacestrant-related AEs. Clinicians should fully consider the overall condition of patients and potential AEs and take necessary measures to reduce or avoid the occurrence of these events.

Conclusions

This study analyzed 3132 reports on elacestrant obtained from the FAERS database. A total of 75 significant risk signals were identified (Sup1). The logistic regression results indicated that the concomitant use of endocrine therapy or chemotherapy drugs were both risk factors for serious AEs related to elacestrant, whereas age was a protective factor. The cumulative distribution curve of the TTO showed that fatal AEs occurred earlier than nonfatal AEs. This suggests that early monitoring of drug reactions is crucial. As this study was exploratory in nature, the findings must be validated through prospective research. In the future, more cohort studies are warranted to help determine the relationship between different drug therapies and age-related AEs so as to guide health professionals in their clinical decision-making.

Abbreviations

FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
AEs	Adverse events
SERD	Selective estrogen receptor downregulator
AIs	Aromatase inhibitors
SOC	System organ class
PDX	Patient-derived xenotransplantation
PFS	Progression-free survival
CTCAE	Common Terminology Criteria for Adverse Events
NES	Not classified elsewhere
PT	Preferred terms
HLT	High-level term
HLGT	High-level group term
PRR	Proportional reporting ratio
EBGM	Empirical Bayes Geometric Mean
CI	Confidence interval
ROR	Reporting odds ratio
OR	Odds ratio
TTO	Time to onset

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00887-2.

Supplementary Material 1

Acknowledgements

The authors thank the FAERS database researchers for providing the data and algorithm developers.

Author contributions

Z.F. was responsible for the literature review, FAERS analysis, discussion, and manuscript writing. Y.X. made significant contributions to the creation of charts and data validation. S.G. was responsible for data processing and data analysis of FAERS. B.S. and Y.M. revised the language of the manuscript, and all authors agreed to publish the final version of the manuscript.

Funding

No funding.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Because of the FAERS is a public database, we don't need access to ethics approval and informed consent.

Consent for publication
All authors agreed to publish the final version of the manuscript.

Competing interests
The authors declare no competing interests.

Received: 18 December 2024 / Accepted: 3 March 2025
Published online: 11 March 2025

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