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BRIEF REPORT | Article in Press

Hepatic adverse-event reporting after CAR T-cell therapy: a pharmacovigilance analysis of FAERS and Canada Vigilance

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Abstract

Hepatic adverse events after chimeric antigen receptor (CAR) T-cell therapy may reflect cytokine release syndrome (CRS), immune effector cell-associated haemophagocytic syndrome/haemophagocytic lymphohistiocytosis (IEC-HS/HLH), or immune-mediated drug-induced liver injury. We characterised product-specific hepatic adverse-event reporting and separated CRS-associated, HLH-associated, and residual patterns. We analysed deduplicated primary-suspect CAR T-cell reports in the FDA Adverse Event Reporting System (FAERS; 2016Q3-2026Q1), with directional comparison in Canada Vigilance. Hepatic events were identified using a prespecified 244-term MedDRA dictionary. The reporting odds ratio, proportional reporting ratio, information component, and empirical Bayes geometric mean were calculated for prespecified comparators. Sensitivity analyses excluded reports mentioning CRS or HLH and examined delayed-onset and hepatic phenotypes. Among 4,700,843 FAERS reports, 19,820 identified a CAR T-cell product as the primary suspect, and 734 contained hepatic events. Median onset was 5 days, with 73.5% occurring within 14 days. CRS was co-mentioned in 77.0% of hepatic reports, compared with 9.5% for HLH-spectrum terms. Excluding CRS reduced the pooled reporting odds ratio from 1.36 to 0.54, whereas excluding HLH preserved the association. Idecabtagene vicleucel showed the most consistent product-level pattern and retained a supportive pattern after excluding CRS-co-mentioned reports (ROR 2.22, 95% CI 1.38–3.57). No product retained four-method positivity beyond 14 days. Phenotype analyses identified product-specific mixed and cholestatic reporting patterns. Canada Vigilance showed a similar CRS co-mention proportion (75.0%), although the small number of hepatic adverse-event reports (n = 4) precluded meaningful product-level analysis. Hepatic adverse-event reporting after CAR T-cell therapy was predominantly early and possibly associated with CRS rather than HLH. Persistent CRS-independent reporting, particularly with idecabtagene vicleucel, warrants prospective clinical evaluation.

Keywords CAR T-cell therapy · Hepatic adverse events · Cytokine release syndrome · Haemophagocytic lymphohistiocytosis · Pharmacovigilance · FAERS

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Introduction

CAR T-cell therapy is increasingly used for relapsed or refractory haematological malignancies and is being evaluated in earlier treatment lines, solid tumours and immune-mediated diseases. Hepatic adverse events after CAR T-cell infusion are common, but their pathogenesis is often uncertain. Abnormal liver biochemistry may reflect cytokine release syndrome (CRS), immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome/haemophagocytic lymphohistiocytosis (IEC-HS/HLH), infection, viral reactivation, hepatotoxic concomitant drugs, lymphodepleting chemotherapy, hepatic disease involvement or immune-mediated drug-induced liver injury (DILI) [1].

This distinction is clinically important. Early CRS-associated liver enzyme elevation is usually managed within established inflammatory-toxicity pathways, including CRS grading, supportive care, anti-cytokine therapy and/or corticosteroids. In contrast, delayed, cholestatic, or mixed hepatic adverse events, or hepatic adverse events occurring without documented CRS, may require broader diagnostic evaluation, product-specific surveillance, and aetiology-directed management. Existing post-marketing studies have characterised CAR T-cell toxicities, but systematic separation of CRS-related, HLH-associated and residual hepatic reporting patterns remains limited [2, 3]. We therefore evaluated hepatic adverse-event reporting across individual CAR T-cell products, examined how estimates changed after exclusion of reports co-mentioning CRS or HLH/IEC-HS, and conducted a directional comparison in Canada Vigilance.

Methods

Data sources and deduplication

Quarterly FAERS data files were obtained from the US Food and Drug Administration public release covering the third quarter of 2016 to the first quarter of 2026 [4]. For each quarter, we extracted demographic, drug, reaction, indication, therapy, outcome and report-source data. Duplicate reports were removed in two stages. First, when several versions of the same case were available, only the most recent case version was retained. Second, reports with identical event-onset date, country, age, sex, drug set, indication set, reaction set and therapy-date set were considered probable duplicates; the most recent report within each group was retained. This process yielded 4,700,843 unique FAERS reports. Canada Vigilance was analysed using the public extract dated 31 December 2025 and Health Canada report identifiers [5].

Exposure and outcome definitions

CAR T-cell exposure was restricted to reports in which a CAR T-cell product was designated as the primary suspect therapy. Five CD19-directed products used in B-cell lymphoid malignancies were included: tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel and obecabtagene autoleucel. Two B-cell maturation antigen-directed products used in multiple myeloma were included: idecabtagene vicleucel and ciltacabtagene autoleucel. Prespecified dictionaries incorporated generic names, brand names and development codes. Drug names were standardised before matching, and the same dictionaries were applied to Canada Vigilance drug-name and active-ingredient fields.

Hepatic adverse events (HAEs) were identified when a report contained at least one preferred term from a prespecified 244-term MedDRA hepatobiliary dictionary [6]. Reports were assigned to one mutually exclusive phenotype: cytolytic, cholestatic, mixed, liver investigation, liver neoplasm or not specified, using published DILI phenotype concepts [7]. CRS was identified using a broad prespecified term set encompassing cytokine release syndrome, cytokine storm, systemic inflammatory response syndrome and related hyperinflammatory terms [8]. HLH/IEC-HS was identified separately using a narrower set centred on haemophagocytic lymphohistiocytosis,

secondary HLH, macrophage activation syndrome, haemophagocytosis and immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome [9].

Statistical analysis

Disproportionality was assessed in four prespecified FAERS comparator populations: all FAERS reports (RG1), reports with haematological-malignancy indications (RG2), adult reports with haematological-malignancy indications (RG3), and all FAERS reports after exclusion of predefined hepatic confounders. Confounders included hepatotoxic comedications, lymphodepleting chemotherapy, chronic liver disease, viral hepatitis and hepatic metastases. Reporting followed READUS-PV principles [10].

For each product-outcome-comparator combination, 2×2 contingency tables were used to calculate the reporting odds ratio (ROR), proportional reporting ratio (PRR) with chi-squared statistic, information component (IC) with lower 2.5% credibility bound (IC025), and empirical Bayes geometric mean (EBGM) with lower 5% bound (EBGM05). A four-method-positive pattern required at least three exposed HAE reports, a lower 95% confidence limit for the ROR greater than 1, PRR at least 2 with chi-squared at least 4, IC025 greater than 0 and EBGM05 greater than 2. A supportive three-method-positive pattern met the ROR, PRR and IC criteria but not the EBGM05 threshold. The four-method tier was prespecified as a conservative classification rule to identify reporting patterns concordant across frequentist and Bayesian approaches and less dependent on any single metric or threshold. Because ROR, PRR, IC, and EBGM were calculated from the same underlying contingency table, concordance was interpreted as evidence of robustness in the reporting pattern, not as independent validation, evidence of causality, or proof of a biological mechanism.

Five sensitivity analyses were prespecified. L1 described HAE reports according to CRS co-mention. L2 excluded all CRS-mentioned reports symmetrically from the numerator and denominator. L3 restricted analyses to events beginning more than 14 days after CAR T-cell therapy. L4 excluded only HLH-spectrum reports. L5 restricted analyses to HLH-mentioned reports to assess hepatic involvement within HLH/IEC-HS. Time to onset was calculated from the earliest recorded CAR T-cell therapy date to the event-onset date. Canada Vigilance was used for directional comparison rather than formal validation; because of small counts, Evans criterion positivity required at least three exposed reports, PRR at least 2, and chi-squared at least 4.

Results

Report characteristics

Among 4,700,843 deduplicated FAERS reports, 19,820 identified a CAR T-cell product as the primary suspect therapy, and 734 met the HAE definition, corresponding to a spontaneous-reporting fraction of 3.7%. Median age was 62 years, and 423 of 683 reports with documented sex involved male patients. Median time to onset was 5 days, and 73.5% of events occurred within 14 days. CRS was co-mentioned in 565 HAE reports (77.0%), whereas HLH-spectrum terms were present in 70 (9.5%) reports.

Primary disproportionality analyses

Idecabtagene vicleucel showed the most consistent product-level HAE reporting pattern (69 of 892 primary-suspect reports; 7.7%). It met all four prespecified thresholds in every comparator analysis, including RG1 (ROR 2.96; 95% CI 2.31–3.78; IC025 1.12; EBGM05 2.25), RG2 (63 reports; ROR 5.31; 95% CI 4.09–6.89; EBGM05 3.76), RG3 (ROR 5.34; 95% CI 4.12–6.94; EBGM05 3.78) and the confounder-excluded cohort (ROR 3.81; 95% CI 2.98–4.87; EBGM05 2.84) (Fig. 1; Table 1).

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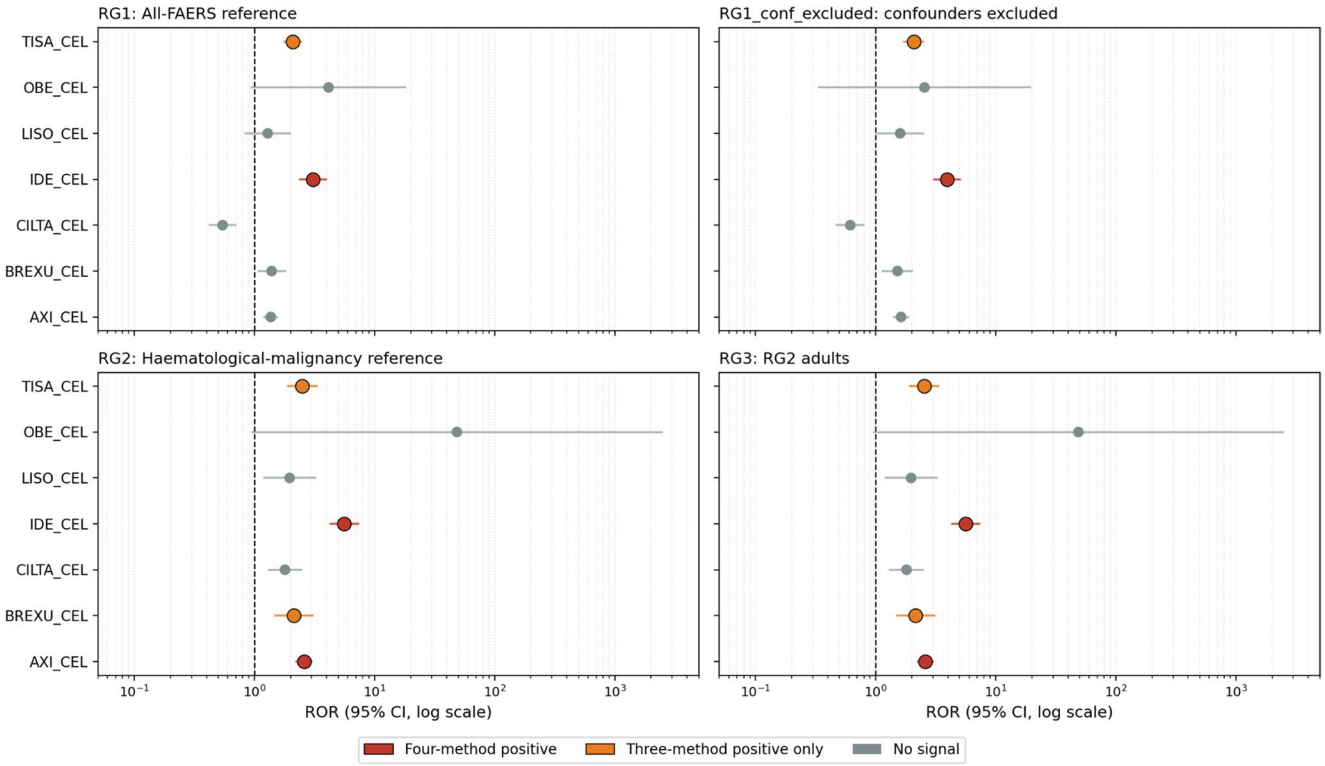


Fig. 1 Primary FAERS disproportionality estimates for CAR T-cell-associated hepatic adverse events by product and comparator cohort. Reporting odds ratios are shown on a log scale with 95% confidence intervals. Red indicates four-method-positive reporting patterns meeting all prespecified ROR, PRR, IC and EBGM thresholds. Amber indicates supportive three-method-positive reporting patterns meeting ROR, PRR and IC thresholds but not the EBGM lower-bound threshold. Grey indicates no disproportionate reporting. IDE-CEL showed the most consistent four-method-positive pattern. AXI-CEL and pooled CAR T-cell exposure were four-method positive in haematological-malignancy-restricted comparators, whereas TISA-CEL and selected BREXU-CEL findings were supportive three-method-positive patterns. The four metrics were derived from the same set of reports; concordance indicates robustness across prespecified thresholds rather than independent validation or causality

Tisagenlecleucel showed a supportive three-method-positive pattern in RG1 (198 of 3,458 reports; 5.7%; ROR 2.14; 95% CI 1.86–2.47; PRR 2.08; IC025 0.84; EBGM05 1.84) and met four-method criteria in the haematological-malignancy comparators. Axicabtagene ciloleucel and pooled CAR T-cell exposure met four-method criteria only in RG2 and RG3. Brexucabtagene autoleucel showed supportive three-method-positive patterns in RG2 and RG3. In contrast, pooled CAR T-cell exposure did not meet PRR or EBGM thresholds in RG1 despite an elevated ROR (734 of 19,820; ROR 1.36; 95% CI 1.26–1.46; PRR 1.34; EBGM05 1.27). Ciltacabtagene autoleucel showed under-disproportionate reporting in RG1 (72 of 4,867; 1.5%; ROR 0.53; 95% CI 0.42–0.67), which persisted after confounder exclusion (ROR 0.61; 95% CI 0.48–0.78).

Sensitivity, phenotype and directional-comparison analyses

After symmetric exclusion of reports co-mentioning CRS, the pooled CAR T-cell HAE ROR decreased from 1.36 to 0.54. Product-level disproportionality was attenuated for all products except idecabtagene vicleucel, which retained a supportive three-method-positive pattern (18/69 HAEs) after this exclusion (ROR 2.22; 95% CI 1.38–3.57). In contrast, exclusion of HLH-spectrum reports preserved the primary estimates; for idecabtagene vicleucel, the ROR remained 2.95 (95% CI 2.30–3.78). No product retained a four-method-positive association

Table 1 Primary FAERS disproportionality estimates for CAR T-cell-associated hepatic adverse events

Cohort	Product	A	ROR (95% CI)	PRR (χ^2)	IC025	EBGM05	Reporting tier	Interpretation
RG1	TISA-CEL	198	2.14 (1.86–2.47)	2.08 (112.46)	0.84	1.84	3-method only	Supportive reporting pattern; EBGM05 below threshold
RG1	AXI-CEL	305	1.37 (1.22–1.53)	1.35 (28.51)	0.27	1.23	No signal	PRR and EBGM05 thresholds not met
RG1	BREXU-CEL	65	1.37 (1.07–1.75)	1.35 (5.86)	0.08	1.10	No signal	PRR and EBGM05 thresholds not met
RG1	LISO-CEL	22	1.21 (0.79–1.86)	1.21 (0.60)	−0.34	0.87	No signal	ROR CI crosses 1; no consistent disproportionality
RG1	IDE-CEL	69	2.96 (2.31–3.78)	2.81 (80.54)	1.12	2.25	4-method	Conservative HAE reporting association
RG1	CILTA-CEL	72	0.53 (0.42–0.67)	0.54 (29.22)	−1.23	0.45	No signal	Under-disproportionate reporting
RG1	OBE-CEL	3	4.07 (1.23–13.44)	3.75 (3.72)	−0.17	1.09	No signal	Sparse reports; chi-square, IC025 and EBGM05 thresholds not met
RG1	CART_ANY	734	1.36 (1.26–1.46)	1.34 (65.74)	0.32	1.27	No signal	PRR and EBGM05 thresholds not met
RG2	TISA-CEL	68	2.68 (2.10–3.43)	2.59 (65.90)	1.00	2.09	4-method	Conservative reporting pattern in haematologic-malignancy comparator
RG2	AXI-CEL	244	2.43 (2.13–2.76)	2.36 (188.94)	1.03	2.09	4-method	Conservative reporting pattern in haematologic-malignancy comparator
RG2	BREXU-CEL	33	2.00 (1.41–2.83)	≈2.00 (14.72)	0.45	1.47	3-method only	Supportive reporting pattern; EBGM05 below threshold
RG2	LISO-CEL	17	1.82 (1.12–2.95)	1.79 (5.22)	0.11	1.22	No signal	PRR and EBGM05 thresholds not met
RG2	IDE-CEL	63	5.31 (4.09–6.89)	4.88 (193.37)	1.86	3.76	4-method	Strongest product-level reporting association
RG2	CILTA-CEL	43	1.70 (1.25–2.31)	1.68 (11.29)	0.30	1.31	No signal	PRR and EBGM05 thresholds not met
RG2	OBE-CEL	0	—	—	—	—	No signal	No exposed HAE reports; sparse-cell estimate not interpretable
RG2	CART_ANY	468	2.52 (2.29–2.77)	2.45 (389.91)	1.11	2.21	4-method	Conservative class-level reporting pattern in haematologic-malignancy comparator
RG3	TISA-CEL	68	2.73 (2.13–3.48)	2.63 (68.24)	1.02	2.12	4-method	Conservative reporting pattern in adult haematologic-malignancy comparator
RG3	AXI-CEL	243	2.43 (2.14–2.77)	2.37 (189.73)	1.03	2.09	4-method	Conservative reporting pattern in adult haematologic-malignancy comparator
RG3	BREXU-CEL	33	2.02 (1.43–2.86)	≈2.00 (15.29)	0.46	1.49	3-method only	Supportive reporting pattern; EBGM05 below threshold
RG3	LISO-CEL	17	1.83 (1.12–2.97)	1.80 (5.33)	0.12	1.22	No signal	PRR and EBGM05 thresholds not met
RG3	IDE-CEL	63	5.34 (4.12–6.94)	4.91 (195.15)	1.87	3.78	4-method	Strongest adult haematologic-malignancy product-level association
RG3	CILTA-CEL	43	1.71 (1.26–2.32)	1.69 (11.57)	0.30	1.32	No signal	PRR and EBGM05 thresholds not met
RG3	OBE-CEL	0	—	—	—	—	No signal	No exposed HAE reports; sparse-cell estimate not interpretable
RG3	CART_ANY	467	2.54 (2.31–2.79)	2.47 (395.22)	1.12	2.22	4-method	Conservative class-level reporting pattern in adult haematologic-malignancy comparator
RG1 confounder-excluded	TISA-CEL	143	2.10 (1.77–2.48)	2.05 (77.34)	0.79	1.78	3-method only	Supportive reporting pattern after confounder exclusion; EBGM05 below threshold
RG1 confounder-excluded	AXI-CEL	269	1.61 (1.43–1.82)	1.59 (59.63)	0.49	1.44	No signal	PRR and EBGM05 thresholds not met
RG1 confounder-excluded	BREXU-CEL	54	1.52 (1.16–1.99)	1.50 (8.66)	0.19	1.20	No signal	PRR and EBGM05 thresholds not met

Table 1 (continued)

Cohort	Product	A	ROR (95% CI)	PRR (χ^2)	IC025	EBGM05	Reporting tier	Interpretation
RG1 confounder-excluded	LISO-CEL	20	1.51 (0.97–2.35)	1.49 (2.82)	−0.08	1.04	No signal	ROR CI crosses 1; IC025 and EBGM05 thresholds not met
RG1 confounder-excluded	IDE-CEL	69	3.81 (2.98–4.87)	3.58 (128.64)	1.46	2.84	4-method	Robust conservative association after confounder exclusion
RG1 confounder-excluded	CILTA-CEL	65	0.61 (0.48–0.78)	0.61 (15.62)	−1.05	0.51	No signal	Under-disproportionate reporting after confounder exclusion
RG1 confounder-excluded	OBE-CEL	2	3.50 (0.83–14.77)	3.31 (1.36)	−0.69	0.89	No signal	Sparse reports; thresholds not met
RG1 confounder-excluded	CART_ANY	622	1.52 (1.40–1.65)	1.50 (106.50)	0.47	1.41	No signal	PRR and EBGM05 thresholds not met

Four-method, all prespecified ROR, PRR, IC and EBGM thresholds met; 3-method only, ROR, PRR and IC thresholds met but EBGM05 threshold not met

A Exposed HAE reports in the corresponding product-comparator cell, *AXI-CEL* Axicabtagene ciloleucel, *BREXU-CEL* Brexucabtagene autoleucel, *CART_ANY* Pooled CAR T-cell exposure, *CILTA-CEL* Ciltacabtagene autoleucel, *EBGM05*, Lower 5% bound of the empirical Bayes geometric mean, *IC025* Lower 2.5% bound of the information component, *IDE-CEL* Idecabtagene vicleucel, *LISO-CEL* Lisocabtagene maraleucel, *OBE-CEL* Obecabtagene autoleucel, *RG1* All-FAERS comparator, *RG2* Haematological-malignancy comparator, *RG3* Adult haematological-malignancy comparator, *TISA-CEL* Tisagenlecleucel

when analysis was restricted to onset after 14 days. This attenuation describes the sensitivity of the estimates to removal of CRS-coded reports and does not establish mediation or causal attribution.

Phenotype-stratified analyses identified associations that were not evident from the pooled endpoint. Mixed-pattern HAEs were disproportionately reported with tisagenlecleucel (ROR 4.85; 95% CI 2.68–8.76), whereas cholestatic HAEs were disproportionately reported with brexucabtagene autoleucel (ROR 4.31; 95% CI 2.50–7.44). HLH/IEC-HS was itself strongly disproportionately reported across CAR T-cell products (pooled FAERS ROR 50.3), but accounted for only a minority of HAE reports. Within HLH-restricted analyses, hepatic involvement was more frequent with tisagenlecleucel (32 of 93 HLH/IEC-HS reports; ROR 2.49; 95% CI 1.61–3.83) and less frequent with ciltacabtagene autoleucel (9 of 102; ROR 0.45; 95% CI 0.22–0.89) (Table 2).

Canada Vigilance contained 393 CAR T-cell reports and four HAEs, precluding product-specific inference. The database was therefore used only for descriptive directional comparison. The CRS co-mention proportion was similar to FAERS (three of four reports; 75.0%), and CRS exclusion reduced the HAE estimate more than HLH-only exclusion. Separately, disproportionate CAR T-cell-HLH reporting met the Evans criterion for pooled CAR T-cell exposure (ROR 106.8; 95% CI 52.4-217.6), tisagenlecleucel (ROR 184; 95% CI 67–503) and axicabtagene ciloleucel (ROR 70.6; 95% CI 22.4–222). These descriptive similarities do not constitute independent confirmation of the FAERS findings, particularly given the four Canadian HAEs.

Discussion

In this large pharmacovigilance analysis, most reported hepatic events after CAR T-cell therapy occurred early and were co-reported with CRS. The pooled HAE association disappeared after symmetric exclusion of CRS-mentioned reports but was essentially unchanged after exclusion of HLH-spectrum reports. These findings support CRS-related systemic inflammation, rather than HLH/IEC-HS, as the possible principal driver of class-level hepatic reporting. They do not imply that CRS is the cause of every reported hepatic event; co-reporting cannot establish individual-level mechanism or causality.

The timing is clinically coherent. CAR T-cell expansion and CRS commonly occur during the first days after infusion, and hepatic dysfunction can accompany the associated systemic inflammatory response [1, 8]. Early liver enzyme elevation in this setting is therefore usually evaluated and managed within CRS pathways while infection, disease involvement and treatment-related hepatotoxicity are considered. By contrast, delayed, cholestatic, mixed or CRS-independent events should prompt broader investigation for alternative causes and possible

Table 2 Sensitivity analyses, phenotype findings and external directional comparison

Analysis component	Finding	Interpretation
CAR T-cell HAE reports in FAERS	734 of 19,820 primary-suspect CAR T-cell reports (3.7%)	Spontaneous-reporting fraction, not incidence
Time-to-onset	Median 5 days; 73.5% within 14 days	Temporal association compatible with acute inflammatory co-reporting; not mechanistic evidence
CRS co-mention	565 of 734 HAE reports (77.0%)	Frequent CRS co-reporting; association does not establish causality
HLH/IEC-HS co-mention	70 of 734 HAE reports (9.5%)	HLH explains a minority of hepatic reports
L2 CRS exclusion, pooled CAR T-cell	ROR fell from 1.36 to 0.54	Pooled estimate attenuated after excluding CRS-co-mentioned reports; no mediation inference
L2 CRS exclusion, IDE-CEL	After exclusion: ROR 2.22 (1.38–3.57); three-method thresholds met	Only product retaining a supportive pattern after exclusion of CRS-co-mentioned reports
L4 HLH-only exclusion, IDE-CEL	ROR 2.95 (2.30–3.78)	Estimate largely unchanged after exclusion of HLH-co-mentioned reports
Phenotype analysis, TISA-CEL	Mixed-pattern HAE: ROR 4.85 (2.68–8.76)	Product-specific mixed-pattern reporting association
Phenotype analysis, BREXU-CEL	Cholestatic HAE: ROR 4.31 (2.50–7.44)	Product-specific cholestatic reporting association
L5 within-HLH, TISA-CEL	32 of 93 HLH/IEC-HS reports; ROR 2.49 (1.61–3.83)	Higher relative reporting of hepatic involvement within this HLH subset
L5 within-HLH, CILTA-CEL	9 of 102 HLH/IEC-HS reports; ROR 0.45 (0.22–0.89)	Lower relative reporting of hepatic involvement within this HLH subset
Canada Vigilance exposure	393 CAR T-cell reports; 4 HAE reports	Per-product directional comparison not feasible
Canada CRS co-mention pattern	3 of 4 CAR T-cell HAE reports co-mentioned CRS (75.0%)	Similar descriptive co-mention proportion; too few HAEs for validation
Canada CART_ANY x HLH	ROR 106.8 (52.4-217.6); Evans criterion met	Directional concordance for class-level HLH reporting
Canada TISA-CEL x HLH	ROR 184 (67–503); Evans criterion met	Directional concordance for product-level HLH reporting
Canada AXI-CEL x HLH	ROR 70.6 (22.4–222); Evans criterion met	Directional concordance for product-level HLH reporting

Abbreviations:CRS Cytokine release syndrome, *FAERS* FDA Adverse Event Reporting System, *HAE* Hepatic adverse event, *HLH* Haemophagocytic lymphohistiocytosis, *IEC-HS* Immune effector cell-associated haemophagocytic syndrome, *ROR* Reporting odds ratio

immune-mediated DILI. The absence of four-method-positive patterns after 14 days provides no disproportionality evidence that delayed idiosyncratic injury dominates the submitted reports, but it cannot exclude rare or under-reported delayed immune-mediated DILI.

Idecabtagene vicleucel was the principal exception. Its HAE reporting pattern was concordant across comparators, remained after the exclusion of predefined hepatic confounders, and met supportive thresholds after the exclusion of reports co-mentioning CRS, though such events were limited. Conversely, ciltacabtagene autoleucel, another BCMA-directed product, showed under-disproportionate reporting. This contrast suggests that products sharing a target may nevertheless have non-identical hepatic reporting profiles. However, differences in indications, treatment era, reporting intensity, patient selection, and concomitant therapy may contribute, and the findings should not be interpreted as comparative incidence estimates or as proof of intrinsic hepatotoxicity.

The phenotype analyses also provide clinically relevant hypotheses. Mixed-pattern reporting with tisagenlecleucel and cholestatic reporting with brexucabtagene autoleucel may identify subsets that warrant targeted review of laboratory trajectories and competing causes. Similarly, the contrasting distribution of hepatic adverse event terms within tisagenlecleucel- and ciltacabtagene-associated HLH/IEC-HS reports suggests possible product-specific organ involvement, but MedDRA terms alone cannot establish biochemical phenotype, severity or causal attribution.

Strengths include rigorous report deduplication, restriction to primary-suspect exposure, disease-restricted comparators, prespecified CRS and HLH sensitivity analyses, phenotype stratification, a conservative rule requiring concordance across four disproportionality metrics, and an external directional comparison. However, the four metrics were derived from the same underlying reports; concordance reflects robustness to metric choice rather than independent validation. Important limitations are inherent to spontaneous reporting. FAERS and Canada Vigilance cannot estimate incidence, provide complete denominators, establish causality, test biological

mediation or consistently distinguish CRS-related transaminitis from DILI. Missing laboratory values, incomplete timing, stimulated reporting, duplicate residuals, coding variability and unmeasured confounding remain possible. The small number of Canadian HAEs precluded product-level confirmation, and co-mention analyses are vulnerable to differential documentation and coding.

These findings support a practical monitoring framework. Early hepatic abnormalities should be interpreted in the context of CRS and competing acute toxicities. Persistent hepatic abnormalities occurring without documented CRS, especially in reports involving idecabtagene vicleucel, and cholestatic or mixed patterns should prompt detailed clinical assessment. Prospective cohorts with serial measurements of alanine aminotransferase, alkaline phosphatase, bilirubin, international normalised ratio, and ferritin, together with CRS grade, IEC-HS criteria, and competing hepatotoxic exposures, are needed to distinguish inflammation-related abnormalities from immune-mediated DILI.

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Author contributions SM and MM conceived and designed the study. SM, MM and AD performed the data analysis. SM and MM drafted the manuscript. AD and GP provided methodological input and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study used publicly accessible, de-identified FAERS and Canada Vigilance data and did not involve direct patient contact; institutional review board approval and informed consent were not required.

Patient consent Not applicable.

Competing interests The authors declare no competing interests.

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