Heliyon 10 (2024) e33417

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Adverse events associated with eteplirsen: A disproportionality analysis using the 2016–2023 FAERS data

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ARTICLE INFO

Keywords:
Eteplirsen
Duchenne muscular dystrophy
FAERS
Adverse event
Disproportionality analyses

ABSTRACT

Background: Eteplirsen (Exondys 51) is an orphan drug approved for the treatment of Duchenne muscular dystrophy (DMD), having received accelerated approval from the U.S. Food and Drug Administration (FDA) in 2016. The primary aim of this study is to closely monitor adverse events (AEs) associated with eteplirsen and to identify emerging signals to better characterize their safety profile.

Methods: AEs due to eteplirsen usage reported from the third quarter (Q3) of 2016 to the fourth quarter (Q4) of 2023 were collected from the FDA Adverse Event Reporting System (FAERS). The role_code of AEs mainly includes primary suspect (PS), secondary suspect (SS), concomitant (C), and interaction (I). This study targeted reports with a role_cod of 'PS.' According to the FDA deduplication rule, the latest FDA_DT is selected when the CASEID is the same, and the higher PRIMARYID is selected when the CASEID and FDA_DT are the same. Disproportionality analyses, encompassing four algorithms for reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian configuration promotion neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS), were utilized to quantify the signals of AEs associated with eteplirsen.

Results: From the FAERS database, a total of 13,205,369 reports were amassed throughout the study duration. Following the eradication of duplicates, the number of reports with eteplirsen designated as the PS amounted to 1480 encompassed 25 organ systems. Among these, "general disorders and administration site conditions," "injury, poisoning, and procedural complications," "respiratory, thoracic, and mediastinal disorders," "infections and infestations," "vascular disorders," and "product issues" met at least one of the four computational criteria. Additionally, 55 Preferred Terms (PTs) aligned with the prescribed algorithms. The median time to AEs in these patients was 903 days with an interquartile range (IQR) of 269–1575 days. Moreover, 70.04 % of AEs manifested one year or more after the initiation of treatment.

Conclusion: As an orphan drug granted accelerated approval, our study has confirmed well-known adverse drug reactions and identified potential safety issues associated with eteplirsen treatment. This has contributed to a deeper understanding of the complex interrelations between adverse reactions and the use of eteplirsen. The findings underscore the critical importance of ongoing

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https://doi.org/10.1016/j.heliyon.2024.e33417
Received 8 April 2024; Received in revised form 20 June 2024; Accepted 20 June 2024
Available online 22 June 2024

monitoring and sustained observation to promptly detect and effectively manage AEs, thereby enhancing the overall safety and well-being of patients treated with eteplirsen for DMD.

1. Introduction

Eteplirsen or Exondys 51 is the first antisense oligonucleotide (AON) to enter clinical trials and was granted accelerated approval by the U.S. FDA in 2016 for the treatment of Duchenne muscular dystrophy (DMD) [1]. DMD is a monogenic genetic disorder, with approximately 60–65 % of patients exhibiting mutations within exon regions, including a high mutation rate of 14 % at exon 5 [2]. The disease incidence is estimated at 15.9 to 19.5 cases per 100,000 live births [3–5]. The average annual direct cost of the disease per patient is estimated to be between $23,920 and $54,270, which is 7–16 times higher than the average per capita medical expenditure [6].

Eteplirsen is a synthetic antisense oligonucleotide belonging to the 30-nucleotide phosphorodiamidate morpholino oligomer category. It is engineered to facilitate the exclusion of aberrant exons during the synthesis of the myotonic dystrophy gene, aiming at treating DMD [7,8]. This medication functions to stimulate the production of dystrophin by rectifying the translational reading frame of DMD. It achieves this by specifically omitting exon 51 in faulty gene variants [9]. As the only drug granted accelerated FDA approval for the treatment of DMD, monitoring adverse events in real-world data is crucial. Concurrently, clinical trial results indicate that while eteplirsen is effective, it also leads to various adverse reactions including balance disorders, vomiting, and contact dermatitis [10]. Given the rarity of DMD and the limited number of clinical trial cases for eteplirsen treatment, there is a significant gap between the increasing use of eteplirsen and our understanding of its safety. Therefore, it is imperative to study and analyze the safety of eteplirsen in real-world settings.

The FAERS is a typical public spontaneous reporting system, which collects spontaneous safety reports and post-marketing clinical studies related to drug use within and outside the United States for all FDA-approved drugs and therapeutic biological products [6]. It has been extensively used for drug safety information screening. Numerous studies have demonstrated the feasibility and practicality of using FAERS to monitor adverse events (AEs) associated with medication use in real-world settings. For example, in Michele's study, safety concerns associated with each type of chimeric antigen receptor T-cell therapy were identified through the application of data mining techniques to the FAERS database [11]. Similarly, Battini's academic research updated the safety profiles of ubrogepant and rimegepant, filling a significant knowledge gap [12]. Therefore, employing the FAERS database as a key tool for assessing the real-world safety of eteplirsen shows remarkable feasibility and holds profound clinical significance.

Our study utilized real-world data extracted from the FAERS database to conduct a comprehensive disproportionality analysis of AEs associated with eteplirsen, employing a robust selection of four different algorithms: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPN), and Empirical Bayesian Geometric Mean (EBGM). This approach, by meticulously examining the strength of signals in real-world data, serves as a reliable mechanism for investigating the efficacy and safety of Eteplirsen treatment, thereby facilitating effective detection and management of AEs. In summary, our research aims to enhance patient safety during eteplirsen treatment by promoting a more comprehensive and effective framework for AEs monitoring and management.

2. Methods

2.1. Data source and collection

FAERS is a spontaneous reporting system that collects reports of suspected adverse drug reactions (ADRs) from around the world. These reports are submitted by a variety of reporters, including healthcare professionals, patients and their families, lawyers, and manufacturers. The FAERS data is made available to the public in different formats: (a) a user-friendly public dashboard that contains numerous duplicates and limited information, and (b) downloadable files in ASCII or XML format, which require preprocessing but allow for more reliable analyses. Suspected ADRs are encoded using Preferred Terms (PT) from the Medical Dictionary for Regulatory Activities (MedDRA). By utilizing "Eteplirsen" or "Exondys 51″ as our query parameters, we meticulously amassed adverse drug reactions associated with eteplirsen from the third quarter (Q3) of 2016 to the fourth quarter (Q4) of 2023. Every preferred term (PT) linked to the system organ class (SOC), representing the highest echelon of the Medical Dictionary for Regulatory Activities (MedDRA), has been meticulously extracted [13]. The data have been preprocessed to retain only the latest update for each report and to remove duplicates, specifically those reports that have identical information in all of the following fields: gender, age, weight, country, date of the adverse drug reaction (ADR), list of medications, and list of ADRs.

2.2. Data cleaning

In this investigation, eteplirsen was delineated as the principal suspect pharmaceutical entity within the FAERS database for the exploration of ADRs. Due to the prevalence of duplicative entries within FAERS, a deduplication protocol was implemented in accordance with FDA directives. According to the FDA's recommended method for removing duplicate reports, the PRIMARYID, CASEID, and FDADT fields of the DEMO table are selected and sorted according to the order of CASEID, FDADT, and PRIMARYID, and the report with the same CASEID is retained with the largest FDA_DT value; followed by the report with the same CASEID and FDADT,

and the report with the largest PRIMARYID value. For reports with the same CASEID, the one with the highest FDA_DT value is retained; secondly, for reports with the same CASEID and FDADT, the one with the highest PRIMARYID is retained [14,15]. The methodology employed for data screening in this study is depicted in Fig. 1.

2.3. Signals analysis algorithms

In our study, we utilized measures of disproportionality, a method commonly employed in pharmacovigilance to detect signals between eteplirsen and adverse events (AEs). This involves comparing the ratio of observed frequencies in exposed and non-exposed populations using a two-by-two contingency Table 1 [16]. We employed four algorithms: the Reporting Odds Ratio (ROR) [17], Proportional Reporting Ratio (PRR) [18], Bayesian Confidence Propagation Neural Network (BCPNN) [19]and Multi-item Gamma Poisson Shrinker (MGPS) [20]. The BCPNN is based on the lower limit of the 95 % confidence interval (CI) of the information component (IC), specifically IC025, and the one-sided 95 % CI lower bound of the Empirical Bayesian Geometric Mean (EBGM), specifically EBGM05, to assess the strength of associations between drugs and adverse reactions. The specific formulas for these algorithms are provided in Table 2.

2.4. Statistical analysis

Descriptive statistics were used to elucidate the AE reports related to eteplirsen. The criteria for positive safety signal detection are as follows: for ROR and PRR, the lower limit of 95 % CI must exceed 1, and the signal strength must be at least 3 [18,21,22]; for BCPNN, IC025 must be greater than 0 [21]; and for positive signal detection in general, EBGM05 must exceed 2 [22,23]. All data manipulations and statistical calculations were performed using R software, version 4.2.2.

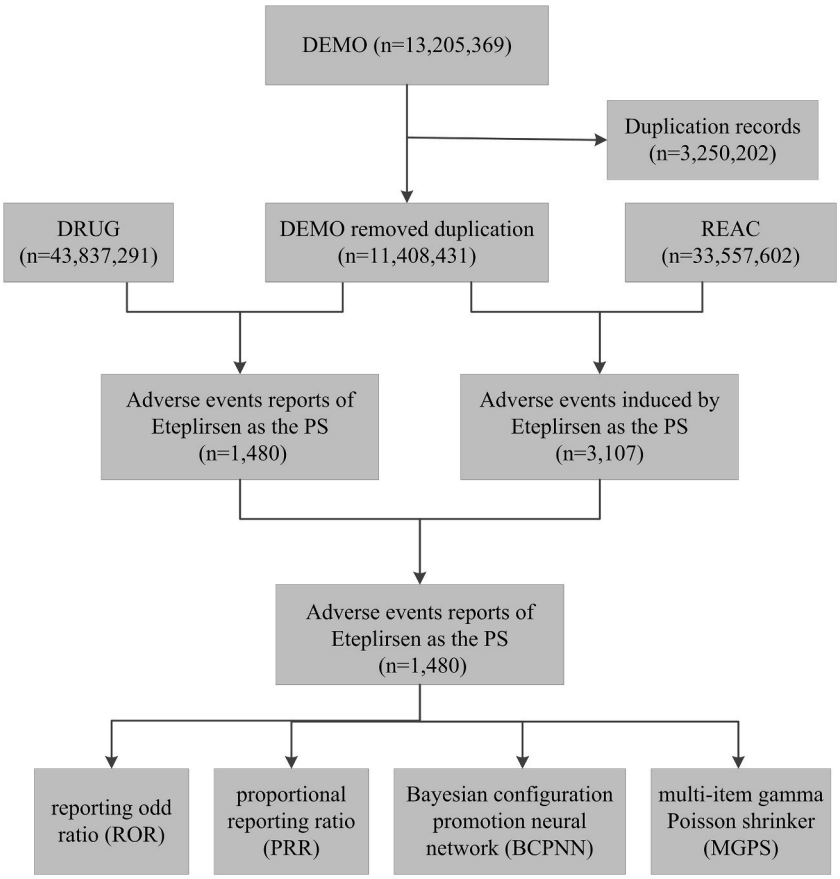

Fig. 1. Flow diagram of this study. A total of 13,205,369 demographic and administrative information was obtained from the FAERS database. After removing 3,250,202 duplicate reports, there are still 11,408,431 reports left. 1480 suspicious drug adverse event reports were screened out from 43,837,291 drug adverse event reports, with eteplirsen as the primary suspect drug. From 33,557,602 preferred terminology for adverse events, 3107 adverse events were screened using eteplirsen as the primary prospect drug. Finally, 1480 adverse event reports were included in the analysis. Abbreviation: DEMO, demographic and administrative information; DRUG, drug information; REAC, preferred terminology for adverse event; PS, primary suspect drug.

Table 1
Two-by-two contingency table for disproportionality analyses.

	Target AEs	Non-Target AEs	Total
Eteplirsen	a	b	a+b
Non-Eteplirsen	c	d	c + d
Total	a+c	b + d	N = a+b + c + d

Abbreviations: AEs; adverse events.

Table 2
Four different types of disproportionality analysis.

Algorithms	Equation	Criteria
ROR	$ROR = (a/c)/(b/d)$ $95\%CI = eln^{(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	95 % CI (lower limit) > 1, a ≥3
PRR	$PRR = [a/(a+b)]/[c/(c + d)]$ $95\%CI = eln^{(PRR)\pm1.96[1/a-1/(a+b)+1/c-1/(c + d)]^{\wedge}0.5}$	95 % CI (lower limit) > 1, a ≥3
BCPNN	$IC = \log_2 a\ (a+b + c + d)/((a+c)\ (a+b))$ $IC025 = e^{\ln(IC)-1.96(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	IC025 > 0, a ≥3
MGPS	$EBGM = a\ (a+b + c + d)/((a+c)\ (a+b))$ $EBGM05 = e^{\ln(EBGM)-1.64(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	EBGM05 > 2, a > 0

Notes: Equation: a, number of reports containing both the target drug and the target adverse drug reaction; b, number of reports containing other adverse drug reactions 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. The MGPS employs an empirical Bayesian approach, whereby maximum likelihood estimates obtain a prior distribution, and the prior and likelihood are combined to obtain a posterior distribution. The fifth percentile of the posterior distribution is denoted by "EBGM05" and is interpreted as the one-sided 95 % confidence lower bound for the EBGM.
Abbreviations: 95 % CI, 95 % confidence interval; N, the number of reports; BCPNN, Bayesian confidence propagation neural network; IC, information component; IC025, the lower limit of the 95 % CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, empirical Bayesian geometric mean lower 95 % CI for the posterior distribution.

3. Result

3.1. Descriptive results

A total of 13,205,369 entries comprised the comprehensive FAERS dataset from Q3 2016 to Q4 2023. After eliminating duplicates, 1480 reports associated with eteplirsen, encompassing 3107 adverse events, were analyzed. The clinical attributes of events related to eteplirsen are delineated in Table 3. The demographics show that 95.1 % of the adverse events occurred in males, mostly under 18 years. The vast majority (99.3 %) of events originated from the United States. Hospitalization was the most frequently cited severe outcome (13.2 % of cases), followed by mortality (2.7 %) and life-threatening incidents (0.6 %). Health professionals were the primary reporters, contributing to 52.6 % of the reports. The year 2023 had the highest number of reports (403), with subsequent years showing varying frequencies.

3.2. Disproportionality analysis

Signal values of reports linked to eteplirsen at the SOC level are delineated in Table 4. Statistically, eteplirsen-associated AEs manifested across 25 organ systems. Among these, six noteworthy SOCs emerged, satisfying at least one of the four computation criteria, including general disorders (ROR = 1.18, CI: 1.08–1.29), administration site conditions (ROR = 1.18, CI: 1.08–1.29), injury poisoning, and procedural complications (ROR = 3.50, CI: 3.24–3.77), Respiratory, thoracic, and mediastinal disorders (ROR = 1.32, CI: 1.13–1.53), infections and infestations (ROR = 1.96, CI: 1.73–2.19), vascular disorders (ROR = 2.66, CI: 2.26–3.13), and product issues (ROR = 2.71, CI: 2.29–3.2).

By computing the signal values of reports linked to eteplirsen at the PT level, 55 PTs with significant disproportionality were identified, concurrently meeting the four calculation criteria. These AEs were then arranged in descending order of ROR, presenting the foremost ten PTs in Table 5. It was observed that the majority of the top ten PTs were reactions associated with the catheter site.

3.3. Onset time of events

Excluding medication dates or AE occurrence dates that were unknown or unreported, the onset time of AEs was calculated based on data extracted from the database. Of the 1480 patients, only 564 (38.11 %) were available for time analysis. The median time to AEs in these patients was 903 days with an interquartile range (IQR) of 269–1575 days. As can be seen in Fig. 2, the majority of AEs in these patients (70.04 %) occurred within one year or more of eteplirsen use.

Table 3
Characteristics of reports associated with eteplirsen.

Factors	Eteplirsen
Number of reports	(N = 1480)
Gender	
Female	29 (2.0 %)
Male	1408 (95.1 %)
Missing	43 (2.9 %)
Age (years)	
<18	774 (52.3 %)
18–64.9	406 (27.4 %)
Missing	300 (20.3 %)
Serious Outcome	
Hospitalization	209 (13.2 %)
Death	43 (2.7 %)
Life-threatening	10 (0.6 %)
Disability	2 (0.1 %)
Reporters	
Health Professional	778 (52.6 %)
Consumer	328 (22.2 %)
Pharmacists	125 (8.4 %)
Medical doctor	88 (5.9 %)
Other	161 (10.9 %)
Reported Countries	
United States	1469 (99.3 %)
Israel	8 (0.5 %)
Canada	1 (0.1 %)
United Kingdom	1 (0.1 %)
India	1 (0.1 %)
Report year	
2016	1
2017	22
2018	229
2019	138
2020	187
2021	261
2022	239
2023	403

4. Discussion

This study represents the first extensive and systematic pharmacovigilance investigation of adverse reactions associated with eteplirsen using the FAERS database following its market release. The primary aim of this research is to provide a detailed and comprehensive characterization and analysis of the AEs related to eteplirsen reported to date. The results presented in this paper offer valuable and precise insights into the safety profile of Eteplirsen in a real-world clinical setting.

Based on the descriptive results, it was observed that the frequency of adverse reactions to eteplirsen was markedly higher among males (95.1 %) than females (2.0 %), attributed to the heightened susceptibility of males to DMD [24], consequently amplifying their likelihood of eteplirsen treatment. Moreover, individuals under the age of 18 receiving eteplirsen were more susceptible to adverse effects, in alignment with DMD epidemiological studies [25]. The number of AEs in the U.S. significantly exceeds that in other countries, likely due to a larger medication-using population. This trend may be attributed to factors such as a larger population size, a stronger willingness to report, earlier market entry, and an earlier expansion of indications, all of which collectively promote the widespread use of the medication.

Of the PTs associated with general disorders and administration site conditions, the top four reported were catheter site bruise, catheter site related reaction, catheter site pain, and catheter site erythema, respectively. In a clinical study, infusion-related reactions occurred in 45 of 79 patients (57.0 %). Most of the infusion-related reactions were mild and resolved [26]. In terms of vascular disorders at the PT level, poor venous access has the highest number of reports, but this adverse effect has not been identified in other studies. Adverse effects of protein urine present were also identified in our study, which is consistent with safety data from multiple clinical trials. The most common Treatment Emergent Adverse Events (TEAEs) reported over 168 weeks in the 4658-US-202 trial (n = 8) included procedural pain (75 %), proteinuria (62 %), vomiting (50 %), hypokalemia (50 %), back pain (50 %), headache (50 %) and balance disorder (50 %) [10]. Another study showed renal TEAEs in eight eteplirsen -treated patients, each with proteinuria, which resolved in all but one patient by the end of the study [26].

In our analysis, noteworthy AE signals included Ewing's sarcoma, fat embolism syndrome, cardiac death, and acute respiratory failure. A prospective study reported an adolescent developing cardiomyopathy while on eteplirsen, consistent with DMD's typical progression [27]. It has also been shown that DMD is associated with an increased likelihood of cardiac events [28]and can precipitate respiratory failure [29]. Whether the causative factors behind these complications are inherent to the disease itself or are triggered or exacerbated by the medication deserves further investigation We call for vigilance in these adverse effects of concern so that

Table 4
Signal values of reports associated with Eteplirsen at the SOC level.

System organ class	AE numbers	ROR (95%Cl)	PRR (95%Cl)	IC025	EBGM05
Gastrointestinal disorders	122	0.46 (0.38–0.55)	0.48 (0.40–0.57)	−2.74	0.41
General disorders and administration site conditions	634	1.18 (1.08–1.29)[a]	1.15 (1.07–1.23)[a]	−1.47	1.07
Investigations	88	0.47 (0.38–0.58)	0.49 (0.40–0.60)	−2.70	0.41
Musculoskeletal and connective tissue disorders	48	0.29 (0.22–0.39)	0.30 (0.23–0.40)	−3.40	0.24
Injury, poisoning, and procedural complications	985	3.50 (3.24–3.77)[a]	2.71 (2.57–2.85)[a]	−0.23	2.54[a]
Renal and urinary disorders	27	0.43 (0.30–0.63)	0.44 (0.30–0.64)	−2.85	0.32
Nervous system disorders	79	0.31 (0.25–0.39)	0.33 (0.26–0.41)	−3.27	0.27
Respiratory, thoracic, and mediastinal disorders	184	1.32 (1.13–1.53)[a]	1.30 (1.13–1.49)[a]	−1.29	1.15
Metabolism and nutrition disorders	50	0.79 (0.60–1.05)	0.80 (0.61–1.05)	−1.99	0.63
Psychiatric disorders	71	0.41 (0.33–0.52)	0.43 (0.34–0.53)	−2.90	0.35
Infections and infestations	313	1.96 (1.73–2.19)[a]	1.85 (1.67–2.06)[a]	−0.78	1.68
Vascular disorders	154	2.66 (2.26–3.13)[a]	2.58 (2.21–3.01)[a]	−0.30	2.25[a]
Skin and subcutaneous tissue disorders	63	0.34 (0.27–0.44)	0.35 (0.28–0.45)	−3.16	0.29
Neoplasms benign, malignant, and unspecified (Incl Cysts and Polyps)	3	0.03 (0.01–0.09)	0.22 (0.21–0.23)	−3.86	0.21
Cardiac disorders	66	1.04 (0.81–1.32)	1.03 (0.81–1.31)	−1.62	0.84
Endocrine disorders	5	0.61 (0.26–1.48)	0.61 (0.26–1.48)	−2.37	0.29
Ear and labyrinth disorders	3	0.22 (0.07–0.69)	0.22 (0.07–0.69)	−3.83	0.09
Eye disorders	12	0.20 (0.11–0.35)	0.20 (0.11–0.35)	−4.00	0.12
Hepatobiliary disorders	6	0.24 (0.11–0.53)	0.24 (0.11–0.53)	−3.74	0.12
Reproductive system and breast disorders	2	0.08 (0.02–0.34)	0.09 (0.02–0.34)	−5.21	0.03
Blood and lymphatic system disorders	6	0.12 (0.05–0.26)	0.12 (0.05–0.26)	−4.75	0.06
Immune system disorders	7	0.18 (0.09–0.38)	0.19 (0.09–0.39)	−4.10	0.10
Social circumstances	11	0.78 (0.43–1.31)	0.78 (0.43–1.31)	−2.02	0.48
Surgical and medical procedures	25	0.58 (0.39–0.85)	0.58 (0.39–0.86)	−2.45	0.42
Product issues	143	2.71 (2.29–3.20)[a]	2.63 (2.24–3.09)[a]	−0.27	2.29[a]

[a] Indicates statistically significant signals in algorithm. IC025 and EBGM05 measure the two types of disproportionality analyses, BCPNN and MGPS, respectively. Abbreviations: SOC, system organ class; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; IC025, the lower limit of 95 % CI of the IC; EBGM05, the lower limit of 95 % CI of EBGM.

Table 5
The top 10 AEs of eteplirsen ranked by the ROR algorithm at the PTs level.

SOC Name	PTs	AEs numbers	ROR (95%Cl)
general disorders and administration site conditions	catheter site bruise	3	222.12 (70.78, 697.12)
general disorders and administration site conditions	catheter site related reaction	5	193.16 (79.71, 468.04)
vascular disorders	poor venous access	103	190.45 (156.23, 232.15)
general disorders and administration site conditions	catheter site pain	12	94.41 (53.42, 166.83)
general disorders and administration site conditions	catheter site erythema	5	46.30 (19.22, 111.54)
investigations	protein urine present	7	28.46 (18.54, 59.81)
investigations	pulmonary function test decreased	3	11.37 (3.66, 35.28)
respiratory, thoracic and mediastinal disorders	acute respiratory failure	11	11.34 (6.27, 20.50)
cardiac disorders	cardiac failure acute	3	8.91 (2.87, 27.64)
vascular disorders	cyanosis	5	8.36 (3.48, 20.11)

Abbreviations: SOC, system organ class; PTs, Preferred terms; AEs, adverse events; ROR, reporting odds ratio; CI, confidence interval.

appropriate preventive measures can be taken.

Currently, due to the rarity of DMD, comprehensive real-world large-sample safety studies on eteplirsen are scarce, with most research found on PubMed focusing on small-scale, single-population studies. Our study, based on the FAERS database, covers the most extensive collection of eteplirsen-related cases to date, including 1480 cases and 3107 adverse reactions. Our research not only integrates previously cataloged adverse reactions based on drug labeling and clinical trials conducted but also identifies some new adverse reactions. These findings provide a comprehensive and valuable insight into the safety of eteplirsen.

However, our observational study using the FAERS database faces inherent limitations typical of spontaneous reporting systems analyses. These include incomplete data capture (e.g., unreported cases), insufficient details on the exposed population (e.g., lacking comprehensive demographic and health background like family history or lifestyle factors), reporting biases (e.g., unverified cases by healthcare professionals), and potential confounding factors (e.g., concurrent drug usage). Additionally, the self-reporting nature of the database means we cannot ascertain the drug's total user base, limiting our ability to generalize these findings. Consequently, our disproportionality analysis, while informative, cannot definitively establish causality or accurately measure incidence rates [30,31].

5. Conclusion

Our study presents spontaneously reported suspected adverse reactions in patients treated with eteplirsen, reinforcing evidence from clinical trials and prior observational studies. Additionally, we identified unexpected signals warranting further evaluation; these

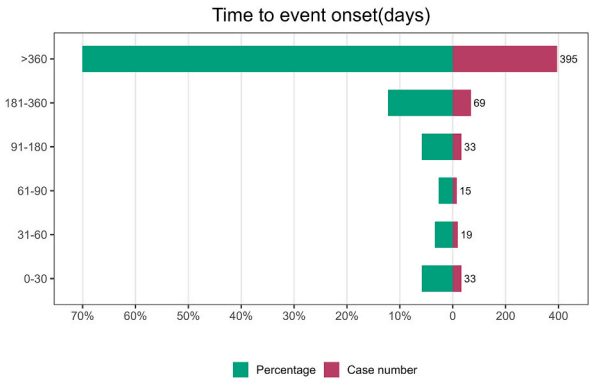

Fig. 2. Time to onset of eteplirsen-related AEs. On the horizontal axis, the left side of "0" represents the percentage of AE numbers, and the right side represents the number of AE. The vertical axis represents the time to event onset of AEs. The time to event onset of AEs equals the onset date of AE minus the start date of Teriparatide administration.
Abbreviation: AEs, adverse events.

include AEs not listed in FDA guidelines but are noteworthy in real-world contexts. Our results deepen the understanding of eteplirsen-related toxicity and provide valuable insights for healthcare professionals to mitigate these risks through post-marketing safety evaluations.

Ethics statement

Not applicable.

Data availability statement

Publicly available datasets are available online for this study. The repository name and accession numbers are available online at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers. Are the data relevant to this study deposited in a publicly available repository, database link: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers.

Funding

This study was funded by the Natural Science Foundation of Shanghai, China (19ZR1440700), Natural Science Foundation of Shanghai, China (20ZR1457400)

CRediT authorship contribution statement

Zhicheng Dai: Writing – original draft, Formal analysis, Data curation. **Guangming Wang:** Writing – original draft, Formal analysis, Data curation. **Jiafeng Zhang:** Writing – original draft, Formal analysis, Data curation. **Qinghua Zhao:** Writing – review & editing, Methodology. **Lei Jiang:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

DMD	Duchenne muscular dystrophy
AEs	adverse events
FDA	Food and Drug Administration
FAERS	Food and Drug Administration Adverse Event Reporting System
IQR	interquartile range
ROR	reporting odds ratio
PRR	proportional reporting ratio
BCPNN	Bayesian confiuration promotion neural network

MGPS	multi-item gamma Poisson shrinker
PS	primary suspect
PTs	Preferred Terms
ADRs	adverse drug reactions
SOC	system organ class

References

[1] R. Xiao, M. Zhou, P. Wang, B. Zeng, L. Wu, Z. Hu, D. Liang, Full-length dystrophin restoration via targeted exon addition in DMD-patient specific iPSCs and cardiomyocytes, Int. J. Mol. Sci. 23 (2022).

[2] C.L. Bladen, D. Salgado, S. Monges, M.E. Foncuberta, K. Kekou, K. Kosma, H. Dawkins, L. Lamont, A.J. Roy, T. Chamova, et al., The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations, Hum. Mutat. 36 (2015) 395–402.

[3] S.C. Kolwicz Jr., J.K. Hall, F. Moussavi-Harami, X. Chen, S.D. Hauschka, J.S. Chamberlain, M. Regnier, G.L. Odom, Gene therapy rescues cardiac dysfunction in Duchenne muscular dystrophy mice by elevating cardiomyocyte deoxy-adenosine triphosphate, JACC Basic Transl Sci 4 (2019) 778–791.

[4] J.R. Mendell, C. Shilling, N.D. Leslie, K.M. Flanigan, R. al-Dahhak, J. Gastier-Foster, K. Kneile, D.M. Dunn, B. Duval, A. Aoyagi, et al., Evidence-based path to newborn screening for Duchenne muscular dystrophy, Ann. Neurol. 71 (2012) 304–313.

[5] S.J. Moat, D.M. Bradley, R. Salmon, A. Clarke, L. Hartley, Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK), Eur. J. Hum. Genet. 21 (2013) 1049–1053.

[6] X.L. Wang, S.S. Xu, J.B. Zhou, Z.H. Song, An observational study on the safety of teprotumumab based on FAERS database, Endocrine (2024) 1–8.

[7] In LiverTox, Clinical and Research Information on Drug-Induced Liver Injury, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda (MD), 2012.

[8] R. Kole, A.M. Krieg, Exon skipping therapy for Duchenne muscular dystrophy, Adv. Drug Deliv. Rev. 87 (2015) 104–107.

[9] K.R. Lim, R. Maruyama, T. Yokota, Eteplirsen in the treatment of Duchenne muscular dystrophy, Drug Des. Dev. Ther. 11 (2017) 533–545.

[10] J.R. Mendell, N. Goemans, L.P. Lowes, L.N. Alfano, K. Berry, J. Shao, E.M. Kaye, E. Mercuri, Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy, Ann. Neurol. 79 (2016) 257–271.

[11] M. Fusaroli, V. Isgrò, P.M. Cutroneo, C. Ferrajolo, V. Cirillo, F. Del Bufalo, E. Raschi, E. Poluzzi, G. Trifirò, Post-marketing surveillance of CAR-T-cell therapies: analysis of the FDA adverse event reporting system (FAERS) database, Drug Saf. 45 (2022) 891–908.

[12] V. Battini, C. Carnovale, E. Clementi, M. Sessa, Ubrogepant and rimegepant: signal detection using spontaneous reports of adverse events from the Food and Drug Administration Adverse Event Reporting System, Expert Opin Drug Saf 22 (2023) 1105–1112.

[13] E.G. Brown, Using MedDRA: implications for risk management, Drug Saf. 27 (2004) 591–602.

[14] Z. Huang, Association between blood lead level with high blood pressure in US (NHANES 1999-2018), Front. Public Health 10 (2022) 836357.

[15] V. Giunchi, M. Fusaroli, M. Hauben, E. Raschi, E. Poluzzi, Challenges and opportunities in accessing and analysing FAERS data: a call towards a collaborative approach, Drug Saf. 46 (2023) 921–926.

[16] A. Mouffak, M. Lepelley, B. Revol, C. Bernardeau, F. Salvo, A. Pariente, M. Roustit, J.L. Cracowski, C. Khouri, High prevalence of spin was found in pharmacovigilance studies using disproportionality analyses to detect safety signals: a meta-epidemiological study, J. Clin. Epidemiol. 138 (2021) 73–79.

[17] A. Bate, S.J. Evans, Quantitative signal detection using spontaneous ADR reporting, Pharmacoepidemiol. Drug Saf. 18 (2009) 427–436.

[18] S.J. Evans, P.C. Waller, S. Davis, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, Pharmacoepidemiol. Drug Saf. 10 (2001) 483–486.

[19] A. Bate, M. Lindquist, I.R. Edwards, S. Olsson, R. Orre, A. Lansner, R.M. De Freitas, A Bayesian neural network method for adverse drug reaction signal generation, Eur. J. Clin. Pharmacol. 54 (1998) 315–321.

[20] A. Szarfman, S.G. Machado, O'Neill RT: **use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database**, Drug Saf. 25 (2002) 381–392.

[21] Y. Noguchi, T. Tachi, H. Teramachi, Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source, Brief Bioinform 22 (2021).

[22] Y. Noguchi, T. Tachi, H. Teramachi, Review of statistical methodologies for detecting drug-drug interactions using spontaneous reporting systems, Front. Pharmacol. 10 (2019) 1319.

[23] G.N. Norén, R. Sundberg, A. Bate, I.R. Edwards, A statistical methodology for drug-drug interaction surveillance, Stat. Med. 27 (2008) 3057–3070.

[24] S. Crisafulli, J. Sultana, A. Fontana, F. Salvo, S. Messina, G. Trifirò, Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis, Orphanet J. Rare Dis. 15 (2020) 141.

[25] J.K. Mah, L. Korngut, J. Dykeman, L. Day, T. Pringsheim, N. Jette, A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy, Neuromuscul. Disord. 24 (2014) 482–491.

[26] C.M. McDonald, P.B. Shieh, H.Z. Abdel-Hamid, A.M. Connolly, E. Ciafaloni, K.R. Wagner, N. Goemans, E. Mercuri, N. Khan, E. Koenig, et al., Open-label evaluation of eteplirsen in patients with Duchenne muscular dystrophy amenable to exon 51 skipping: PROMOVI trial, J. Neuromuscul. Dis. 8 (2021) 989–1001.

[27] L. Randeree, G.D. Eslick, Eteplirsen for paediatric patients with Duchenne muscular dystrophy: a pooled-analysis, J. Clin. Neurosci. 49 (2018) 1–6.

[28] A. Fayssoil, N. Mansencal, L.S. Nguyen, O. Nardi, R.B. Yaou, F. Leturcq, H. Amthor, K. Wahbi, H.M. Becane, F. Lofaso, et al., Prognosis of right ventricular systolic dysfunction in patients with Duchenne muscular dystrophy, J. Am. Heart Assoc. 12 (2023) e027231.

[29] A. Chikamoto, R. Tochinai, S.I. Sekizawa, M. Kuwahara, Plasticity occurs in a specific phenotype of neurons in the nucleus tractus solitarius of dystrophin gene-mutated rats, Eur. J. Neurosci. 58 (2023) 4282–4297.

[30] R.J. Yu, M.S. Krantz, E.J. Phillips, C.A. Stone Jr., Emerging causes of drug-induced anaphylaxis: a review of anaphylaxis-associated reports in the FDA adverse event reporting system (FAERS), J. Allergy Clin. Immunol. Pract. 9 (2021) 819–829.e812.

[31] C. Zhou, S. Peng, A. Lin, A. Jiang, Y. Peng, T. Gu, Z. Liu, Q. Cheng, J. Zhang, P. Luo, Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database, EClinicalMedicine 59 (2023) 101967.