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EMERGING DISPROPORTIONALITY SIGNALS OF ADVERSE EVENTS FOR TEPLIZUMAB IN REAL-WORLD USE FOR DELAYING TYPE-1 DIABETES ONSET: A FAERS-BASED PHARMACOVIGILANCE ANALYSIS

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Abstract

Teplizumab, approved by the FDA in 2022 to delay the onset of type 1 diabetes, requires ongoing safety monitoring. This study analyzes its adverse event profile using the FDA Adverse Event Reporting System (FAERS) to identify both known and new safety signals. We extracted reports from the FAERS database for the first quarter of 2023 through the fourth quarter of 2024, in which Teplizumab was listed as the primary suspect drug. We categorized adverse events using MedDRA by Preferred Terms and System Organ Classes (SOCs). Disproportionality analysis was performed to detect significant safety signals. 279 reports for Teplizumab were found, involving 1,015 adverse events. Strong disproportionality signals appeared in several SOCs, especially Gastrointestinal Disorders (such as nausea with Reporting Odds Ratio, ROR: 5.887; vomiting with ROR: 5.278), Skin and Subcutaneous Tissue Disorders (rash with ROR: 9.089; pruritic rash with ROR: 25.857), and General Disorders (fatigue with ROR: 4.289; pyrexia with ROR: 8.556; chills with ROR: 9.776). Newly identified safety signals included hyperglycemia (ROR: 9.677), increased glycosylated hemoglobin (ROR: 7.952), and influenza-like illness (ROR: 10.047), none of which were previously highlighted in FDA labeling. Headache (ROR: 5.487) and cytokine release syndrome (ROR: 12.590) were also notably linked to Teplizumab use. This analysis confirms known risks and identifies new potential adverse events linked to Teplizumab. The results indicate that gastrointestinal, skin-related, and general disorders may be more common in clinical practice than previously recognized. The emergence of signals such as hyperglycemia and influenza-like illness underscores the need for further research and clinical vigilance.

Rezumat

Teplizumab, aprobat de FDA în 2022 pentru întârzierea debutului diabetului zaharat de tip 1, necesită monitorizare continuă a siguranței. Acest studiu a analizat reacțiile adverse raportate în baza de date FAERS între trimestrul I 2023 și trimestrul IV 2024, utilizând clasificarea MedDRA și analiza de disproporționalitate. Au fost identificate 279 de raportări, incluzând 1.015 evenimente adverse. Cele mai puternice semnale au fost observate pentru tulburări gastrointestinale (greață, vărsături), afecțiuni cutanate (erupții cutanate, prurit) și tulburări generale (fatigabilitate, febră, frisoane). Au fost identificate și semnale noi, neincluse anterior în informațiile FDA, precum hiperglicemia (ROR: 9,677), creșterea hemoglobinei glicozilate (ROR: 7,952) și sindromul pseudogripal (ROR: 10,047). Rezultatele confirmă riscurile cunoscute și evidențiază potențiale reacții adverse noi, subliniind necesitatea unei monitorizări clinice atente și a unor cercetări suplimentare.

Keywords: teplizumab, adverse events, diabetes, system organ classes, gastrointestinal disorders

Introduction

Teplizumab is a monoclonal antibody that targets the CD3 receptor on T lymphocytes and is primarily used to manage Type 1 Diabetes (T1D). The FDA approval of Teplizumab in 2022 marked an astonishing milestone in the advancement of treatment for this autoimmune condition (1). It spares beta-cell function in T1D patients by modulating the immune system to prevent the destruction of insulin-secreting pancreatic beta cells, thus preserving beta-cell function. Because of its novel mechanism of action, it becomes imperative for the evolving pharmacotherapy of T1D patients (2). Nonetheless, as with any new treatment, the long-term safety profile, particularly the safety of Teplizumab, remains a dominant unanswered question (3, 4). This remains crucial for

evaluation post-marketing, considering the population one administers it to, as compared to trial participants, despite trials proving effectiveness. Like other therapies that modulate the immune response, Teplizumab is likely to cause immune-mediated adverse reactions relevant to its mechanism of action (5). The FDA Adverse Event Reporting System (FAERS) is a valuable post-marketing monitoring system regarding the safety of Teplizumab that represents the emerging database for the monitoring of post-marketing safety.

The FAERS database receives contributions from healthcare practitioners, patients, and drug manufacturers concerning adverse drug events. It helps evaluate safety signals and perform risk assessments for marketed drugs (6). While trials suggest that Teplizumab is tolerable within well-controlled environments, the FAERS database can uncover rare adverse events and chronic safety concerns. In addition, adverse event reporting in FAERS is unstructured, allowing unbounded deviations, which aid in identifying safety signals often missed in randomized clinical trials (7), especially for immunomodulating therapies such as Teplizumab, which pose the risk of broad impacts across the immune system. Teplizumab has been reported to be associated with a wide range of adverse drug reactions (ADRs) multi-systemically, as stated in the FDA-approved labeling and pre-marketing clinical trials. The most commonly reported reactions included skin rash, lymphocytopenia, leukopenia, and headache – all of which are consequences of dermatologic, hematologic, and neurologic involvement – with an incidence greater than 10%. Adverse effects such as diarrhea, nausea, neutropenia, and elevated alanine aminotransferase with an incidence of 1% to 10% indicate gastrointestinal, hematologic, and hepatic involvement (7, 8).

In addition, cytokine release syndrome and serum sickness have been recognized as significant hypersensitivity reactions, and serious infections, including abscesses, cellulitis, gastroenteritis, pneumonia, sepsis, and wound infections, have also been reported (9). Notably, the FDA-approved dosing regimen differs from that used in premarket clinical trials due to differences in pharmacokinetics between the formulations. It suggests that the ADR rates reported in the labelling may differ from those observed with the currently marketed product (10). For Teplizumab, its recently granted marketing authorization needs extensive post-marketing monitoring to understand the safety profile completely (11). The clinical trials have reported the efficacy of Teplizumab; however, enduring dominance and safety in day-to-day clinical practice require further assessment. FAERS, as mentioned, could aid in addressing concerns about new adverse effects of Teplizumab and help physicians make decisions about off-label prescribing.

The study aims to evaluate the adverse effects of Teplizumab using the FAERS database. The primary goal is to detect newly reported safety signals and estimate the risks of adverse drug reactions relative to other similar immunotherapies, such as insulin and immune checkpoint inhibitors. Emphasis will be placed on disproportionality techniques for the outcome analysis of adverse events, with a specific focus on system organ class (SOC) and preferred term (PT) groupings to identify significant adverse reactions using Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) analyses.

Materials and Methods

Data source

The U.S. FAERS database, which collects AEs, medication errors, and product quality grievances from healthcare professionals, patients, and manufacturers, served as the data source for this study. Reports about Teplizumab (brand name Tzield) were specifically extracted from the database for the period from Q1 2023 to Q4 2024, given the FDA approval date of 17 November 2022.

Ethical approval

This study utilized publicly available, de-identified data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). As the FAERS database contains no patient identifiers and all data are anonymized prior to public release, Institutional Review Board (IRB) or ethical approval was not required. Therefore, this research was exempt from ethical review in accordance with international guidelines for studies using secondary, non-identifiable public data.

Data extraction

Our retrieval strategy for Teplizumab-related AE reports from FAERS was exhaustive. We narrowed down reports where Teplizumab was captured as a primary suspect (PS) drug. We included both mono- and combination-therapy cases to capture the rich tapestry of adverse events. Using key fields CASEID, PRIMARYID, and FDA_DT, we identified duplicate reports; only the most recent was retained for each unique case. Validation was conducted by reviewing key fields, with discrepancies flagged. All dates or events in conflict with each other, alongside other potential errors, were examined.

Adverse event classification

Reports came in the form of the Medical Dictionary for Regulatory Activities MedDRA v27.1. Systematization of terminology improves coherency MTB by standardizing reporting language for adverse event reporting. Each report was assigned a PT and categorized into SOCs.

Proposed classification of adverse events

All adverse events in FAERS were encoded systematically with MedDRA version 27.1. The Medi-

cal Dictionary for Regulatory Activities analyzes medical information through a hierarchical classification system consisting of: System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), PT, and Lowest Level Term (LLT). The top-level SOC of MedDRA groups related terms into broader sections based on the organ system they relate to. All medical terms within each SOC are clinically related to numerous medical specialties or systems. Every adverse event is initially categorized under a PT, which provides a detailed description of the adverse event. After a PT has been assigned, the event is classified according to SOC. A system is in place that ensures AEs are grouped logically according to the organ system affected.

Signal detection

In relation to safety signal detection for Teplizumab, disproportionality was analyzed and a set of disproportionality analysis methods was applied according to pharmacovigilance conventions. Such methods measure the strength of association between a drug and a particular adverse event (AE) by determining its co-occurrence with other events for the drug in question within a database. While measuring the AEs linked to Teplizumab, the ROR was determined. The ROR is determined as the odds of an AE occurring with Teplizumab, over the odds of that same event occurring with all other drugs in the FAERS database. A positive signal was deemed to have been generated when the ROR was greater than 3, with a 95% CI not containing 1. Proportional Reporting Ratio (PRR) is applied in measuring AEs reported for Teplizumab compared to all other drugs. A PRR that exceeds 2 while the 95% CI does not include 1 also indicates a signal.

Empirical Bayesian Geometric Mean (EBGM) computes the geometric mean of the observed and expected frequencies of an AE to determine the rate of occurrence for the suspected, rare, and serious adverse event. A signal is regarded as meaningful if the EBGM is greater than two, with higher values providing stronger associations.

The Information Component (IC) is a Bayesian measure that attempts to find disproportionality, capturing the strength and quality of the observed signal, including its precision. A positive signal is indicated by the IC exceeding 1.5; higher IC values indicate a stronger association between the drug and the adverse event.

Also, Yule's Q and Chi-Square statistics were used to assess the strength and significance of the associations. Yule's Q indicates the association between two categorical binary events and, in this case, the degree of association between Teplizumab and an adverse event. In FAERS studies, a Yule's Q value higher than 0.1 is generally regarded as indicating a weak association, becoming moderate for values above 0.5, and strongly positive for values above 0.9. The Chi-Square test assesses the strength of disproportionality signals for Teplizumab and the adverse event. Values of Chi-Square in FAERS studies indicate that values above 1 suggest a signal, but values beyond 10 and 100 provide a stronger statistical claim that Teplizumab is linked to the adverse event.

Results and Discussion

FAERS data extraction process

The process of data extraction from the FAERS database for Teplizumab is depicted in Figure 1.

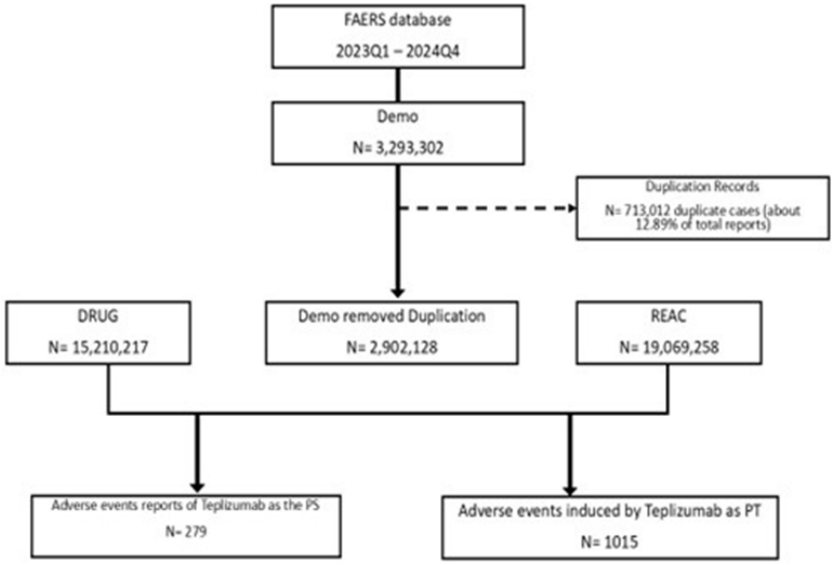

Figure 1.
Flowchart of the data extraction and case selection process for teplizumab adverse event analysis from the FAERS database

Initially, the database contained a total of 3,293,302 reports for the period from 2023Q1 to 2024Q4. After excluding duplicate records (a total of 713,012, which account for approximately 12.89% of the total reports), the dataset was refined to 2,902,128 unique reports. Out of these, 279 reports were identified where Teplizumab was listed as the primary suspect (PS) drug. Following further analysis, a total of 1,015 adverse events (AEs) associated with Teplizumab as a Preferred Term (PT) were analyzed. This comprehensive process ensured that only relevant, unique, and non-duplicated adverse event reports were included, providing a solid foundation for the analysis of Teplizumab's real-world safety profile.

Demographics and characteristics of adverse event reports

A comprehensive demographic and clinical characteristics analysis of the adverse event reports associated with Teplizumab is presented in Table I.

Table I

Demographic and clinical characteristics of adverse event reports for teplizumab (Tzield) from the FAERS database

Gender	
Female	141 (50.5%)
Male	91 (32.6%)
Unknown	47 (16.8%)
Age	
< 18	57 (20.4%)
30 - 50	74 (26.5%)
50 - 65	25 (8.96%)
≥ 65	2 (0.72%)
≥ 75	1 (0.36%)
Unknown	50 (17.9%)
Missing	70 (25.1%)
Weight	
< 40 kg	6 (2.15%)
40 - 60 kg	10 (3.58%)
60 - 80 kg	10 (3.58%)
80 - 100	9 (3.22%)
≥ 100 kg	4 (1.43%)
Missing	240 (86.02%)
Reported countries	
United States	278 (99.6%)
Not specified	1 (0.36%)
Outcomes	
Other serious	18 (6.45%)
Hospitalization	8 (2.87%)
Life-Threatening	3 (1.08%)
Required Intervention	1 (0.36%)
Missing	249 (89.2%)
Onset time of adverse effects (days)	
< 7 days	6 (2.15%)
8 - 14 days	34 (12.19%)
Onset time of adverse effects (days)	
15 - 21 days	25 (8.96%)
22 - 28 days	18 (6.45%)
29 - 60 days	46 (16.49%)
More than 60 days	87 (31.18%)
Missing	58 (20.79%)
Occupation of reported	
Consumer	106 (38.1%)
Physician	104 (37.4%)
Health Professional	60 (21.6%)
Pharmacist	8 (2.88%)

The majority of reports were from females (141 cases, 50.5%), followed by males (91 cases, 32.6%), and unknown gender (47 cases, 16.8%). Age distribution shows that 20.4% of the reports were from individuals under 18 years of age, while 26.5% were from those aged 30 - 50. A small percentage of reports came from individuals over 65 years of age (only 1% from individuals aged ≥ 65). The weight distribution was highly skewed, with 86.02% of cases having missing weight data, making it difficult to draw conclusions about weight-related trends. The majority of reports came from the United States (99.6%). Concerning outcomes, the most common reported outcomes were serious adverse events (6.45%) and hospitalizations (2.87%). A significant portion of reports did not specify the outcome (89.2%). The onset of adverse effects was most commonly reported as occurring more than 60 days after the start of Teplizumab treatment (31.18%), while a smaller number of reports indicated a shorter onset time (< 7 days: 2.15%). Finally, healthcare professionals (including physicians and health professionals) accounted for 59.5% of the reported cases, with consumers contributing 38.1%.

Signal detection for system organ classes

Table II presents the results of the disproportionality analysis for Teplizumab across 22 of the 27 SOCs where adverse events (AEs) were reported. Gastrointestinal Disorders emerged as the most prominent SOC, with 139 cases reported. The ROR for Gastrointestinal Disorders was 2.732 (95% CI: 2.312 - 3.229), and the PRR was similarly 2.732 (95% CI: 2.312 - 3.229) indicating a significant association. Skin and Subcutaneous Tissue Disorders also showed a strong positive signal, with a ROR of 4.859 (95% CI: 4.153 - 5.685) and a PRR of 4.859 (95% CI: 4.153 - 5.685), suggesting significant associations with dermatological effects. The Chi-Square value of 478.076 further supports the statistical significance of this finding. Other notable findings included Investigations (ROR: 7.730, 95% CI: 6.624 - 9.020) and Metabolism and Nutrition Disorders (ROR: 2.694, 95% CI: 1.773 - 4.095), both showing strong associations with Teplizumab. These findings highlight potential issues related to abnormal laboratory tests or metabolic disturbances. The Musculoskeletal and Connective Tissue Disorders (with ROR of 1.266, PRR of 1.266) and Nervous System Disorders (with ROR of 2.327, PRR of 2.327) also showed significant associations, although they were not as prominent as Gastrointestinal or Skin Disorders. On the other hand, Injury, Poisoning and Procedural Com-

plications (with a ROR of 1.024), Psychiatric Disorders (with ROR of 1.365), and Renal and Urinary Disorders (with ROR of 7.693) showed weaker associations or were marginally significant but still met the threshold for signal detection. Reproductive System and Breast Disorders had the highest ROR at 60.724, signaling a strong association. In contrast, Social Circumstances and Infections and Infestations showed lower ROR and PRR values, below 2, indicating weaker or no significant associations with Teplizumab.

Table II

Disproportionality analysis of adverse events for teplizumab by system organ classes (SOCs)

SOC	Frequency	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)	Yule's Q	Chi-Square
Blood and lymphatic system disorders	7	2.729 (1.3 - 5.728)	2.726 (1.3 - 5.715)	1.446 (1.402)	2.725 (1.298)	0.464	7.653
Cardiac disorders	9	1.799 (0.935 - 3.46)	1.796 (0.935 - 3.449)	0.845 (0.794)	1.796 (0.934)	0.285	3.181
Ear	2	5.406 (1.35 - 21.651)	5.397 (1.351 - 21.557)	2.432 (2.343)	5.395 (1.347)	0.688	7.164
Eye disorders	11	3.166 (1.753 - 5.721)	3.163 (1.752 - 5.709)	1.661 (1.628)	3.162 (1.750)	0.520	16.275
Gastrointestinal disorders	139	2.732 (2.312 - 3.229)	2.718 (2.303 - 3.207)	1.442 (1.420)	2.717 (2.299)	0.464	151.335
General disorders and administration site conditions	233	2.767 (2.432 - 3.147)	2.754 (2.423 - 3.13)	1.461 (1.446)	2.754 (2.421)	0.469	260.933
Hepatobiliary disorders	2	5.808 (1.45 - 23.261)	5.798 (1.452 - 23.16)	2.535 (2.446)	5.796 (1.447)	0.706	7.940
Immune system disorders	10	2.947 (1.583 - 5.486)	2.937 (1.583 - 5.451)	1.554 (1.492)	2.937 (1.578)	0.493	12.795
Infections and infestations	26	1.249 (0.85 - 1.836)	1.249 (0.851 - 1.834)	0.321 (0.299)	1.249 (0.850)	0.111	1.292
Injury, poisoning and procedural complications	33	1.024 (0.728 - 1.441)	1.024 (0.728 - 1.44)	0.035 (0.012)	1.024 (0.728)	0.012	0.019
Investigations	162	7.73 (6.624 - 9.02)	7.7 (6.603 - 8.979)	2.944 (2.929)	7.695 (6.595)	0.771	944.346
Metabolism and nutrition disorders	22	2.694 (1.773 - 4.095)	2.689 (1.772 - 4.081)	1.427 (1.393)	2.689 (1.769)	0.459	23.361
Musculoskeletal and connective tissue disorders	33	1.266 (0.899 - 1.781)	1.265 (0.9 - 1.778)	0.339 (0.312)	1.265 (0.899)	0.117	1.834
Nervous system disorders	87	2.327 (1.885 - 2.873)	2.321 (1.882 - 2.862)	1.214 (1.193)	2.320 (1.880)	0.399	65.509
Psychiatric disorders	13	1.365 (0.792 - 2.351)	1.364 (0.792 - 2.348)	0.448 (0.414)	1.364 (0.791)	0.154	1.263
Renal and urinary disorders	2	7.693 (1.92 - 30.816)	7.68 (1.922 - 30.679)	2.940 (2.851)	7.675 (1.916)	0.770	11.615
Reproductive system and breast disorders	1	60.724 (8.501 - 433.741)	60.665 (8.51 - 432.486)	5.915 (5.827)	60.351 (8.449)	0.968	58.374
Respiratory, thoracic and mediastinal disorders	25	1.229 (0.83 - 1.82)	1.228 (0.83 - 1.817)	0.297 (0.270)	1.228 (0.830)	0.103	1.064
Skin and subcutaneous tissue disorders	157	4.86 (4.154 - 5.685)	4.836 (4.137 - 5.652)	2.273 (2.255)	4.834 (4.132)	0.659	478.076
Social circumstances	16	0.312 (0.191 - 0.509)	0.314 (0.192 - 0.512)	1.672 (1.712)	0.314 (0.192)	-0.525	24.260
Surgical and medical procedures	1	2869.262 (320.422 - 25693.177)	2866.436 (320.66 - 25623.553)	11.163 (11.074)	2293.349 (256.097)	0.999	2291.550
Vascular disorders	24	1.997 (1.338 - 2.982)	1.995 (1.338 - 2.975)	0.996 (0.968)	1.995 (1.336)	0.333	11.924

Signal detection for adverse events of teplizumab based on preferred terms

Table III presents the results of the disproportionality analysis for Teplizumab by Preferred Terms. Gastrointestinal Disorders showed the most prominent associations, particularly with nausea and vomiting. The ROR for nausea was 5.887 (95% CI: 4.562 - 7.597) and for vomiting it was 5.278 (95% CI: 3.767 - 7.395), both well above the threshold of 3, indicating a strong positive signal. Additionally, the

PRR for nausea was 5.584 (95% CI: 4.396 - 7.093) and for vomiting it was 5.130 (95% CI: 3.705 - 7.105), both indicating that the frequency of these AEs with Teplizumab is significantly higher than with other drugs in the FAERS database. The Chi-Square values for these events were also high, 239.611 for nausea and 117.122 for vomiting, confirming the statistical significance of the association. General Disorders and Administration Site Conditions also presented strong signals. The ROR for fatigue was 4.289 (95% CI: 3.297 - 5.579) and pyrexia had a ROR of 8.556 (95% CI: 6.402 - 11.434), both indicating significant associations with Teplizumab. Particularly, pyrexia and chills showed exceptionally high values for EBGM, with pyrexia showing EBGM of 8.193 (95% CI: 6.131), and chills showing EBGM of 9.613 (95% CI: 6.03), further reinforcing the robustness of these associations.

Skin and Subcutaneous Tissue Disorders showed a high incidence of rash (60 cases), with a ROR of 9.089 (95% CI: 7.001 - 11.799) and PRR of 8.611 (95% CI: 6.736 - 11.007), which indicates a strong association with Teplizumab. Similarly, rash pruritic (21 cases) showed an even higher ROR of 25.857 (95% CI: 16.775 - 39.855), which indicates a very strong signal for this dermatologic side effect. Investigations showed significant associations with lymphocyte count decreased (24 cases), which had a ROR of 65.781 (95% CI: 43.83 - 98.724), indicating a very strong association with Teplizumab. Similarly, white blood cell counts decreased (14 cases) and hepatic enzymes increased (12 cases) showed high ROR values, further supporting the strong association between Teplizumab and changes in laboratory parameters. Immune System Disorders, particularly cytokine release syndrome, was associated with a ROR of 12.59 (95% CI: 6.529 - 24.276), suggesting a significant link with Teplizumab, indicating the potential for immune-related adverse effects. Infections and Infestations, such as influenza-like illness (11 cases), presented a ROR of 10.047 (95% CI: 5.545 - 18.205), indicating a positive signal for infections related to Teplizumab.

Table III

Disproportionality analysis of adverse events associated with teplizumab by preferred terms discussion

SOC	PT	Frequency	ROR (95% CI)	PRR (95% CI)	EBGM (EBGM05)	IC (IC025)	Yule's Q	Chi-Square
Gastrointestinal disorders	Nausea	63	5.887 (4.562 - 7.597)	5.584 (4.396 - 7.093)	5.582 (4.325)	2.481 (2.392)	0.71	239.611
	Vomiting	35	5.278 (3.767 - 7.395)	5.13 (3.705 - 7.105)	5.129 (3.66)	2.359 (2.27)	0.681	117.122
General disorders and administration site conditions	Fatigue	59	4.289 (3.297 - 5.579)	4.097 (3.198 - 5.249)	4.096 (3.149)	2.034 (1.946)	0.622	140.088
	Pyrexia	48	8.556 (6.402 - 11.434)	8.199 (6.22 - 10.807)	8.193 (6.131)	3.034 (2.946)	0.791	304.931
	Chills	18	9.776 (6.132 - 15.584)	9.62 (6.085 - 15.21)	9.613 (6.03)	3.265 (3.176)	0.814	139.176
	Peripheral swelling	13	4.254 (2.461 - 7.352)	4.212 (2.454 - 7.229)	4.211 (2.436)	2.074 (1.985)	0.619	31.927
	Night sweats	5	8.53 (3.542 - 20.546)	8.493 (3.542 - 20.368)	8.488 (3.524)	3.085 (2.997)	0.79	33.049
	Feeling cold	4	9.569 (3.583 - 25.555)	9.535 (3.584 - 25.367)	9.528 (3.568)	3.252 (3.163)	0.811	30.546
	Infusion site erythema	3	22.92 (7.371 - 71.266)	22.855 (7.375 - 70.827)	22.812 (7.337)	4.512 (4.423)	0.916	62.581
	Infusion site pruritus	3	22.92 (7.371 - 71.266)	22.855 (7.375 - 70.827)	22.812 (7.337)	4.512 (4.423)	0.916	62.581
Nervous system disorders	Headache	50	5.487 (4.129 - 7.292)	5.266 (4.019 - 6.901)	5.264 (3.961)	2.396 (2.308)	0.692	174.356
Investigations	Lymphocyte count decreased	24	65.781 (43.83 - 98.724)	64.249 (43.22 - 95.509)	63.896 (42.575)	5.998 (5.909)	0.97	1486.569
	White blood cell count decreased	14	6.825 (4.027 - 11.569)	6.745 (4.009 - 11.35)	6.742 (3.978)	2.753 (2.664)	0.744	68.607
	Hepatic enzyme increased	12	9.482 (5.366 - 16.758)	9.382 (5.345 - 16.469)	9.375 (5.305)	3.229 (3.14)	0.809	89.904
	Alanine aminotransferase increased	9	11.588 (6.01 - 22.343)	11.494 (5.996 - 22.034)	11.483 (5.956)	3.521 (3.433)	0.841	86.208
	Liver function test increased	9	18.586 (9.637 - 35.845)	18.43 (9.612 - 35.338)	18.402 (9.542)	4.202 (4.113)	0.898	148.195

SOC	PT	Frequency	ROR (95% CI)	PRR (95% CI)	EBGM (EBGM05)	IC (IC025)	Yule's Q	Chi-Square
	Platelet count decreased	9	4.547 (2.359 - 8.766)	4.516 (2.356 - 8.655)	4.514 (2.342)	2.175 (2.086)	0.639	24.674
	Lymphopenia	9	34.999 (18.14 - 67.529)	34.698 (18.088 - 66.56)	34.596 (17.931)	5.113 (5.024)	0.944	293.728
	Aspartate aminotransferase increased	8	12.016 (5.991 - 24.103)	11.93 (5.98 - 23.798)	11.918 (5.942)	3.575 (3.486)	0.846	80.076
	Body temperature increased	7	19.235 (9.141 - 40.477)	19.11 (9.128 - 40.007)	19.079 (9.067)	4.254 (4.165)	0.901	119.977
	Lymphocyte count abnormal	7	4.103 (1.951 - 8.63)	4.082 (1.951 - 8.541)	4.081 (1.94)	2.029 (1.94)	0.608	16.309
	Blood glucose decreased	6	13.241 (5.932 - 29.558)	13.169 (5.927 - 29.257)	13.155 (5.893)	3.718 (3.629)	0.86	67.422
	Neutrophil count decreased	5	5.294 (2.198 - 12.749)	5.273 (2.199 - 12.643)	5.271 (2.189)	2.398 (2.309)	0.682	17.319
	Blood glucose fluctuation	4	37.768 (14.125 - 100.989)	37.623 (14.125 - 100.214)	37.504 (14.026)	5.229 (5.14)	0.948	142.149
	Glycosylated hemoglobin increased	3	7.952 (2.559 - 24.706)	7.931 (2.561 - 24.56)	7.926 (2.551)	2.987 (2.898)	0.777	18.166
Skin and subcutaneous tissue disorders	Rash	60	9.089 (7.001 - 11.799)	8.611 (6.736 - 11.007)	8.605 (6.629)	3.105 (3.017)	0.802	406.104
	Rash pruritic	21	25.857 (16.775 - 39.855)	25.343 (16.589 - 38.715)	25.289 (16.407)	4.66 (4.572)	0.926	490.343
	Rash erythematous	13	16.487 (9.536 - 28.504)	16.288 (9.487 - 27.965)	16.267 (9.408)	4.024 (3.935)	0.886	186.429
	Urticaria	12	4.83 (2.733 - 8.534)	4.784 (2.726 - 8.397)	4.783 (2.707)	2.258 (2.169)	0.657	35.995
	Skin swelling	5	30.127 (12.498 - 72.622)	29.984 (12.492 - 71.965)	29.908 (12.407)	4.902 (4.814)	0.936	139.743
	Rash papular	4	15.819 (5.922 - 42.259)	15.76 (5.923 - 41.94)	15.74 (5.892)	3.976 (3.888)	0.881	55.234
	Pallor	3	8.793 (2.83 - 27.323)	8.77 (2.832 - 27.16)	8.764 (2.821)	3.132 (3.043)	0.796	20.644
Infections and infestations	Influenza like illness	11	10.047 (5.545 - 18.205)	9.949 (5.526 - 17.912)	9.941 (5.486)	3.313 (3.225)	0.819	88.564
Immune system disorders	Cytokine release syndrome	9	12.59 (6.529 - 24.276)	12.487 (6.514 - 23.938)	12.474 (6.469)	3.641 (3.552)	0.853	95.067
Vascular disorders	Flushing	5	5.171 (2.147 - 12.454)	5.151 (2.148 - 12.351)	5.149 (2.138)	2.364 (2.276)	0.676	16.733
Metabolism and nutrition disorders	Hyperglycemia	4	9.677 (3.624 - 25.846)	9.643 (3.625 - 25.655)	9.636 (3.608)	3.268 (3.18)	0.813	30.974
Injury, poisoning and procedural complications	Dose calculation error	4	251.605 (93.251 - 678.869)	250.617 (93.241 - 673.621)	245.278 (90.906)	7.938 (7.85)	0.992	973.229
Eye disorders	Periorbital oedema	3	3.271 (1.053 - 10.161)	3.264 (1.054 - 10.106)	3.264 (1.051)	1.707 (1.618)	0.532	4.715

In this study, we aimed to evaluate the adverse event profile of Teplizumab using data from the FAERS database, focusing on identifying both newly emerging safety signals and well-established adverse events. Our analysis revealed strong associations between Teplizumab and several adverse events, particularly within the Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders, General Disorders, and Investigative organ systems. We identified significant disproportionality signals in 22 SOCs, with Gastrointestinal Disorders and Skin Disorders being the most prominent. Specifically, nausea, vomiting, rash,

fatigue, and pyrexia were flagged as significant concerns. Additionally, laboratory abnormalities, such as decreased lymphocyte count and elevated hepatic enzymes, were identified as significant, indicating potential risks associated with Teplizumab's impact on the immune system and liver function.

In our study, gastrointestinal disorders were among the most commonly reported adverse events, specifically nausea (ROR: 5.887, PRR: 5.584) and vomiting (ROR: 5.278, PRR: 5.13). These findings are consistent with clinical trials and the FDA prescribing information for Teplizumab, which also reported gastrointestinal symptoms as one of the common adverse effects, particularly nausea in approximately 5% of patients (1, 12, 13). Our study, however, highlights a stronger association between Teplizumab and gastrointestinal symptoms, suggesting that these issues may occur more frequently in real-world settings compared to what was observed in controlled clinical trials. Compared to other immunotherapies, nausea and vomiting are commonly observed in treatments such as nivolumab and pembrolizumab, with both reporting gastrointestinal symptoms as part of their side effect profile (14, 15). The higher ROR in our study indicates the need for close monitoring of gastrointestinal side effects in Teplizumab therapy, especially given the stronger frequency in the post-marketing setting.

Our analysis revealed significant findings in the General Disorders and Administration Site Conditions category, particularly with fatigue (ROR: 4.289, PRR: 4.097), pyrexia (ROR: 8.556, PRR: 8.199), and chills (ROR: 9.776, PRR: 9.62). These findings align with the FDA-approved label, where fatigue and pyrexia are among the most frequently reported adverse events, affecting over 20% of patients receiving Teplizumab (1, 16). However, our study identified stronger associations between Teplizumab and these symptoms, suggesting that their frequency is higher in real-world settings compared to clinical trials. This observation is consistent with immune checkpoint inhibitors like ipilimumab, in which fatigue and pyrexia are commonly observed, although at lower frequencies than with Teplizumab (17, 18). Furthermore, our study identified significant infusion site reactions such as erythema and pruritus, both with RORs of 22.92, indicating hypersensitivity reactions that were not extensively discussed in Teplizumab clinical trials. These findings are consistent with those observed in rituximab and nivolumab treatments, where infusion site reactions are well-documented and frequently occur as part of immune-related adverse events (16, 19). In addition to fatigue and pyrexia, we observed several new emerging signals, including chills (ROR: 9.776), peripheral swelling (ROR: 4.254), and night sweats (ROR: 8.53), which were less frequently addressed in clinical trials or FDA labeling. The high RORs for these symptoms suggest "Teplizumab" may increase patient discomfort, possibly due to immune activation and cytokine release associated with immunotherapy.

These symptoms are consistent with immune-related adverse events observed with other immunotherapies, which are commonly linked to immune activation and its effects on various organ systems. The nervous system disorder associated with Teplizumab in our results is headache (ROR: 5.487, PRR: 5.266), which appeared in 50 cases. This signal is consistent with previous studies of immunotherapies such as nivolumab and pembrolizumab, where headache has been reported as a common adverse event in about 15% to 20% of patients (20). Teplizumab appears to have a stronger association with headache than seen in other immunotherapies, which suggests that headache might be a unique characteristic of Teplizumab, requiring better management strategies to mitigate its effects.

Our analysis of adverse events in the Investigations category revealed both known and emerging signals. Well-established adverse events such as lymphocyte count decreased (ROR: 65.781), white blood cell count decreased (ROR: 6.825), hepatic enzyme increased (ROR: 9.482), and liver function test increased (ROR: 18.586) align with the FDA-approved label and are consistent with known immune-related adverse events observed in other immunotherapies, including nivolumab and pembrolizumab (21, 22). However, our study also identified emerging signals, including blood glucose fluctuations (ROR: 37.768) and increased glycosylated hemoglobin (ROR: 7.952), which have not been widely reported in previous clinical trials or in the FDA labelling for Teplizumab. These findings suggest that Teplizumab may have a more significant impact on the glucose metabolism than previously acknowledged, warranting further investigation. Additionally, neutrophil count decreased (ROR: 5.294), platelet count decreased (ROR: 4.547), and aspartate aminotransferase increased (ROR: 12.016), though not new, further corroborate previous findings from other immune-modulating therapies and reinforce their expected association with Teplizumab (23).

In the Skin and Subcutaneous Tissue Disorders category, we observed significant signals for rash (ROR: 9.089), pruritic rash (ROR: 25.857), and skin swelling (ROR: 30.127). These reactions are consistent with the FDA prescribing information, which notes that rash is a common side effect observed in 36% of patients treated with Teplizumab (1, 9). However, our results indicate a stronger association with pruritic rash and skin swelling, which were not as prominently reported in pre-marketing studies. It suggests a higher incidence of dermatologic reactions than previously expected, aligning with reports of skin issues in other immunomodulatory therapies, such as rituximab and ipilimumab, where skin rashes were also commonly observed.

According to the Teplizumab prescribing information (1, 9, 20), influenza-like illness is not explicitly listed as an adverse event. However, the prescribing information does mention that serious infections, including both viral and bacterial infections, are a recognized concern. This aligns with our findings, where we observed an increased incidence of influenza-like illness (ROR: 10.047) in Teplizumab-treated patients. This finding suggests that influenza-like illness could be a more specific manifestation of infections not previously emphasized in the FDA labeling. Although the FDA labeling refers to viral and bacterial infections as known adverse events associated with Teplizumab, it does not specifically highlight influenza-like illness, which is distinct in its clinical presentation. Our study, therefore, contributes a more specific signal related to respiratory infections in the post-marketing setting, reinforcing the need for vigilant infection monitoring in Teplizumab-treated patients. Additionally, infections with nivolumab and pembrolizumab are known to cause similar symptoms, underscoring the need for infection surveillance in immunotherapy treatments like Teplizumab.

The signal for cytokine release syndrome (ROR: 12.59) is particularly notable, as it aligns with the known side effects of Teplizumab (1, 9). This suggests that immune modulation with Teplizumab could lead to immune activation, triggering the release of pro-inflammatory cytokines. Flushing (ROR: 5.171) and hyperglycemia (ROR: 9.677) are also significant findings. Flushing, though less commonly reported in Teplizumab's clinical trials, is a recognized side effect of immunotherapies, especially those that modulate the immune system. Hyperglycemia, as seen with other immune-modulating therapies, may be a new emerging signal for Teplizumab, with previous studies on immune checkpoint inhibitors indicating similar concerns (24). These findings suggest that Teplizumab may induce disturbances in glucose metabolism, which warrants further investigation into its impact on metabolic health, especially in patients with pre-existing diabetes or metabolic syndrome.

One of the major strengths of this study is the use of the FAERS database, which captures a broad spectrum of real-world adverse events across a diverse patient population. However, our study has limitations inherent to the FAERS database, including the potential for underreporting and the inability to establish causality, as the data rely on spontaneous adverse event reporting.

Future research should focus on understanding the emerging signals identified in this study, such as blood glucose fluctuations, glycosylated hemoglobin increases, and influenza-like illness, which were not previously highlighted in clinical trials or FDA labeling for Teplizumab. These findings suggest a greater impact on glucose metabolism and immune system function than previously known. Prospective cohort studies are needed to establish causality and explore interactions between Teplizumab and other medications. Additionally, long-term safety studies, particularly in patients with pre-existing conditions like diabetes, are essential to fully evaluate Teplizumab's impact on metabolic health and immune responses. Further research will help optimize clinical use and patient management strategies.

Conclusions

This comprehensive FAERS-based disproportionality analysis provides an updated and real-world perspective on the safety profile of Teplizumab following its recent FDA approval. Our findings confirm several well-established adverse events – such as gastrointestinal disturbances, dermatologic reactions, fatigue, pyrexia, and laboratory-based immune alterations – while also highlighting important newly emerging safety signals. Notably, hyperglycemia, increased glycosylated hemoglobin, blood glucose fluctuations, and influenza-like illness demonstrated strong associations that are not yet emphasized in FDA labeling or pre-marketing clinical trials, suggesting potential metabolic and infectious risks that warrant closer clinical attention. The significant signals detected for lymphocyte count reductions, hepatic enzyme elevations, cytokine release syndrome, and infusion-related reactions further underscore the immunomodulatory impact of Teplizumab in routine clinical practice.

Although FAERS data cannot establish causality, the strength and consistency of the signals observed – across multiple SOCs and preferred terms – suggest that certain adverse events may occur more frequently or present differently in post-marketing settings than previously anticipated. These findings reinforce the need for vigilant monitoring, early recognition of immune- and metabolism-related toxicities, and proactive management strategies in patients receiving Teplizumab. Future prospective studies and real-world cohorts are essential to validate these emerging signals, clarify underlying mechanisms, and guide risk mitigation. Overall, this analysis enhances current understanding of Teplizumab's evolving safety landscape and provides valuable evidence to inform clinicians, regulators, and patients as its use expands in the management of type 1 diabetes.

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Availability of data and materials

The database was accessed *via* FDA's FAERS Public Dashboard (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html).

Ethics approval and consent to participate

This study utilized publicly available, de-identified data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). As the FAERS database contains no patient identifiers and all data are anonymized prior to public release, IRB (Institutional Review Board) or ethical approval was not required. Therefore, this research was exempt from ethical review in accordance with international guidelines for studies using secondary, non-identifiable public data.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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