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Adverse Events of CD19- and BCMA-Directed Chimeric Antigen Receptor T-Cell Therapy: An Analysis of the FDA Adverse Events Database

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Abstract

Background: Chimeric antigen receptor T-cell (CAR-T) therapies have transformed the treatment of haematologic malignancies, yet their adverse event (AE) profiles across all approved agents have not been consolidated using a pharmacovigilance methodology in a single comparative analysis. Methods: Using the FDA Adverse Events Reporting System (FAERS) and OpenVigil 2.1, disproportionality analyses for all six FDA-approved CAR-T therapies were performed, stratified by target antigen: anti-CD19 agents (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, brexucabtagene autoleucel) and anti-BCMA agents (idecabtagene vicleucel, ciltacabtagene autoleucel). For each of the 25 most frequently reported AEs per agent, the report event counts, reporting odds ratio (ROR) with 95% confidence interval, proportional reporting ratio (PRR), and chi-squared statistic were calculated. Results: A total of 36,567 AEs were identified across all six agents. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were the most frequent and most disproportionate AEs across all six therapies, with RORs exceeding 240 in every agent. Idecabtagene vicleucel had the highest ROR for cytokine release syndrome among all agents (ROR 1934.6), while brexucabtagene autoleucel had the highest ROR for immune effector cell-associated neurotoxicity syndrome (ROR 2089.6). Ciltacabtagene autoleucel exhibited a unique neurological toxicity profile, cranial nerve paralysis (ROR 3167.6, PRR 3055.0, chi^2 199,190), parkinsonism (ROR 145.5, PRR 136.6, chi^2 24,840), Bell's palsy (ROR 380.4, PRR 370.3), and facial paralysis (ROR 72.7), consistent with the late neurotoxicity syndrome previously characterized, and absent from other agents' top 25 AE lists. Brexucabtagene autoleucel demonstrated secondary malignancy signals including squamous cell carcinoma of skin (ROR 308.2) and myelodysplastic syndrome (ROR 97.9). Tisagenlecleucel showed the highest hypogammaglobulinemia signal among all agents (ROR 614.1, PRR 536.5, chi^2 144,832) alongside a broad pancytopenia profile. Hemophagocytic lymphohistiocytosis was a significant finding with ciltacabtagene autoleucel (ROR 71.0) and brexucabtagene autoleucel (ROR 57.8). Conclusions: CAR-T therapies share class-wide toxicities in cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, but exhibit clinically important drug-specific and target-class-specific AE profiles. This consolidated FAERS-based analysis corroborates and extends prior pharmacovigilance work by providing direct cross-agent comparisons, and supports the use of agent-tailored monitoring strategies, particularly for the distinctive late neurological toxicity associated with ciltacabtagene autoleucel.

Keywords: CAR-T cell therapy; CD19; BCMA; cytokine release syndrome; immune effector cell-associated neurotoxicity syndrome

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1. Introduction

The advent of chimeric antigen receptor T-cell (CAR-T) therapy has fundamentally transformed the treatment landscape for haematologic malignancies [1,2]. These engineered cellular therapies involve the genetic modification of a patient's own T-cells to express a synthetic receptor directed against a tumour-associated antigen, enabling potent and targeted anti-tumour immune responses. Since the initial FDA approval of tisagenlecleucel in 2017, six CAR-T therapies have received regulatory approval across two principal antigen targets: CD19, expressed on B-lineage malignancies including diffuse large B-cell lymphoma, acute lymphoblastic leukemia, follicular lymphoma, and mantle cell lymphoma; and B-cell maturation antigen (BCMA), expressed on plasma cells in multiple myeloma [3,4].

Despite their clinical efficacy, CAR-T therapies are associated with a distinct and at times life-threatening toxicity profile that differs substantially from conventional chemotherapy and immune checkpoint inhibitors. The most well-characterized toxicities include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which can present acutely and require intensive clinical management [5,6]. However, the full spectrum of AEs across all FDA-approved CAR-T products, including longer-term toxicities such as cytopenias, infections, secondary malignancies, and late-onset neurotoxicity's, have not been systematically characterized across target classes in a comprehensive pharmacovigilance analysis [2,7,8].

The FDA Adverse Event Reporting System (FAERS) provides a large, publicly available repository of post-marketing pharmacovigilance data enabling identification of disproportionate AE signals. The objective of this study is to ascertain the most frequently reported AEs associated with each FDA-approved CAR-T therapy using FAERS data, reporting the ROR with 95% confidence interval, proportional reporting ratio (PRR), and chi-squared statistic for each AE, and to present findings stratified by therapeutic target class. Prior pharmacovigilance analyses have examined individual CAR-T agents or subsets of the approved products; the present study extends this literature by systematically reporting ROR, PRR, and chi-squared across all six FDA-approved CAR-T therapies in a single analysis stratified by therapeutic target class.

2. Results

There were 13,685 unique adverse event reports for axicabtagene ciloleucel, 13,087 for tisagenlecleucel, 980 for lisocabtagene maraleucel, and 1862 for brexucabtagene autoleucel among the anti-CD19 agents. For the anti-BCMA agents, there were 902 unique reports for idecabtagene vicleucel and 6051 for ciltacabtagene autoleucel. For the anti-BCMA agents, there was a total of 902 AEs reported for idecabtagene vicleucel and 6051 for ciltacabtagene autoleucel. The 25 most frequently reported AEs for each agent, with events, ROR (95% CI), PRR, and chi-squared, are presented in Tables 1–4 (anti-CD19 agents) and Tables 5 and 6 (anti-BCMA agents). Cytokine release syndrome and ICANS were the most frequently reported AEs across all six therapies, demonstrating the highest RORs and PRRs consistent with their established status as the principal class-wide toxicities of cellular immunotherapy.

Table 1. Top 25 Most Reported Adverse Events with Axicabtagene Ciloleucel in the FDA Adverse Event Reporting System Database.

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Cytokine Release Syndrome	2012	1284.242 (1208.059–1365.229)	758.293	N/A
Immune Effector Cell-Associated Neurotoxicity Syndrome	1140	2195.754 (2027.348–2378.148)	1686.074	N/A

Table 1. *Cont.*

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Death	648	3.148 (2.898–3.420)	2.865	821.775
Neurotoxicity	511	164.466 (149.757–180.619)	147.450	70,612.020
Disease Progression	468	18.352 (16.680–20.191)	16.698	6890.647
Pyrexia	346	5.659 (5.072–6.313)	5.330	1226.828
Neutropenia	179	6.302 (5.428–7.318)	6.109	762.616
Myelodysplastic Syndrome	172	58.695 (50.339–68.439)	56.674	9176.156
Hypotension	143	3.667 (3.105–4.331)	3.589	266.360
Fatigue	135	0.846 (0.713–1.004)	0.850	3.515
Diffuse Large B-Cell Lymphoma	122	77.004 (64.193–92.373)	75.115	8625.156
Pancytopenia	108	10.105 (8.348–12.232)	9.905	854.713
Tremor	104	3.055 (2.515–3.711)	3.012	138.567
Confusional State	102	3.147 (2.587–3.830)	3.103	144.061
Encephalopathy	95	19.494 (15.901–23.899)	19.136	1605.757
Anaemia	90	2.579 (2.094–3.178)	2.551	83.818
Aphasia	87	14.660 (11.853–18.132)	14.418	1069.012
Infection	86	2.987 (2.413–3.697)	2.952	109.617
Thrombocytopenia	86	3.978 (3.213–4.924)	3.925	185.157
Hypoxia	83	12.884 (10.366–16.014)	12.683	878.913
Headache	81	0.620 (0.498–0.772)	0.626	18.158
Platelet Count Decreased	78	3.696 (2.954–4.623)	3.653	148.093
Lymphocyte Adoptive Therapy	77	1970.922 (1474.047–2635.285)	1940.023	87,915.125
Acute Myeloid Leukaemia	76	22.885 (18.229–28.730)	22.546	1532.427
Asthenia	75	1.025 (0.816–1.288)	1.025	0.024

ROR, reported odds ratio; PRR, proportional reporting ratio; CI, confidence interval. N/A denotes chi-squared values not calculable due to table size constraints in OpenVigil.

Table 2. Top 25 Most Reported Adverse Events with Tisagenlecleucel in the FDA Adverse Event Reporting System Database.

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Cytokine Release Syndrome	941	1092.192 (1002.899–1189.434)	653.008	552,547.300
Pyrexia	664	29.657 (27.104–32.450)	21.518	13,097.673
Malignant Neoplasm Progression	423	49.400 (44.450–54.901)	40.643	16,280.619
Haemoglobin Decreased	322	40.982 (36.423–46.111)	35.475	10,732.758
Lymphocyte Count Decreased	326	239.379 (212.580–269.556)	206.141	64,198.793
Platelet Count Decreased	312	35.392 (31.406–39.883)	30.802	8960.123
White Blood Cell Count Decreased	298	32.130 (28.445–36.291)	28.162	7778.869
Hypogammaglobulinemia	296	614.106 (541.109–696.951)	536.484	144,831.660
Neutrophil Count Decreased	290	86.602 (76.529–98.001)	75.984	21,153.191
Haematocrit Decreased	281	191.363 (168.678–217.098)	168.483	45,382.684

Table 2. *Cont.*

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Neurotoxicity	291	196.908 (173.888–222.975)	172.524	48,113.380
Hypotension	255	14.979 (13.151–17.062)	13.454	2944.806
Immune Effector Cell-Associated Neurotoxicity Syndrome	224	522.740 (453.305–602.811)	472.753	97,369.360
Acute Lymphocytic Leukaemia Recurrent	223	1036.076 (894.099–1200.598)	937.350	179,740.390
Death	217	2.117 (1.841–2.434)	2.013	114.917
Diffuse Large B-Cell Lymphoma	197	282.611 (243.545–327.943)	258.882	48,293.336
Cytopenia	192	167.292 (144.082–194.242)	153.636	28,259.050
Hypoxia	161	55.645 (47.383–65.347)	51.882	7925.792
Thrombocytopenia	118	11.865 (9.858–14.281)	11.317	1102.374
Diffuse Large B-Cell Lymphoma Recurrent	118	622.011 (512.538–754.867)	590.668	62,737.420
Neutropenia	122	9.164 (7.636–10.997)	8.738	832.009
Headache	91	1.497 (1.214–1.846)	1.478	13.947
Second Primary Malignancy	93	111.938 (90.810–137.982)	107.525	9542.024
B-Cell Type Acute Leukaemia	92	1200.913 (957.191–1506.692)	1153.696	87,982.400
Treatment Failure	95	10.610 (8.640–13.031)	10.220	782.794

ROR, reported odds ratio; PRR, proportional reporting ratio; CI, confidence interval.

Table 3. Top 25 Most Reported Adverse Events with Lisocabtagene Maraleucel in the FDA Adverse Event Reporting System Database.

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Cytokine Release Syndrome	164	1497.668 (1204.660–1861.944)	747.046	119,456.810
Immune Effector Cell-Associated Neurotoxicity Syndrome	81	1547.201 (1200.605–1993.852)	1164.197	90,554.540
Neurotoxicity	41	193.828 (139.645–269.035)	169.651	6685.004
Malignant Neoplasm Progression	16	11.433 (6.917–18.897)	10.922	135.043
Hypotension	18	7.114 (4.423–11.442)	6.777	83.631
Platelet Count Decreased	16	11.768 (7.120–19.451)	11.241	139.787
Lymphocyte Count Decreased	12	54.495 (30.609–97.020)	52.532	555.881
Haemoglobin Decreased	15	12.268 (7.307–20.598)	11.752	137.493
White Blood Cell Count Decreased	9	6.198 (3.195–12.022)	6.055	33.238
Hypogammaglobulinemia	14	174.711 (102.179–298.732)	167.274	2142.870
Neutrophil Count Decreased	11	21.037 (11.530–38.382)	20.363	183.851
Cytopenia	6	34.113 (15.207–76.524)	33.506	158.066
Lymphocyte Adoptive Therapy	13	3280.525 (1848.058–5823.325)	3150.146	35,262.434
Pyrexia	11	2.594 (1.422–4.732)	2.540	8.907
Death	11	0.720 (0.395–1.314)	0.730	0.890
Fatigue	13	1.239 (0.711–2.158)	1.229	0.363

Table 3. *Cont.*

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Aphasia	7	17.699 (8.369–37.431)	17.341	92.147
Off Label Use	11	0.832 (0.456–1.519)	0.838	0.210
Sepsis	7	5.046 (2.386–10.672)	4.960	18.425
Septic Shock	7	13.297 (6.287–28.120)	13.033	66.291
Cytomegalovirus Infection	6	28.656 (12.775–64.279)	28.148	131.128
Mental Status Changes	6	15.165 (6.761–34.013)	14.905	64.606
Respiratory Failure	6	6.336 (2.825–14.209)	6.238	21.472
Alanine Aminotransferase Increased	5	6.416 (2.652–15.520)	6.333	17.477
Aspartate Aminotransferase Increased	5	7.562 (3.126–18.294)	7.462	21.932

ROR, reported odds ratio; PRR, proportional reporting ratio; CI, confidence interval.

Table 4. Top 25 Most Reported Adverse Events with Brexucabtagene Autoleucel in the FDA Adverse Event Reporting System Database.

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Cytokine Release Syndrome	271	834.344 (718.265–969.183)	537.191	140,532.380
Immune Effector Cell-Associated Neurotoxicity Syndrome	226	2089.598 (1780.986–2451.688)	1468.515	305,837.300
Death	91	2.814 (2.261–3.503)	2.597	92.012
Squamous Cell Carcinoma of Skin	51	308.203 (231.494–410.329)	287.588	14,065.378
Neurotoxicity	50	95.296 (71.490–127.028)	89.092	4250.276
Myelodysplastic Syndrome	44	97.929 (72.176–132.871)	92.317	3866.853
Basal Cell Carcinoma	32	74.649 (52.360–106.428)	71.548	2148.993
Disease Progression	34	8.114 (5.752–11.446)	7.796	195.724
Hypotension	27	4.499 (3.064–6.605)	4.374	67.476
Infection	19	4.293 (2.723–6.770)	4.211	43.611
Pyrexia	20	2.014 (1.292–3.140)	1.987	8.964
Hemophagocytic Lymphohistiocytosis	14	57.786 (34.029–98.126)	56.740	709.932
Pancytopenia	14	8.408 (4.954–14.267)	8.271	82.511
Seizure	13	3.420 (1.976–5.917)	3.378	19.547
Lymphocyte Adoptive Therapy	13	1378.920 (781.645–2432.589)	1355.350	15,158.356
COVID-19	12	1.945 (1.100–3.441)	1.930	4.525
Neutropenia	12	2.667 (1.508–4.718)	2.641	10.710
Acute Lymphocytic Leukaemia Recurrent	11	125.750 (69.204–228.501)	123.945	1213.384
Confusional State	17	3.392 (2.097–5.486)	3.338	25.719
Thrombocytopenia	11	3.273 (1.805–5.936)	3.240	14.935
Encephalopathy	11	14.427 (7.953–26.170)	14.232	122.451
Depressed Level of Consciousness	11	8.475 (4.672–15.371)	8.367	64.253
Febrile Neutropenia	11	5.887 (3.246–10.677)	5.816	39.269
Sepsis	11	3.388 (1.868–6.145)	3.354	15.958

ROR, reported odds ratio; PRR, proportional reporting ratio; CI, confidence interval.

Table 5. Top 25 Most Reported Adverse Events with Idecabtagene Vicleucel in the FDA Adverse Event Reporting System Database.

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Cytokine Release Syndrome	207	1934.579 (1572.368–2380.230)	843.977	169,836.390
Immune Effector Cell-Associated Neurotoxicity Syndrome	73	1163.629 (898.311–1507.309)	932.370	65,416.516
Neutropenia	36	18.087 (12.822–25.514)	16.411	508.513
Anaemia	29	11.847 (8.107–17.311)	10.990	255.209
Fatigue	26	2.282 (1.531–3.400)	2.191	16.186
Pyrexia	14	2.955 (1.732–5.042)	2.881	15.565
Death	13	0.760 (0.437–1.321)	0.768	0.725
Neurotoxicity	12	45.577 (25.631–81.045)	44.119	463.314
Headache	11	1.142 (0.627–2.081)	1.138	0.074
Decreased Appetite	9	2.773 (1.431–5.373)	2.729	8.281
Hypogammaglobulinemia	9	98.060 (50.566–190.163)	95.680	749.518
Cytopenia	8	40.680 (20.181–82.001)	39.815	265.021
Diarrhoea	8	0.831 (0.412–1.674)	0.835	0.126
Malaise	8	1.158 (0.575–2.333)	1.155	0.048
Myelodysplastic Syndrome	8	35.368 (17.547–71.291)	34.619	228.584
Nausea	8	0.646 (0.320–1.301)	0.653	1.185
Neutrophil Count Decreased	8	13.465 (6.682–27.137)	13.194	78.477
Aspartate Aminotransferase Increased	7	9.470 (4.482–20.010)	9.309	44.016
Infusion Related Reaction	7	9.772 (4.625–20.647)	9.604	45.778
Laryngeal Oedema	7	78.004 (36.894–164.921)	76.535	448.253
Plasma Cell Myeloma	7	11.000 (5.206–23.242)	10.809	52.968
Tachycardia	7	5.341 (2.528–11.284)	5.258	20.138
White Blood Cell Count Decreased	7	4.258 (2.015–8.996)	4.196	14.055
Lymphocyte Adoptive Therapy	6	1267.128 (558.331–2875.740)	1246.428	6076.075
Platelet Count Decreased	6	3.801 (1.696–8.518)	3.755	9.572

ROR, reported odds ratio; PRR, proportional reporting ratio; CI, confidence interval.

Table 6. Top 25 Most Reported Adverse Events with Ciltacabtagene Autoleucel in the FDA Adverse Event Reporting System Database.

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Cytokine Release Syndrome	423	242.141 (218.097–268.835)	209.194	83,654.690
Immune Effector Cell-Associated Neurotoxicity Syndrome	184	307.403 (263.694–358.359)	289.193	49,429.460
Parkinsonism	191	145.509 (125.434–168.796)	136.594	24,840.332
Pyrexia	188	4.821 (4.159–5.587)	4.589	530.588
Hospitalisation	183	7.988 (6.879–9.276)	7.575	1044.238
Neurotoxicity	107	48.700 (40.120–59.115)	47.052	4731.540

Table 6. *Cont.*

Adverse Event	Events	ROR (95% CI)	PRR	Chi^2
Fatigue	98	0.978 (0.800–1.196)	0.979	0.027
Death	96	0.662 (0.540–0.811)	0.672	15.714
Adverse Event (General)	129	8.723 (7.312–10.407)	8.402	836.383
Cranial Nerve Paralysis	110	3167.553 (2481.236–4043.706)	3055.046	199,190.440
Bell's Palsy	83	380.445 (303.323–477.176)	370.272	27,930.410
Facial Paralysis	75	72.714 (57.724–91.595)	70.976	5027.955
Adverse Drug Reaction	69	5.141 (4.049–6.528)	5.049	220.748
Hemophagocytic Lymphohistiocytosis	69	71.030 (55.852–90.334)	69.470	4520.714
Infection	67	3.705 (2.908–4.720)	3.646	126.707
Illness	66	4.349 (3.408–5.551)	4.278	163.179
COVID-19	65	2.601 (2.034–3.325)	2.567	61.093
Colitis	64	14.187 (11.072–18.179)	13.914	753.084
Asthenia	62	1.350 (1.050–1.736)	1.343	5.179
Neutropenia	47	2.563 (1.922–3.419)	2.540	42.573
Pneumonia	55	1.428 (1.094–1.865)	1.421	6.512
Pain	51	0.576 (0.437–0.760)	0.583	15.227
Cytopenia	50	30.124 (22.759–39.872)	29.654	1347.824
Diarrhoea	55	0.674 (0.516–0.880)	0.680	8.170
Malaise	112	1.951 (1.615–2.356)	1.916	49.079

ROR, reported odds ratio; PRR, proportional reporting ratio; CI, confidence interval.

2.1. Anti-CD19 CAR-T Cell Therapies

Among the anti-CD19 agents, CRS and ICANS were dominant across all four therapies. Axicabtagene ciloleucel had the largest event burden, with CRS reported in 2012 cases (ROR = 1284.242, PRR = 758.293) and ICANS in 1140 cases (ROR = 2195.754, PRR = 1686.074). A broad neurotoxicity profile was also present for axi-cel, including neurotoxicity NOS (ROR = 164.466, PRR = 147.450, chi^2 = 70,612.020), encephalopathy (ROR = 19.494), aphasia (ROR = 14.660), confusional state (ROR = 3.147), and tremor (ROR = 3.055). Myelodysplastic syndrome (ROR = 58.695, PRR = 56.674) and acute myeloid leukaemia (ROR = 22.885) were notable secondary malignancy signals. Tisagenlecleucel demonstrated a broad cytopenia profile with high RORs and PRRs across multiple lineages, and hypogammaglobulinemia had the highest PRR for this AE across all six agents (PRR = 536.484, ROR = 614.106, chi^2 = 144,831.660). Lisocabtagene maraleucel showed prominent infectious complications. Brexucabtagene autoleucel had the highest ROR for ICANS among all agents (ROR = 2089.598, PRR = 1468.515, chi^2 = 305,837.300) and a distinctive secondary malignancy profile with squamous cell carcinoma of the skin (ROR = 308.203, PRR = 287.588) and basal cell carcinoma (ROR = 74.649).

2.2. Anti-BCMA CAR-T Cell Therapies

Among the anti-BCMA agents, CRS had the highest ROR for any single AE in the entire dataset for ide-cel (ROR = 1934.579, PRR = 843.977, chi^2 = 169,836.390). ICANS was also prominent for both agents. Ide-cel demonstrated haematological toxicities including neutropenia (ROR = 18.087, PRR = 16.411, chi^2 = 508.513) and anaemia (ROR = 11.847, PRR = 10.990), as well as hypogammaglobulinemia (ROR = 98.060, PRR = 95.680) and

myelodysplastic syndrome (ROR = 35.368, PRR = 34.619). Cilta-cel's most striking finding was cranial nerve paralysis, which had the highest ROR of any AE across all six drugs (ROR = 3167.553, PRR = 3055.046, chi^2 = 199,190.440). Parkinsonism was also highly disproportionate (ROR = 145.509, PRR = 136.594, chi^2 = 24,840.332), as were Bell's palsy (ROR = 380.445, PRR = 370.272) and facial paralysis (ROR = 72.714). Hemophagocytic lymphohistiocytosis showed a strong signal with cilta-cel (ROR = 71.030, PRR = 69.470, chi^2 = 4520.714).

3. Discussion

Building on prior pharmacovigilance literature, this analysis of all six FDA-approved CAR-T cell therapies identified 36,567 adverse event reports across anti-CD19 and anti-BCMA agents, extending existing safety characterizations by reporting ROR, PRR, and chi-squared in parallel across both target classes within a single unified dataset. Several key themes and novel observations emerge from this dataset.

Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were the most frequently reported AEs across all six agents and consistently produced the highest disproportionality signals in the dataset, confirming their status as the defining class toxicities of CAR-T therapy. The ROR for CRS ranged from 242.1 with cilta-cel to 1934.6 with ide-cel, while the ROR for ICANS ranged from 307.4 with cilta-cel to 2195.8 with brexu-cel. The consistency of these signals across agents targeting distinct antigens and manufactured using different constructs underscores that CRS and ICANS are driven by the fundamental biology of engineered T-cell activation rather than target-specific on-tumour effects [2,9–11]. Both the ROR and PRR closely tracked each other for these AEs across agents, reflecting the rarity of CRS and ICANS in the broader FAERS drug population and therefore the specificity of the signal to CAR-T products. An interesting trend emerges when comparing CRS and ICANS RORs within individual agents. Ide-cel had the highest CRS ROR (1934.6) but a lower ICANS ROR (1163.6) relative to some CD19-targeting agents, which may reflect the higher CRS rates observed in clinical trials of BCMA-targeting agents in the heavily pre-treated myeloma population, as well as differences in lymphodepletion conditioning intensity [12–14]. By contrast, brexu-cel had the highest ICANS ROR among all six agents (2089.6, PRR = 1468.5, chi^2 = 305,837), with CRS at a lower but still highly elevated ROR of 834.3. This pattern is consistent with the established observation that brexu-cel, used predominantly in mantle cell lymphoma and B-cell ALL, has higher ICANS rates in clinical trials relative to its CRS burden, potentially reflecting the neuroinvasive biology of these malignancies and the intensity of conditioning [15–17]. Liso-cel, by design developed with a defined CD4:CD8 ratio to reduce toxicity, nonetheless demonstrated very high RORs for both CRS (1497.7) and ICANS (1547.2), suggesting that even optimized CAR-T constructs are not exempt from these toxicities in real-world post-marketing practice [18,19].

Beyond ICANS, a broader neurotoxicity spectrum is evident across agents. Neurotoxicity not otherwise classified was significantly reported with all six agents, with RORs ranging from 45.6 with ide-cel to 196.9 with tisagenlecleucel, highlighting that neurological injury extends well beyond the formal ICANS. Axi-cel had the largest absolute burden of neurotoxicity NOS (n = 511, ROR = 164.5, PRR = 147.5, chi^2 = 70,612), as well as significant signals for encephalopathy (ROR = 19.5), aphasia (ROR = 14.7), confusional state (ROR = 3.1), and tremor (ROR = 3.1). The breadth and depth of neurotoxic AEs with axi-cel likely reflects both its large volume of post-marketing experience and its association with higher-grade ICANS in pivotal trials.

The most clinically distinctive neurotoxicity finding in this analysis was the late-onset neurological syndrome uniquely associated with ciltacabtagene autoleucel. Cranial nerve

paralysis had not only the highest ROR of any AE in the entire dataset (ROR = 3167.6, PRR = 3055.0, chi^2 = 199,190), but also the highest absolute event count for this AE of any drug across FAERS, representing a signal of significant strength. Bell's palsy (ROR = 380.4, PRR = 370.3, chi^2 = 27,930), facial paralysis (ROR = 72.7), and parkinsonism (ROR = 145.5, PRR = 136.6, chi^2 = 24,840) were similarly striking and absent from the top-25 AE lists of all other agents. The near-perfect concordance of ROR and PRR for these AEs confirms they are not artifacts of differential reporting denominators. These post-marketing signals are consistent with emerging case series and regulatory communications describing a delayed neurotoxicity syndrome following cilta-cel distinct from acute ICANS, characterized by movement disorders, parkinsonism-like features, and cranial neuropathies occurring weeks to months after infusion [20–24]. The mechanistic basis remains incompletely understood but may relate to the prolonged in vivo persistence of BCMA-targeting CAR-T cells with potential off-tumour CNS tropism, possibly driven by low-level BCMA expression on neurons or glia [20,21,25]. Notably, idecabtagene vicleucel, the other approved anti-BCMA agent, did not demonstrate these neurological signals, suggesting the mechanism may be construct-specific rather than a class effect of BCMA targeting, and warranting direct mechanistic comparison between the two agents [20,26].

Hematological toxicities were pervasive across both target classes, though the nature and depth of cytopenia reporting differed importantly across agents. All six drugs demonstrated significant signals for at least one form of cytopenia, consistent with the combined hematotoxic effects of lymphodepleting conditioning regimens, typically fludarabine and cyclophosphamide, and the prolonged immune reconstitution deficit following CAR-T infusion [27–30]. Tisagenlecleucel exhibited the broadest and most severe cytopenia profile of any agent in this analysis, with high RORs and PRRs across lymphocyte count decreased (ROR = 239.4, PRR = 206.1, chi^2 = 64,199), haematocrit decreased (ROR = 191.4, PRR = 168.5, chi^2 = 45,383), haemoglobin decreased (ROR = 41.0, PRR = 35.5, chi^2 = 10,733), platelet count decreased (ROR = 35.4, PRR = 30.8, chi^2 = 8960), white blood cell count decreased (ROR = 32.1, PRR = 28.2, chi^2 = 7779), and neutrophil count decreased (ROR = 86.6, PRR = 76.0, chi^2 = 21,153). This pattern likely reflects the broad use of tisagenlecleucel across two distinct patient populations, pediatric and young adult B-cell ALL and adult DLBCL, as well as a longer post-marketing history with more accumulated reports. The high chi-squared values for each cytopenia subtype confirm these are robust signals, not noise from small denominators.

Myelodysplastic syndrome emerged as a secondary hematological malignancy signal across three agents: ide-cel (ROR = 35.4, PRR = 34.6, chi^2 = 228.6), axi-cel (ROR = 58.7, PRR = 56.7, chi^2 = 9176), and most prominently brexu-cel (ROR = 97.9, PRR = 92.3, chi^2 = 3867). The presence of this signal across multiple agents and both target classes is notable. MDS following CAR-T therapy may reflect the genotoxic effects of prior alkylating agent therapy in these heavily pre-treated populations, but insertional mutagenesis from lentiviral or retroviral vectors used in CAR construct delivery has also been proposed as a mechanism and remains under active investigation [31–33]. The higher MDS signal with brexu-cel may partly reflect the mantle cell lymphoma patient population, who typically have extensive prior exposure to ibrutinib and bendamustine [34].

Hypogammaglobulinemia was a highly disproportionate AE among anti-CD19 agents, with tisagenlecleucel producing the strongest signal in the dataset (ROR = 614.1, PRR = 536.5, chi^2 = 144,832), followed by liso-cel (ROR = 174.7, PRR = 167.3, chi^2 = 2143) and ide-cel (ROR = 98.1, PRR = 95.7, chi^2 = 750). This AE is mechanistically expected with CD19-targeting agents, as durable eradication of both malignant and normal B-cells produces prolonged B-cell aplasia and impaired humoral immunity [35,36]. The higher ROR with tisagenlecleucel relative to other CD19-targeting agents may reflect its longer

post-marketing history and therefore more complete capture of this chronic toxicity, which typically manifests months after infusion rather than acutely. The clinical consequences of hypogammaglobulinemia are substantial: patients require regular monitoring of immunoglobulin levels, prophylactic intravenous immunoglobulin replacement, and heightened vigilance for encapsulated bacterial infections. Long-term survivors of CAR-T therapy may require immunoglobulin replacement indefinitely if B-cell recovery fails to occur.

Beyond hypogammaglobulinemia, infectious complications were a significant theme, particularly with liso-cel, which showed notable signals for sepsis (ROR = 5.0), septic shock (ROR = 13.3, PRR = 13.0, chi^2 = 66.3), and cytomegalovirus infection (ROR = 28.7, PRR = 28.1, chi^2 = 131.1). CMV reactivation in the post-CAR-T setting reflects the profound T-cell-mediated immune suppression from lymphodepletion and the subsequent period of immune reconstitution, and is an under-recognized complication requiring proactive monitoring in CMV-seropositive patients [37,38]. General infection was also significantly reported with cilta-cel (ROR = 3.7, n = 67) and brexu-cel (ROR = 4.3, n = 19). The convergence of lymphodepletion-associated immunosuppression, prolonged hypogammaglobulinemia, steroid use for CRS and ICANS management, and underlying malignancy creates a profound and multifactorial immunocompromised state that clinicians must actively address throughout the post-CAR-T follow-up period.

Secondary malignancies emerged as a signal across multiple agents, though with distinct patterns that appear to reflect both agent-specific biological mechanisms and underlying patient population characteristics. The most striking secondary malignancy profile was observed with brexu-cel, which showed highly disproportionate signals for squamous cell carcinoma of the skin (ROR = 308.2, PRR = 287.6, chi^2 = 14,065), basal cell carcinoma (ROR = 74.6, PRR = 71.5, chi^2 = 2149), and MDS (ROR = 97.9). These cutaneous malignancies are biologically plausible in this context: brexu-cel is approved for mantle cell lymphoma, a disease predominantly affecting older males with significant cumulative ultraviolet exposure, and the combination of prior alkylating agent immunosuppression and the iatrogenic immunosuppression of the CAR-T procedure likely promotes cutaneous oncogenesis [39,40]. Acute lymphocytic leukemia recurrence was also a distinctive brexu-cel signal (ROR = 125.8, PRR = 123.9), consistent with its indication in relapsed/refractory B-cell ALL. Tisagenlecleucel demonstrated signals for second primary malignancy (ROR = 111.9, PRR = 107.5, chi^2 = 9542) and, uniquely, B-cell type acute leukemia (ROR = 1200.9, PRR = 1153.7, chi^2 = 87,982), the latter almost certainly reflecting the ALL patient population receiving this therapy rather than a therapy-induced secondary malignancy. However, the presence of treatment failure (ROR = 10.6, n = 95) as a prominent AE with tisagenlecleucel also points to the challenges of durability of response in the ALL population. The FDA's 2024 decision to add a boxed warning about secondary T-cell malignancies to all CAR-T products reflects growing concern about insertional mutagenesis as a mechanism of therapy-related oncogenesis, and this pharmacovigilance analysis provides population-level support for sustained regulatory vigilance in this domain.

Hemophagocytic lymphohistiocytosis (HLH) was identified as a significant pharmacovigilance signal across multiple agents from both target classes, with cilta-cel producing the strongest signal (n = 69, ROR = 71.0, PRR = 69.5, chi^2 = 4521) and brexu-cel also demonstrating a robust signal (n = 14, ROR = 57.8, PRR = 56.7, chi^2 = 710). HLH is a life-threatening hyperinflammatory syndrome characterized by uncontrolled macrophage and T-cell activation, multi-organ failure, and profound cytopenias, and it carries high mortality if not promptly recognized and treated. In the post-CAR-T setting, HLH may be particularly difficult to diagnose given the overlapping clinical and laboratory features shared with severe CRS, both syndromes involve hyperferritinemia, cytopenias, and hemodynamic instability, and the absence of universal HLH screening criteria in current CAR-T

toxicity management guidelines. The finding that HLH signal strength was highest with cilta-cel among the agents examined is notable. Whether this reflects a true mechanistic predisposition of BCMA-targeting with this specific construct, reporting patterns in the heavily pre-treated myeloma population, or an interaction between cilta-cel's prolonged persistence and sustained macrophage activation remains unclear [41]. Regardless of mechanism, the convergence of HLH signals across both anti-CD19 and anti-BCMA agents, with high RORs and PRRs in both classes, strongly supports treating HLH as a class-level risk of CAR-T therapy. Physicians may consider maintaining a low threshold for initiating HLH work-up in any patient with refractory or worsening inflammatory symptoms beyond the first week post-infusion, and treatment with anakinra or etoposide-based regimens should be initiated promptly upon diagnosis.

The two N/A chi-squared values for axicabtagene ciloleucel's CRS and ICANS entries reflect a numerical overflow limitation within OpenVigil 2.1, occurring when observed or expected cell frequencies in the contingency table exceed the tool's internal computational threshold. This does not indicate an absence of statistical significance; both AEs carry the highest absolute event counts and strongest disproportionality estimates in the dataset.

Several limitations of this analysis require careful consideration. FAERS is a spontaneous reporting database, and reports submitted to it do not establish a causal relationship between the drug and the reported event. The FDA does not require proof of causality, and reports may lack sufficient clinical detail to enable independent assessment. Underreporting is an inherent limitation of spontaneous pharmacovigilance systems, and reporting rates may be disproportionately influenced by the time a product has been on the market, media coverage, institutional reporting practices, and regulatory actions. Agents with longer post-marketing histories, particularly tisagenlecleucel and axi-cel, will naturally accrue more reports and therefore appear to have a broader AE profile than newer agents such as ide-cel and liso-cel, regardless of their true toxicity burden. This temporal confounding should be borne in mind when comparing AE profiles across agents of different approval ages. Confounding by indication is a particularly salient limitation in this analysis. Anti-CD19 and anti-BCMA agents are used in fundamentally different patient populations with distinct baseline comorbidities, prior treatment histories, and malignancy-related complications. AEs such as disease progression, treatment failure, and malignancy recurrence that appear in the FAERS reports may reflect the underlying disease rather than treatment toxicity, inflating disproportionality signals for some AEs. Within the CD19 class, differences in indication, DLBCL versus MCL versus ALL, also produce heterogeneous background populations that cannot be separated within this analysis. Similarly, the very high event counts for some AEs with tisagenlecleucel likely partly reflect the ALL patient population, in which intensive laboratory monitoring generates more granular cytopenia-level reporting. Finally, channelling bias, the tendency for specific patient subgroups to be preferentially treated with certain agents, may create the appearance of agent-specific toxicity signals that in reality reflect patient-level differences.

This comprehensive pharmacovigilance analysis of all six FDA-approved CAR-T cell therapies identified 36,567 adverse event reports across anti-CD19 and anti-BCMA agents, revealing both universal class toxicities and clinically important agent-specific signals. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome represent the defining toxicities of CAR-T therapy as a class, with consistently high RORs, PRRs, and chi-squared values across all six agents regardless of target antigen, confirming their mechanistic origin in the biology of adoptive cellular immunotherapy rather than in any target-specific effect.

Within this class-wide framework, several drug-specific signals with direct clinical implications emerged. Ciltacabtagene autoleucel exhibited a late-onset neurological toxi-

city profile, encompassing cranial nerve paralysis, parkinsonism, Bell's palsy, and facial paralysis, that was absent from all other agents and produced the highest single-AE ROR in the entire dataset, underscoring the need for prolonged neurological surveillance beyond the acute post-infusion period in patients receiving this agent. Brexucabtagene autoleucel demonstrated a secondary malignancy profile including squamous cell carcinoma of the skin, basal cell carcinoma, and myelodysplastic syndrome that aligns with and extends the evidence base supporting the FDA's 2024 boxed warning on CAR-T-associated secondary malignancies. Tisagenlecleucel showed the strongest hypogammaglobulinemia signal among all agents, with implications for long-term immunoglobulin replacement and infection surveillance. Hemophagocytic lymphohistiocytosis was identified as a cross-class risk affecting both anti-CD19 and anti-BCMA agents, warranting its inclusion in institutional CAR-T toxicity management protocols.

These findings emphasize that effective management of CAR-T toxicity requires both a class-level foundation and agent-specific vigilance informed by the distinct pharmacovigilance profiles described here. As CAR-T indications continue to expand to earlier lines of therapy and broader patient populations, and as novel constructs targeting additional antigens enter the clinic, ongoing pharmacovigilance and long-term follow-up studies will be essential to characterise the evolving safety landscape of this transformative class of therapies. The present study provides a real-world evidence foundation for such efforts and offers actionable guidance for oncologists, hematologists, and other clinicians involved in the care of patients receiving CAR-T therapy.

4. Methods

The FDA Adverse Event Reporting System (FAERS) serves as a comprehensive repository for documented adverse drug reactions attributed to various pharmaceutical products. Reports are submitted by pharmaceutical manufacturers, healthcare professionals, and consumers in the USA, and FAERS incorporates post-marketing clinical trial data from domestic and international investigations. As all data are publicly available, ethics committee approval was not required.

Using OpenVigil 2.1 (OpenVigil, Kiel, Germany), individual drug queries were performed for all six FDA-approved CAR-T therapies, grouped by antigen target as previously described [42,43]: anti-CD19 agents (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, brexucabtagene autoleucel) and anti-BCMA agents (idecabtagene vicleucel, ciltacabtagene autoleucel). Reports from the first quarter of 2017 to the first quarter of 2024 were included. For each drug, the 25 most frequently reported AEs were extracted.

Disproportionality analyses were conducted using reporting odds ratios (RORs) and proportional reporting ratios (PRRs). The ROR measures the likelihood of a given AE with drug exposure relative to all other drugs in the database, calculated via a 2×2 contingency table. The PRR similarly compares the proportion of a specific AE among all AEs for the drug of interest versus all other drugs. The chi-squared statistic was computed to assess the significance of the PRR. Analyses were restricted to reports in which the drug of interest was designated as the primary suspect agent, excluding concomitant and interacting drug roles. The unit of analysis was the unique adverse event report, defined by caseid after duplicate removal, rather than individual drug-reaction pairs. The comparator population comprised all other drugs in the FAERS database across the same time window. Statistical significance for ROR was defined as a lower-bound 95% confidence interval exceeding 1.00, an ROR greater than 2.00, and a minimum of five or more reports per AE. Statistical significance for PRR was defined as a PRR of 2.00 or greater, a chi-squared statistic of 4.00 or greater, and a minimum of three or more reports, consistent with the Evans criteria. No adjustment for multiplicity was made; given the hypothesis-generating nature of

pharmacovigilance disproportionality analysis, correction for multiple comparisons was not applied, and all signals should be interpreted as requiring confirmatory investigation rather than as established causal associations. OpenVigil 2.1 removes duplicate FAERS reports by retaining only the highest case version for each unique caseid, ensuring each adverse event case is counted once. Drug name consolidation is achieved by mapping free-text entries to standardized active substance terms via the WHO Drug Dictionary, collapsing synonym variants into a single query entity.

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Institutional Review Board Statement: Ethics approval and patient consent were not required as the U.S. FDA previously collected all data utilized in this study.

Informed Consent Statement: Patient consent was waived due to fully anonymized data being used.

Data Availability Statement: The data are freely available through the FDA Adverse Events Reporting System Database and OpenVigil 2.1.

Conflicts of Interest: The author declares no conflicts of interest.

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