Mining and Analysis of Adverse Event Signals of Tislelizumab Based on FAERS Database

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Abstract: Objective: To mine the adverse drug event signals of tislelizumab based on the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database, and provide reference for clinical safe medication. Methods: Adverse event data of tislelizumab in the FAERS database from its launch (December 26, 2019) to December 31, 2024 were collected, and data mining was conducted using the Reporting Odds Ratio (ROR) and the Medicines and Healthcare products Regulatory Agency (MHRA) method in the disproportionality method. Results: 2745 ADE reports with tislelizumab as the primary suspect were screened, with annual increases. Among reports with age/gender data, 18-64 was the main age group and males outnumbered females. Medical professionals (98.51%) were main reporters. Of 108 positive signals, common ADEs included myelosuppression (unlisted in instructions), decreased white/neutrophil counts, rash, pruritus. High-intensity signals (e.g., elevated cytokines) existed, some unlisted. SOC showed ADEs mainly involved blood/lymphatic, immune, skin/subcutaneous systems. Conclusion: It is recommended that in the clinical use of tislelizumab, focus on the patient's hematological indicators (such as white blood cell and neutrophil counts) and immune-related adverse reactions (such as pancreatitis, myasthenia gravis, etc.), and take timely intervention measures to ensure the safety of patients' medication.
***Keywords*:** tislelizumab; adverse drug event; data mining; reporting odds ratio method; comprehensive standard method; myelosuppression

1. Introduction

Tislelizumab, as a new type of tumor immunotherapy drug, belongs to the programmed death receptor 1 (PD-1) inhibitor. It inhibits the binding of PD-1 to programmed death ligand 1 (PD-L1), activates T lymphocytes, and thus uses the body's own immune system to produce a continuous anti-tumor effect[1].First approved in China in December 2019, tislelizumab's application scope has expanded steadily. As of August 2024, it has 13 approved indications covering multiple malignancies (e.g., classical Hodgkin's lymphoma, urothelial carcinoma, non-small cell lung cancer, hepatocellular carcinoma). Among these, 11 are included in China's national medical insurance catalog, making it the PD-1 inhibitor with the most health insurance included approved indications.

Although tumor immunotherapy is generally considered to have high safety, immune-related adverse events (irAE) still occur from time to time [2]. The mechanism of irAE caused by PD-1/PD-L1 inhibitors is mainly that the weakened activity of T lymphocytes leads to increased cytokine production, and B lymphocytes mediate the production of autoimmune antibodies[3]. This inflammatory reaction and immune overactivation can occur in specific organs, damaging the function and structure of the organ, and may also cause systemic non-specific symptoms due to the release of cytokines[4,5]. Although based on current clinical observations and related studies, the degree of tislelizumab irAE is mostly mild and does not lead to treatment interruption, some patients may still experience severe adverse reactions, even life-threatening[6].

Thus, in-depth study of tislelizumab's adverse events is clinically significant. This study aims to inform its safe clinical use by mining and analyzing its post-marketing adverse event data in the FAERS database, while helping improve rational drug use, reduce unnecessary medical risks and resource waste, and better ensure patients' medication safety and therapeutic efficacy.

2. Materials and Methods

2.1 Data Source

The data in this study were obtained from FAERS through OpenVigil2.1. The drug name "tislelizumab" or "tevimbra" was used as the key word, and the search range was all ADE reports of tislelizumab from its launch (December 26, 2019) to December 31, 2024.

2.2 Data Screening and Processing

ADE reports were classified and described according to the Preferred Terms (PT) and System Organ Classes (SOC) in the Medical Dictionary for Regulatory Activities (MedDRA) (Version 26.0), and then the same PT items were merged. In addition, duplicate or non-drug-induced ADEs were excluded, and adverse event reports with tislelizumab as the primary suspected drug were selected.

2.3 Signal Detection and Mining

At present, the only data mining technology used to identify adverse events at home and abroad is the ratio imbalance method, among which the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR) and the comprehensive standard method of the UK Medicines and Healthcare products Regulatory Agency (MHRA) are commonly used. Based on the four-grid table (Table 1) of the proportional imbalance method, ROR and PRR values were calculated respectively. PRR is prone to false positive signals when the number of reports is small, so this study used ROR and MHRA to mine the adverse event signals of tislelizumab. The signal judgment criteria are: ROR case reports ≥ 3, 95% Confidence Interval (CI) lower limit of ROR value > 1; MHRA case reports ≥ 3, PRR value > 2, χ^2 value ≥ 4. The specific algorithms and positive signal judgment criteria are shown in Table 1 and Table 2 Microsoft Excel 2019 and Graphpad prism 8.0 software were used for data analysis.

Table 1. Four table of ratio imbalance measurement method

Drug	Number of target event reports	Number of other event reports	Total
Target drug	a	b	a + *b*
Other drugs	c	d	c + *d*
Total	a + *c*	b + *d*	a + *b* + *c* + *d*

Table 2. Calculation formulas and corresponding thresholds of ROR and MHRA

Method	Calculation formula	Threshold
ROR	ROR = (a / c) / (b / d) $95\%CI = e^{\ln(ROR)\pm1.96\sqrt{1/a+1/b+1/c+1/d}}$	a ≥ 3 and the lower bound of the 95% confidence interval for ROR > 1
MHRA	PRR = [a/(a + b)] / [c/(c + d)] $\chi^2 = (a + b + c + d)(ad - bc)^2 / [(a + c)(a + b)(c + d)(b + d)]$	a ≥ 3, PRR ≥ 2 and $\chi^2 \geq 4$

3. Results

3.1 Basic Information of ADE Reports

From December 26, 2019 to December 31, 2024, 2,745 adverse event (ADE) reports with tislelizumab as the primary suspected drug were collected after sorting and screening, with annual increases. In terms of age: 79.89% of reports lacked age data; among those with known age, 18-64 years old accounted for 11.48% (the largest share), followed by 65-85 years old (8.52%). For gender: 79.16% of reports had no clear gender; among known cases, males (15.45%) outnumbered females (5.39%). Regarding reporters: 0.04% had unrecorded categories; medical professionals (98.51%) were far more than consumers (1.46%).

3.2 Top 20 Risk Signals in Terms of Number of Reports and Signal Intensity of Tislelizumab-Related Adverse Events

Among the top 20 tislelizumab-related adverse event risk signals by report count, main Preferred Terms (PTs) are myelosuppression, decreased white blood cell count, decreased neutrophil count, rash, and pruritus. Notably, myelosuppression, decreased granulocyte count, and disease progression are unlisted in the drug label.

For the top 20 signals by intensity, PTs like elevated cytokines, myelosuppression, decreased granulocyte count, immune-mediated pancreatitis, and immune-mediated myasthenia gravis show strong signals. Among these, elevated cytokines, myelosuppression, decreased granulocyte count, immune-mediated myasthenia gravis, myocardial injury, immune-mediated hypophysitis, and decreased cortisol are not in the label.

3.3 SOC Involved in Tislelizumab-Related Adverse Events

A total of 108 positive signals were detected by both ROR and MHRA methods. These 108 ADE positive signals were classified and ranked according to MedDRA SOC, involving 24 SOCs. The SOCs with the highest cumulative number of

reports were blood and lymphatic system diseases and examinations and investigations.

4. Discussion

4.1 Basic Info Analysis of Adverse Event Reports

From December 26, 2019 to December 31, 2024, 2,745 adverse event (ADE) reports with tislelizumab as the primary suspected drug were collected, with annual increases possibly tied to expanded clinical use, better monitoring, and higher reporting awareness.

Nearly 80% of reports lacked clear age data, hindering full assessment of age-related adverse reaction differences. Among reports with known ages, 18-64 (11.48%) was the largest group, followed by 65-85 (8.52%), showing wide use in middle-aged, young, and elderly patients. Further studies on age-specific traits are needed.

Almost 80% of reports missed gender info. Males were more common in known-gender reports, hinting at greater male sensitivity, but this needs caution due to data gaps; gender data collection and research should be strengthened.

98.51% of reporters were medical professionals, consumers only 1.46%. Low consumer reporting may delay reaction detection; patient education should be boosted to encourage active reporting for thorough drug safety evaluation.

4.2 Analysis of Key Adverse Event Signals

Tislelizumab's common hematological adverse events: myelosuppression (654 cases), decreased white blood cell count (173 cases), decreased neutrophil count (159 cases)—signaling critical safety issues. Rash, pruritus, abnormal liver function are also frequent, implying immune-related reactions and hepatotoxicity may link to its mechanism.

Strongest signals: elevated cytokines (PRR=349.17), myelosuppression (PRR=313.33), decreased granulocyte count (PRR=257.28). Signals for elevated cytokines, immune-mediated myasthenia gravis, myocardial injury are particularly strong; others like immune-mediated pancreatitis, hypophysitis, decreased cortisol also show strong signals, affecting endocrine/immune systems.

Blood/lymphatic system disorders (1,164 cases) and investigations (573 cases) have most reports. Other common SOCs: skin/subcutaneous (352), gastrointestinal (344), general disorders (332)—indicating multi-organ involvement. Unlisted myelosuppression (PRR=313.33, ROR=497.35) raises infection/bleeding risks; monitor blood. Elevated cytokines (PRR=349.17, ROR=349.76) and immune-mediated myasthenia gravis (PRR=225.62, ROR=226.13) suggest excessive immune activation.

4.3 Analysis of Newly Identified Adverse Event Signals

Several high-risk adverse events unlisted in the package insert were identified, with high frequencies and significant signal intensities:

Highest frequency (654 cases, PRR=313.33, ROR=497.35), raising infection/bleeding risks; close blood monitoring and prompt intervention are needed.

Strongest signal (PRR=349.17, ROR=349.76) among unlisted events. Only 3 cases, but high intensity means high risk; further research is required.

Immune-mediated myasthenia gravis (PRR=225.62, ROR=226.13), myocardial injury (PRR=170.52, ROR=171.59) (neuromuscular/cardiovascular toxicity); immune-mediated hypophysitis (PRR=104.25, ROR=104.43), decreased cortisol (PRR=85.76, ROR=86.05) (endocrine impact)—clinical vigilance is needed.

Via ROR/MHRA analysis of U.S. FAERS, 2,745 ADE reports (tislelizumab as primary suspect) were found. Beyond known reactions (e.g., rash), new signals (myelosuppression, etc.) emerged, affecting blood/immune/skin systems. Clinicians should monitor closely; future large-scale studies need to validate signals and explore dosage/duration links.

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References

[1] Sun, P., Zhang, Y., Tian, S., et al. (2024). Analysis of efficacy and safety for the combination of tislelizumab and regorafenib in advanced hepatocellular carcinoma: A prospective clinical study. Journal of Cancer Research and Therapeutics, 20(4), 1344-1349.

[2] Zhou, X., Chen, X., Han, L., et al. (2022). Mechanisms underlying immune-related adverse events during checkpoint

immunotherapy. Clinical Science, 136(10), 771-785.
[3] Bhardwaj, M., Chiu, M. N., Pilkhwal Sah, S. (2022). Adverse cutaneous toxicities by PD-1/PD-L1 immune checkpoint inhibitors: pathogenesis, treatment, and surveillance. Cutaneous and Ocular Toxicology, 41(1), 73-90.
[4] Hu, J., Li, M. T. (2024). Comparison of the efficacy and safety of domestically produced tislelizumab, camrelizumab, and imported pembrolizumab in the treatment of advanced NSCLC: A real-world retrospective study. Clinical and Translational Oncology, 1-9.
[5] Yin, H., Diao, Y., Zheng, Z., et al. (2024). Tislelizumab-induced cytokine release syndrome: the first case report and review of the literature. Immunotherapy, 16(18-19), 1113-1122.
[6] Wang, Y., Huang, S., Shen, Q., et al. (2024). Analysis of 79 cases of tislelizumab-related adverse reactions. Chinese Journal of Pharmacovigilance, (10), 1148-1153.

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