BTCE induced Atrial Fibrillation

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Background

Bispecific T-cell engagers (BTCEs) therapies activate cytotoxic T cells and promote cytokine release, which may contribute to atrial fibrillation (AF) by inducing inflammation that alters atrial electrophysiology, disrupts autonomic regulation, and facilitates atrial arrhythmogenesis. AF has been reported with other immunotherapies, including chimeric antigen receptor T-cell (CAR-T) therapies and immune checkpoint inhibitors. Despite having a biological plausibility, the atrial arrhythmic risk of BTCE therapies has not been well-characterized in post-marketing studies.

Objectives

- Identify the mechanism of BTCEs and other T-cell mediated immunotherapies that may increase a patient's risk for atrial fibrillation
- Describe case-non-case and disproportionality analysis methodologies
- Calculate and interpret signals of disproportionality (SDR) including reporting odds ratios (ROR) and information components (ICs) with corresponding 95% confidence interval (CIs) or credible intervals

Additional Materials

Scan the QR code for review of the abstract, references, and manuscript.

QR code place holder

DISCLOSURES: No financial relationships or compensation exist related to this study.

Methods

- **Study Design:** case–non-case disproportionality analysis
- **Data source:** Individual case safety reports from FAERS database
- **Timeframe**: March 29, 2014 to December 31, 2024
- **Data Processing:** Cleaned & deduplicated with DiAna 2.1.0 package and R version 4.4.2
- **Analysis methods:**

Figure 1: 2x2 Contingency Table for Reporting Odds Ratio (ROR) & Information Component (IC)

	AF Present	AF Absent	Total
BiTE Therapy	a	b	a + b
Other Drugs	c	d	c + d
Total	a + c	b + d	N = a + b + c + d

Where:

Reporting Odds Ratio (ROR) = (a/b) / (c/d)

Information Component (IC) = $\log_2((a * N) / ((a + b)(a + c)))$

Results

Total reports: 14,337 adverse event (AE) reports related to BTCE therapies.

AF cases: 97 reports (0.67%) involved atrial fibrillation (AF).

Demographics:

- 49.5% male
- Majority aged ≥65 years
- 53.6% AF within 14 days of BTCE

Signals:

- All BTCEs
- Epocoritamab
- Mosunetuzumab
- CAR-T (+)

Drug	N_{AF}	Approval	ROR (95%CI)	IC (95%CrI)*
All BTCEs	97	2014-24	1.28 (1.04 to 1.57)	0.35 (0.02 to 0.60)
Blinatumomab	23	2014	0.60 (0.38 to 0.91)	-0.71 (-1.41 to -0.22)
Tebentafusp	3	2022	1.80 (0.37 to 5.33)	0.69 (-1.38 to 1.89)
Mosunetuzumab	11	2022	3.88 (1.92 to 7.01)	1.76 (0.74 to 2.46)
Teclistamab	14	2022	1.51 (0.82 to 2.55)	0.57 (-0.33 to 1.19)
Glofitamab	6	2023	1.10 (0.40 to 2.42)	0.13 (-1.28 to 1.04)
Epcoritamab	32	2023	2.95 (2.01 to 4.18)	1.5 (0.91 to 1.92)
Talquetamab	3	2023	0.89 (0.18 to 2.62)	-0.14 (-2.21 to 1.16)
Elranatamab	3	2023	0.89 (0.18 to 2.61)	-0.15 (-2.22 to 1.06)
Tarlatamab	2	2024	N/A†	N/A†
CAR-T (+)	143	N/A	2.74 (2.30 to 3.23)	1.43 (1.15 to 1.63)
Paracetamol (–)	420	N/A	0.45 (0.42 to 0.50)	-1.12 (-1.28 to -1.00)

Discussion

The analysis revealed a SDR for AF with BTCEs, particularly epcoritamab and mosunetuzumab, though it may reflect the Weber effect given their recent approvals. The association is biologically plausible, as BTCE-induced cytokine release can cause autonomic imbalance, ion channel disruption, and electrical instability, especially in elderly or those with cardiovascular comorbidities. Compared with a prior study (Syed et al.) which found no SDR for AF, the inclusion of additional FAERS data and newer BTCEs in this analysis allowed detection of a SDR. Findings align with observations from other immunotherapies (CAR-T, ICIs) which show elevated AF risk linked to T-cell activation. Limitations include potential underreporting, residual duplicate cases, incomplete FAERS data and the risk of false positives inherent to disproportionality analyses. However, our study's use of positive and negative controls strengthens confidence that AF signals with BiTE therapy may represent a true safety concern warranting further investigation.

Conclusions

A positive SDR for AF with BTCEs was detected, though causality cannot be confirmed. This signal highlights the need for further evaluation in clinical and epidemiologic studies. Future analyses should restrict cases by indication and be repeated once newer BTCEs accumulate sufficient data