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A Disproportionality Analysis of the Serious Adverse Drug Events Associated with Gene Therapy Products Using the FDA Adverse Event Reporting System (FAERS)

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Background

- Gene therapy products are being approved without sufficient clinical evidence to ensure safety at the time of approval.
- As a result, there is a growing need to monitor post-marketing safety.

Objective

To evaluate the safety profile of gene therapy products by examining the adverse events (AEs) reported to the FDA Adverse Event Reporting System (FAERS) by the pharmaceutical industry, healthcare providers, and consumers.

Methods

- A retrospective pharmacovigilance analysis was conducted using FAERS AEs reports.
- Descriptive statistics were performed.
- Disproportionality analyses of serious AEs for gene therapeutics compared to the available alternatives for the same proposed indications was calculated using reporting odds ratios (RORs) with 95% confidence intervals (CI) at $p < 0.05$.

Results

Table 1. Types of adverse events of gene therapy products submitted to the FAERS.

	Axicabtagene ciloleucel	Brexucabtagene autoleucel	Tisagenlecleucel	Idecabtagene vicleucel	Onasemnogene abeparvovec	Talimogene laherparepvec	Lisocabtagene maraleucel	Voretigene neparvovec
AEs*	n (%)							
Blood and lymphatic system disorders	85 (3%)	14 (6%)	112 (5%)	0 (0%)	0 (0%)	0 (0%)	18 (15%)	0 (0%)
Cardiac Disorders	181 (6%)	23 (9%)	138 (6%)	1 (2%)	40 (4%)	8 (1%)	5 (4%)	0
Gastrointestinal Disorders	158 (5%)	21 (9%)	151 (7%)	2 (4%)	309 (32%)	77 (8%)	3 (2%)	0 (0%)
General Disorders and Administration Site Conditions	818 (28%)	97 (40%)	1012 (46%)	14 (30%)	300 (31%)	346 (35%)	9 (7%)	15 (26%)
Immune System Disorders	1634 (56%)	151 (62%)	995 (45%)	31 (67%)	0 (0%)	9 (1%)	33 (27%)	0 (0%)
Infection	217 (7%)	16 (7%)	402 (18%)	0 (0%)	102 (11%)	34 (3%)	12 (10%)	1 (2%)
Nervous System Disorders	653 (22%)	60 (25%)	401 (18%)	0 (0%)	17 (2%)	35 (4%)	16 (13%)	3 (5%)
Psychiatric Disorders	54 (2%)	13 (5%)	49 (2%)	0 (0%)	14 (1%)	8 (1%)	1 (1%)	3 (5%)
Respiratory, Thoracic and Mediastinal Disorders	163 (6%)	25 (10%)	267 (12%)	2 (4%)	59 (6%)	17 (2%)	3 (2%)	0 (0%)
Vascular Disorders	310 (11%)	50 (20%)	379 (17%)	1 (2%)	31 (3%)	25 (3%)	7 (6%)	2 (3%)
Metabolism and nutrition disorders	38 (1%)	6 (2%)	27 (1%)	1 (2%)	47 (5%)	8 (1%)	2 (2%)	0 (0%)
Renal and urinary disorders	50 (2%)	10 (4%)	81 (4%)	0 (0%)	1 (0%)	8 (1%)	0 (0%)	0 (0%)

*A patient may have multiple outcomes.

Table 2. Disproportionality analyses of serious AEs for gene therapeutics.

	All		Single active ingredient		Combination of ingredients	
Active ingredient	ROR (95% CI)	p-value	ROR (95% CI)	p-value	ROR (95% CI)	p-value
Axicabtagene ciloleucel	Ref		Ref		Ref	
Carboplatin	0.25 (0.153–0.416)	0.000	1.77 (0.415–7.582)	0.434	1.60 (0.370–6.925)	0.525
Cisplatin	0.20 (0.118–0.322)	0.000	0.92 (0.123–6.847)	0.934	1.31 (0.303–5.625)	0.720
Cytarabine	0.28 (0.206–0.390)	0.000	1.12 (0.529–2.362)	0.771	1.83 (0.448–7.472)	0.393
Dexamethasone	0.35 (0.255–0.493)	0.000	0.58 (0.139–2.395)	0.444	2.44 (0.596–9.967)	0.200
Etoposide	0.28 (0.204–0.383)	0.000	0.49 (0.117–2.006)	0.307	1.93 (0.473–7.843)	0.352
Ifosfamide	0.33 (0.227–0.483)	0.000	2.91 (1.559–5.416)	0.000	1.69 (0.403–7.063)	0.469
Methylprednisolone	0.22 (0.110–0.446)	0.000	0.00 (0.000–NaN)	0.477	1.56 (0.337–7.264)	0.565
Rituximab	1.01 (0.791–1.290)	0.000	3.01 (2.337–3.871)	0.000	3.00 (0.745–12.060)	0.104
Onasemnogene abeparvovec	Ref		Ref		Ref	
Nusinersen	1.46 (1.252–1.695)	0.000	1.38 (1.179–1.609)	0.000	1.77 (0.7267–4.334)	0.204
Brexucabtagene autoleucel	Ref		Ref		Ref	
Mantle cell lymphoma (relapsed or refractory)						
Acalabrutinib	3.97 (1.864–8.462)	0.000	3.90 (1.794–8.455)	0.000	Inf (NaN–Inf)	0.000
Bendamustine	1.52 (0.742–3.102)	0.000	5.33 (2.583–11.009)	0.000	Inf (NaN–Inf)	0.000
Bortezomib	1.29 (0.620–2.692)	0.000	4.22 (1.982–8.984)	0.000	Inf (NaN–Inf)	0.000
Ibrutinib	4.11 (2.020–8.379)	0.000	4.08 (1.994–8.364)	0.000	Inf (NaN–Inf)	0.000
Lenalidomide	8.47 (4.162–17.222)	0.000	7.99 (3.907–16.338)	0.000	Inf (NaN–Inf)	0.000
Rituximab	0.67 (0.331–1.372)	0.000	1.85 (0.903–3.796)	0.000	Inf (NaN–Inf)	0.000
Zanubrutinib	3.44 (1.444–8.176)	0.000	4.70 (1.900–11.644)	0.000	Inf (NaN–Inf)	0.000
Idecabtagene vicleucel	Ref		Ref		Ref	
Daratumumab	0.30 (0.147–0.623)	0.000	0.65 (0.313–1.367)	0.000	Inf (NaN–Inf)	0.000
Belantamab mafodotin-blmf	0.14 (0.060–0.333)	0.000	0.17 (0.071–0.399)	0.000	NaN (NaN–NaN)	NaN
Bortezomib	0.38 (0.186–0.784)	0.000	0.63 (0.305–1.316)	0.000	Inf (NaN–Inf)	0.000
Doxorubicin	0.05 (0.021–0.098)	0.000	0.18 (0.064–0.494)	0.000	Inf (NaN–Inf)	0.000
Elotuzumab	0.21 (0.102–0.444)	0.000	0.65 (0.299–1.394)	0.000	Inf (NaN–Inf)	0.000
Panobinostat	0.70 (0.338–1.464)	0.000	1.54 (0.727–3.270)	0.000	Inf (NaN–Inf)	0.000
Ccarfilzomib	0.76 (0.370–1.563)	0.000	1.43 (0.686–2.964)	0.000	Inf (NaN–Inf)	0.000
Lenalidomide	1.30 (0.634–2.668)	0.000	1.35 (0.652–2.804)	0.000	Inf (NaN–Inf)	0.000
Melphalan flufenamide	0.05 (0.025–0.111)	0.000	0.20 (0.089–0.444)	0.000	Inf (NaN–Inf)	0.000
Ixazomib	0.91 (0.443–1.869)	0.000	1.60 (0.770–3.328)	0.000	Inf (NaN–Inf)	0.000
Pomalidomide	1.56 (0.758–3.194)	0.000	1.69 (0.814–3.502)	0.000	Inf (NaN–Inf)	0.000
Isatuximab	0.06 (0.027–0.151)	0.000	0.57 (0.205–1.592)	0.000	Inf (NaN–Inf)	0.000
Selinexor	2.65 (1.285–5.460)	0.000	3.22 (1.546–6.720)	0.000	Inf (NaN–Inf)	0.000

	All		Single active ingredient		Combination of ingredients	
Active ingredient	ROR (95% CI)	p-value	ROR (95% CI)	p-value	ROR (95% CI)	p-value
Lisocabtagene maraleucel	Ref		Ref		Ref	
Axicabtagene ciloleucel	0.48 (0.204–1.138)	0.000	0.12 (0.048–0.318)	0.000	Inf	0.567
Bendamustine	1.08 (0.472–2.489)	0.000	1.06 (0.421–2.685)	0.000	Inf	0.180
Lenalidomide	6.05 (2.644–13.828)	0.000	1.59 (0.636–3.993)	0.000	Inf	0.048
Polatuzumab	0.15 (0.056–0.427)	0.000	0.18 (0.046–0.707)	0.000	Inf	0.480
Rituximab	0.48 (0.210–1.101)	0.000	0.37 (0.147–0.927)	0.000	Inf	0.328
Selinexor	7.69 (3.226–18.331)	0.000	2.25 (0.861–5.882)	0.000	NaN	NaN
Tafasitamab	6.00 (2.315–15.551)	0.000	4.35 (1.419–13.361)	0.000	Inf	0.076
Tisagenlecleucel	0.77 (0.320–1.853)	0.000	0.20 (0.075–0.518)	0.000	Inf	0.387
Talimogene laherparepvec	Ref		Ref		Ref	
Dacarbazine	0.15 (0.053–0.456)	0.000	0.06 (0.023–0.144)	0.000	0.15 (0.053–0.456)	0.000
Pembrolizumab	0.67 (0.310–1.444)	0.000	0.36 (0.298–0.445)	0.000	0.67 (0.310–1.444)	0.000
Trametinib	2.45 (1.190–5.052)	0.000	0.86 (0.653–1.129)	0.000	2.45 (1.190–5.052)	0.000
Nivolumab	0.60 (0.291–1.252)	0.000	0.19 (0.152–0.230)	0.000	0.60 (0.291–1.252)	0.000
Interleukin-2	0.28 (0.090–0.881)	0.000	0.11 (0.057–0.231)	0.000	0.28 (0.090–0.881)	0.000
Dabrafenib	2.43 (1.178–5.004)	0.000	0.51 (0.401–0.661)	0.000	2.43 (1.178–5.004)	0.000
Ipilimumab	0.59 (0.287–1.231)	0.000	0.30 (0.247–0.367)	0.000	0.59 (0.287–1.231)	0.000
Vemurafenib	0.66 (0.314–1.394)	0.000	0.37 (0.303–0.452)	0.000	0.66 (0.314–1.394)	0.000
Tisagenlecleucel	Ref		Ref		Ref	
Large B-cell lymphoma (relapsed or refractory)						
Prednisone	0.22 (0.155–0.300)	0.000	0.92 (0.214–3.942)	0.909	1.04 (0.256–4.212)	0.958
Acute lymphoblastic leukemia						
Blinatumomab	5.74 (3.966–8.304)	0.000	6.44 (4.417–9.403)	0.000	7.52 (1.025–55.234)	0.000
Clofarabine	0.61 (0.385–0.959)	0.000	1.28 (0.751–2.197)	0.000	2.09 (0.281–15.572)	0.000
Vincristine sulfate liposome injection	0.69 (0.466–1.031)	0.000	1.27 (0.733–2.196)	0.000	3.58 (0.496–25.762)	0.000

Limitations

- We did not investigate comorbidities in these reports. These comorbidities have the potential to deceive the safety profile of gene therapeutics.
- The use of ROR might overestimate the strength of association.
- The spontaneous AE reports might be biased, incomplete, and do not represent every reported case.

Conclusions

- The use of a gene therapy regimen was often associated with a lower incidence of serious AEs than the standard of care.
- However, the observed relationship between the gene therapies and the adverse events does not necessarily imply causality. Further investigation is needed to assess the potential causal relationship between the gene therapies and the adverse events.