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ORIGINAL ARTICLE

Analysis of the adverse reactions of atezolizumab: A real-world study based on FAERS database

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Abstract

Objective In this study, we aimed to determine the incidence of adverse drug reactions (ADRs) of atezolizumab, identify ADR signals that are significantly related to atezolizumab, and provide a reference for the rational use of atezolizumab in the clinic through the statistical analysis of its adverse drug events (ADEs) reported in the American Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database.

Methods In total, 4796 cases of atezolizumab ADEs reported in the American FAERS database from 2017 to 2019 were retrospectively analyzed.

Results The top three ADEs were febrile neutropenia (3.7%), anemia (2.9%), and acute renal failure (2.3%). In addition, the incidence rates of some ADEs were significantly different according to sex and age. The systematic organ classification of atezolizumab ADEs involved 32 systems, among which the top three were blood and lymphatic system disorders (585 cases, 12.2%), gastrointestinal disorders (433 cases, 9.0%), and infections and infestations (401 cases, 8.4%). The reporting odds ratio (ROR) method was used to detect the ADR signals of atezolizumab. The ROR (95% confidence interval) of the top ADE, febrile neutropenia, was 39.236 (33.757–45.604). In addition, we found 121 cases of complications associated with immune-related ADEs.

Conclusion The ADRs of atezolizumab reported in the FAERS database were consistent with those mentioned in the instructions for atezolizumab use, suggesting that atezolizumab has an acceptable and controllable drug effect.

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Key words: atezolizumab; adverse reactions; Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database; rational drug use

Currently, three main global databases are used worldwide to collect information about adverse drug events (ADEs): the World Health Organization (WHO)-Vigibase, the European Information System for Suspected Drug Adverse Reactions (Eudravigilance), and the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). The FAERS database has been open to the public since 2004, and data are updated quarterly. The large amount of data included in the FAERS database can be effectively used for post-market safety monitoring and risk evaluation. In addition, the number of ADE cases as well as detailed information about the ADEs for each drug, including age, gender, combination therapy, and outcome, can be found in the FAERS database. The mining and analysis of large-scale ADE databases allow us to determine the incidence rate of several ADEs and provide a reference for the rational clinical drug use. Because of its rich content, extensive coverage, and large scale, the FAERS database has an important research value in drug safety evaluation [1].

Atezolizumab is the first clinically approved synthetic immunoglobulin (Ig) G1 monoclonal antibody developed against programmed death-ligand 1 (PD-L1). Because of its favorable safety and efficacy, it was approved by the US FDA in 2016 as a second-line treatment for advanced non-small-cell lung carcinoma (NSCLC) and urothelial bladder cancer [2–4]. Fig. 1 shows the top 20 indications for atezolizumab use among 4796 cases of atezolizumab

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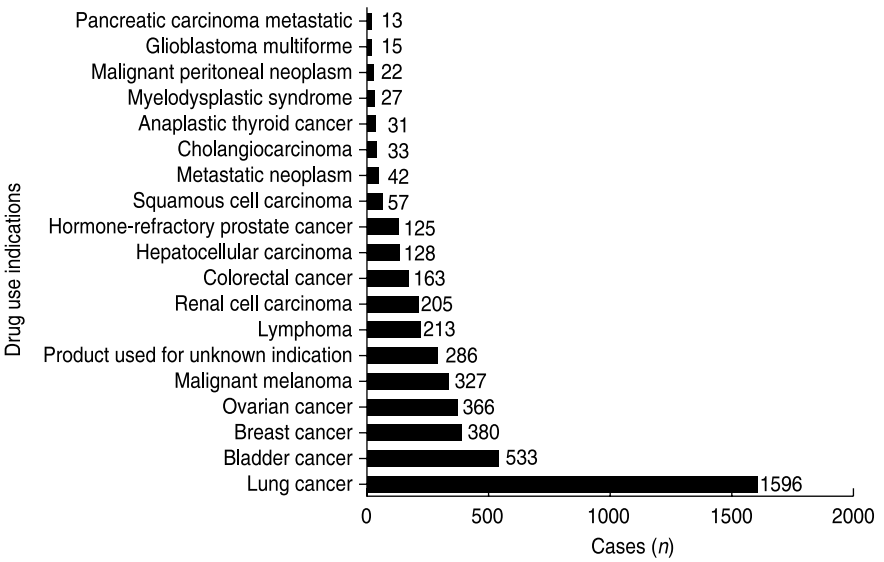

Fig. 1 Distribution of the top 20 indications for atezolizumab use. For a more intuitive impression, we unified small cell lung cancer and non-small cell lung cancer as lung cancer

Table 1 Four-grid table of the ratio imbalance measurement method

Drugs	Number of target adverse event reports	Number of other adverse event reports	Total
Target drug	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	n = a + b + c + d

ADEs reported in the FAERS database. These data may indirectly reflect the worldwide use of atezolizumab for the treatment of various tumors. However, with the increasingly widespread use of atezolizumab in clinical practice, concerns about the adverse drug reactions (ADRs) associated with its use have gradually emerged. In this study, we aimed to reveal the incidence of atezolizumab ADRs, identify the ADR signals that are significantly related to atezolizumab, and provide a reference for its rational use in the clinic. We analyzed a total of 4796 atezolizumab ADE cases reported in the US FAERS database from 2017 to 2019.

Methods

Data sources and processing

Data used in this study were obtained from the US FAERS database. The US FAERS database is a spontaneous reporting system database that does not require a reporter to prove the causal relationship between drugs and reported ADEs and does not require the report to include sufficient information to evaluate the causal relationship between drugs and ADEs.

The generic name of the target drug is "atezolizumab" (Tecentriq®). We exported the atezolizumab ADE reports for the period from the first quarter of 2017 to the fourth quarter of 2019 from the FAERS database, removed duplicate data, and used the Medical Dictionary for Regulatory Activities (MedDRA) terminology to standardize the ADR description in the report. After data cleaning, a total of 4796 reports of atezolizumab ADEs were obtained for statistical analysis.

Signal detection and analysis

In this study, descriptive statistical analysis was used to analyze the 4796 reports of atezolizumab ADEs extracted from the US FAERS database. The data included clinical manifestations, organs and systems involved, and major ADR signals. The reporting odds ratio (ROR) method, which is widely used for ADR signal mining, was employed to detect the main ADRs related to atezolizumab. This method has a high sensitivity and can eliminate a large number of deviations. The algorithm was based on a four-grid table as listed in Table 1. The formula used for calculating the ROR is as follows: ROR = (a/c)/(b/d); ROR 95% confidence interval (95% CI) = $e^{In\,(ROR)\pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$. The signal detection standard was set as follows: the ROR value should be ≥ 3, and the lower limit of ROR 95% CI should be > 1 to indicate a suspicious signal. The stronger the ADR signal, the stronger the correlation between the drug and the ADR.

Results

ADE overview

Of the 4796 ADE reports included, 4787 included the source region; among these, 1298 reports (27%) were from the United States and remaining were from Japan (539 cases), France (413 cases), Spain (387 cases), and China

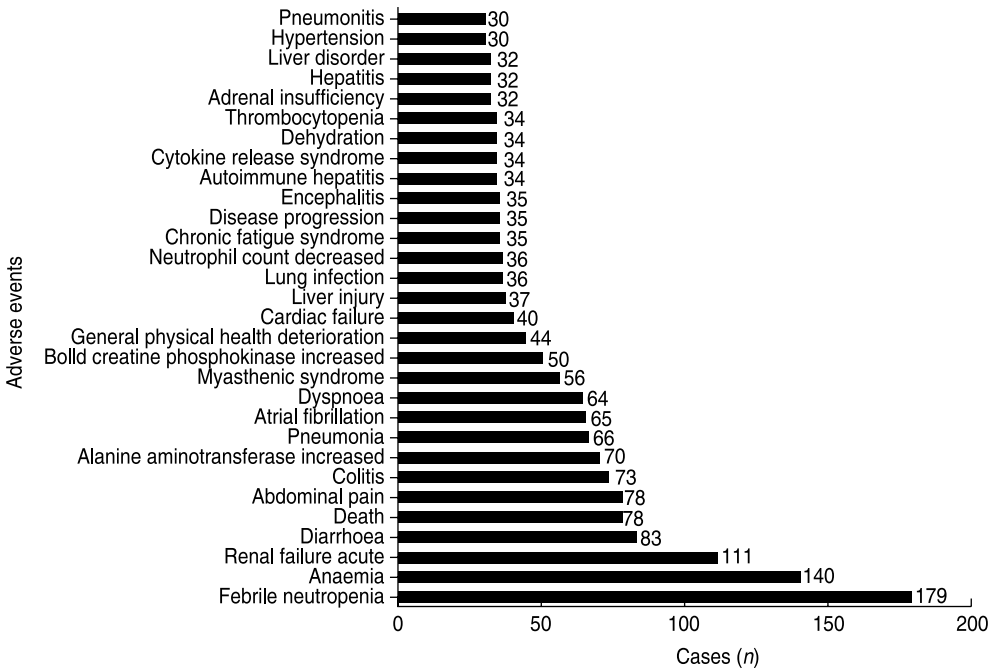

Fig. 2 The top 20 ADEs associated with atezolizumab use

(309 cases). The vast majority of reports (approximately 70%) were from economically developed Western countries, whereas the remaining reports were mainly from Southeast Asia, followed by South America. No reports were obtained from Africa and the Middle East. This difference in the source of ADE reports might be attributed to differences in the frequency of atezolizumab use and the development of the ADE reporting systems in different regions.

In 2017, the number of reported ADEs of atezolizumab in the four quarters was 322, 320, 244, and 299, respectively; in 2018, there were 344, 389, 447, and 501 reports, respectively; and in 2019, there were 465, 435, 447, and 583 reports, respectively. Therefore, the annual atezolizumab ADEs reported in the FAERS database showed a year-on-year upward trend from 2017 to 2019, whereas the quarterly distribution was more uniform. However, potential differences in the quarterly distribution of ADE reports require further investigation.

Among the 4796 ADE reports, sex was effectively recorded in 4702 reports (98%), including 2597 males (55.23%) and 2123 females (45.15%). In addition, age was recorded in 4601 reports (95%) and could be divided into four groups: 8 cases < 18-years old, 532 cases between 18- and 50-years old (including 18-years old), 1761 cases between 50- and 65-years old (including 50-years old), and 2300 cases ≥ 65-years old, indicating that most of the reported atezolizumab ADEs occurred in patients aged more than 50-years old. However, this did not necessarily imply that men or individuals aged more than 50-years old are more likely to have ADRs related to atezolizumab use because the incidence of atezolizumab use might differ according to sex and age, in addition to the presence of other potential confounding factors.

Reporting frequency of the major atezolizumab ADEs

The reporting frequency of ADEs can reveal the incidence rate of ADRs and reflect the impact of ADRs on the patients' health, thus indicating the key direction for risk management [2]. In this study, 4796 cases of ADEs related to atezolizumab use were analyzed. Based on the number of ADEs, the top 20 reported ADEs included febrile neutropenia (179 cases), anemia (140 cases), acute renal failure (111 cases), diarrhea (83 cases), death (78 cases), colitis (73 cases), and elevated alanine aminotransferase (70 cases; Fig. 2). Notably, 51 cases of skin-related ADRs with similar nature but different names, including rash, dermatitis, eczema, and empyema, were reported.

In addition, we used the unique identification codes of ADEs, the number of ADEs, sex, age, country and region, indications, adverse reaction outcomes, and other indicators to exclude data that might be reported by the same person at different times; however, very few records of ADEs reported by the same person to the FAERS database could not be excluded because some individuals might have used atezolizumab at different ages. Accordingly, 4023 cases of atezolizumab-related ADEs were included in this analysis and divided into three age groups: 532 reports between 18- and 50-years old (including 18-years old), 1761 cases between 50- and

Table 2 Differences in the incidence rate of the top 20 ADEs by sex

ADE	Sig	*P* value	Indication*
Febrile neutropenia	7.433	0.006	F > M
Anaemia	4.195	0.041	M > F
Renal failure acute	3.135	0.077	
Diarrhoea	0.982	0.322	
Death	0.108	0.743	
Abdominal pain	0.332	0.564	
Colitis	0.008	0.928	
Alanine aminotransferase increased	3.018	0.082	
Pneumonia	1.533	0.216	
Atrial fibrillation	4.456	0.035	M > F
Dyspnoea	0.013	0.910	
Myasthenic syndrome	1.266	0.261	
Blood creatine phosphokinase increased	2.655	0.103	
General physical health deterioration	0.509	0.476	
Cardiac failure	0.840	0.359	
Liver injury	0.587	0.443	
Lung infection	2.478	0.115	
Neutrophil count decreased	14.476	0.000	F > M
Chronic fatigue syndrome	11.811	0.001	F > M
Disease progression	9.334	0.002	M > F
Encephalitis	2.619	0.106	
Autoimmune hepatitis	0.016	0.901	
Cytokine release syndrome	2.064	0.151	
Dehydration	1.531	0.216	
Thrombocytopenia	8.004	0.005	F > M
Adrenal insufficiency	0.444	0.505	
Hepatitis	0.424	0.515	
Liver disorder	0.210	0.647	
Hypertension	5.386	0.020	F > M
Pneumonitis	0.959	0.327	

Notes: Chi-squared test cross-table composition of sex differences: if the number of adverse drug events in males is χ_1 and that in females is χ_2, the positive number of adverse drug events in males in the cross table is χ_1, and the negative number is total – χ_1; the positive number of adverse reaction events in females is χ_2, and the negative number is total – χ_2. *, F > M indicates that the incidence of the ADE in females is higher than that in males, and M > F indicates that the incidence of the ADE in males is higher than that in females

Table 3 Differences in the incidence rate of the top 20 ADEs by age

PT	Sig	*P* value	Significant difference*
Febrile neutropenia	12.904	0.002	y
Anaemia	2.318	0.314	n
Renal failure acute	6.232	0.044	y
Diarrhoea	2.260	0.323	n
Death	6.142	0.046	y
Abdominal pain	2.253	0.324	n
Colitis	0.879	0.645	n
Alanine aminotransferase increased	0.265	0.876	n
Pneumonia	0.211	0.900	n
Atrial fibrillation	11.947	0.003	y
Dyspnoea	1.146	0.564	n
Myasthenic syndrome	6.862	0.032	y
Blood creatine phosphokinase increased	3.806	0.149	n
General physical health deterioration	1.518	0.468	n
Cardiac failure	8.599	0.014	y
Liver injury	14.324	0.001	y
Lung infection	1.769	0.413	n
Neutrophil count decreased	6.166	0.046	y
Chronic fatigue syndrome	5.508	0.064	n
Disease progression	3.469	0.176	n
Encephalitis	0.620	0.734	n
Autoimmune hepatitis	0.206	0.902	n
Cytokine release syndrome	10.985	0.004	y
Dehydration	15.047	0.001	y
Thrombocytopenia	2.471	0.291	n
Adrenal insufficiency	4.333	0.115	n
Hepatitis	5.850	0.054	n
Liver disorder	4.357	0.113	n
Hypertension	1.088	0.580	n
Pneumonitis	4.488	0.106	n

Notes: Chi-square test cross-table composition of age differences: if the number of ADEs in the 18–49 age group is χ_1, the number of ADEs in the 50–64 age group is χ_2, and the number of ADEs in the ≥ 65 age group is χ_3, the positive number of ADE in the 18–49 age group in the cross table is χ_1, the negative number is 4023 – χ_1; the positive number of ADEs in the 50–64 age group is χ_2, the negative number is 4023 – χ_2; the positive number of ADEs in the ≥ 65 age group is χ_3, and the negative number is 4023 – χ_3. *, y indicates that the occurrence of an adverse reaction in each age group is statistically significant. If the difference is significant, the probability of an ADE in the three age groups is not equal

65-years old (including 50-years old), and 2300 cases ≥ 65-years old. The difference in the incidence of ADEs according to different ages and sex was analyzed using chi-squared test (Tables 2 and 3).

In addition, chi-squared test was performed using the three age groups for each ADE and showed significant differences among different age groups (Table 4).

Involved organs and systems

The MedDRA is a multi-axial, five-tiered hierarchical terminology used by regulatory authorities and biopharmaceutical industry for the coding (classification) of clinical data in ADE/ADR reports. Therefore, it has become an international standard terminology for ADR reports [5]. According to the MedDRA terms, a total of 4796 atezolizumab ADEs were recorded and classified using the ADE Preferred Terminology (PT) and Systematic Organ Classification (SOC) codes. The details of the ADEs of each SOC that contained PT > 100 are shown in Fig. 3 and Table 5 (the percentage base of "proportion" in Table 5 is 4796 ADEs). The number of "product usage problems" and "incorrect product management approaches" was 9. There was no relevant description in the MedDRA, which might be because of terminology changes due to the MedDRA biannual updates [2, 6]. The ROR method was used to detect the signal strength of ADEs, and five ADEs with strong ADR signals were selected from the top ten

Table 4 Incidence rate of each ADE in the three age groups

ADE	18–49 and 50–64 years			18–49 and > 64 years			50–64 and > 64 years		
	Sig	*P* value	Indication	Sig	*P* value	Indication	Sig	*P* value	Indication
Febrile neutropenia	12.173	0.000	18–49 > 50–64	8.366	0.004	18–49 > 64	0.662	0.416	n
Renal failure acute	0.695	0.405	n	3.857	0.050	64 > 18–49	3.684	0.055	n
Atrial fibrillation	1.563	0.120	n	6.253	0.012	64 > 18–49	6.140	0.013	64 > 50–64
Myasthenic syndrome	0.962	0.327	n	3.581	0.058	n	2.702	0.100	n
Death	2.879	0.090	n	3.832	0.050	64 > 18–49	3.832	0.050	64 > 18–49
Cardiac failure		0.017	50–64 > 18–49		0.018	64 > 18–49	0.006	0.940	n
Liver injury	4.351	0.037	18–49 > 50–64	15.329	0.000	18–49 > 64	4.006	0.045	50–64 > 64
Neutrophil count decreased	1.434	0.231	n	6.397	0.011	18–49 > 64	2.410	0.121	n
Cytokine release syndrome	2.979	0.084	n	11.854	0.001	18–49 > 64	3.584	0.058	n
Dehydration		0.356	n		0.007	64 > 18–49	7.090	0.008	64 > 50–64

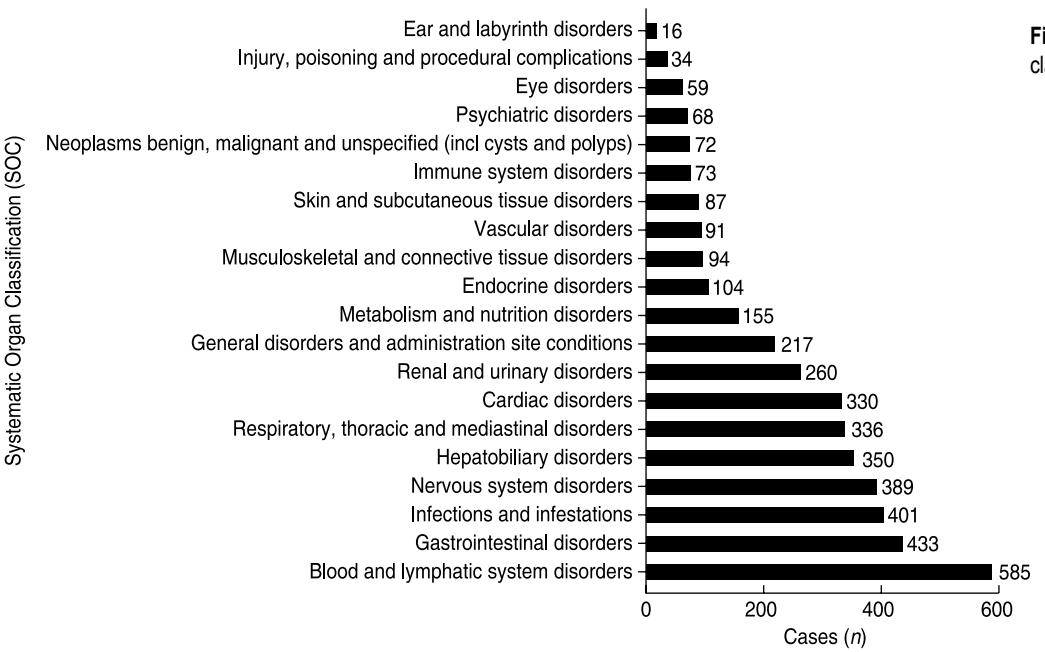

Fig. 3 The systematic organ classification (SOC) of ADEs

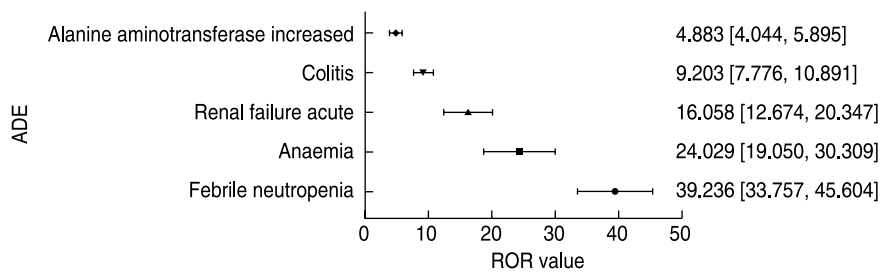

Fig. 4 ADE signal detection value (ROR, 95% CI). Notes: Data on the right side of the graph show the ROR values with 95% CI of each ADR

ADEs: febrile neutropenia, anemia, renal failure acute, colitis, and elevated alanine aminotransferase (Fig. 4).

IrAEs-related complications

There have been some reports of atezolizumab-related autoimmune pancreatitis and hepatitis. Although these adverse reactions are uncommon, they pose a great threat to the patient life. Therefore, we extracted the immune-related ADE (irAE)-related complications from the 4796 reports of ADRs. We found that the incidence of irAE-related complications was low. In particular, a total of 121 cases of 14 irAEs-related complications were reported (Fig. 5). In addition, there were several ADEs that might indicate irAEs-related complications, including nine cases of amylase increase that might indicate pancreatitis and three cases of hepatitis.

Table 5 The major ADEs of each SOC

SOC	Number of cases/proportion	Cases (*n*)
Blood and lymphatic system disorders	585/12.2%	Febrile neutropenia (178), Anaemia (140), Thrombocytopenia (34), Neutrophil count decreased (34)
Gastrointestinal disorders	433/9.0%	Diarrhoea (83), Colitis (73), Ascites (27)
Infections and infestations	401/8.4%	Pneumonia (66), Lung infection (36), Bronchitis (21), Sepsis(20)
Nervous system disorders	389/8.1%	Myasthenic syndrome (56), Encephalitis (35), Syncope (21), Cerebral infarction (20)
Hepatobiliary disorders	350/7.3%	Alanine aminotransferase increased (70), Liver injury (37), Autoimmune hepatitis (34), Hepatitis (32), Liver disorder (32), Hyperbilirubinaemia (19)
Cardiac disorders	330/6.9%	Atrial fibrillation (65), Cardiac failure (40), Myocarditis (21), Pericardial effusion (20), Acute myocardial infarction (20)
Respiratory, thoracic and mediastinal disorders	336/7.0%	Dyspnoea (64), Pneumonitis (30), Respiratory failure (28), Interstitial lung disease (25), Haemoptysis (24)
Renal and urinary disorders	260/6.2%	Renal failure acute (111), Nephritis (24), Glomerulonephritis acute (24), Tubulointerstitial nephritis (17), Renal impairment (17), Renal failure (17)
General disorders and administration site conditions	217/5.4%	Death (78), General physical health deterioration (44), Chronic fatigue syndrome (35), Immediate post-injection reaction (27)
Metabolism and nutrition disorders	155/3.2%	Dehydration (34), Hyponatraemia (25), Hypercalcaemia (17), Hyperglycaemia (13), Diabetes mellitus (10)
Endocrine disorders	104/2.2%	Adrenal insufficiency (32), Hypothyroidism (17), Hyperthyroidism (14)

Discussion

Atezolizumab has been previously shown to exhibit acceptable and controllable tolerance. Therefore, it is a valuable treatment option for patients with NSCLC, melanoma, urological tumors, and breast cancer who progress during or after chemotherapy [7–10].

As an immune checkpoint inhibitor (ICI), atezolizumab (anti-PD-L1) may subsequently lead to various autoimmune manifestations with a specific clinical spectrum called irAEs [11]. These effects result from an overall immune enhancement, and thus, they may affect any body system; however, they mainly involve the skin, colon, lungs, endocrine glands, and liver [12] and are related to the tumor types [13]. Some rare complications, such as atezolizumab-induced photo-distributed bullous pemphigoid [14], atezolizumab-related encephalitis [15], and ileal perforation secondary to atezolizumab enterocolitis [16], were also investigated in this study.

Previous studies have shown that approximately 66% of the patients treated with anti-PD-L1 or PD-L1 antibodies experience at least one ADR, whereas approximately 14% of the patients have severe ADRs. The incidence of these ADRs was not significantly different among different types of tumors [17]. In addition, the occurrence of ADRs did not affect the efficacy of treatment [18]. In a meta-analysis of clinical trials including 8730 patients [19], atezolizumab had the lowest risk of IrAEs. In addition, there was no significant difference in the risk associated with atezolizumab and avelumab. Based on the literature and reports in the FAERS database, the clinical manifestations of common ADEs of ICIs (such as navumab and pamumab) were relatively consistent and mainly concentrated in the gastrointestinal tract, skin, and respiratory system, including diarrhea, heart attack, vomiting, colitis, rash, dyspnea, and pneumonia. These reported ADEs might be considered ICI-induced IrEAs.

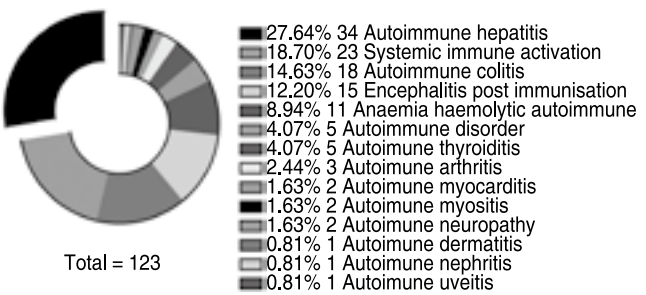

Fig. 5 irAEs-related complications of atezolizumab

Conclusion

The ADRs of atezolizumab reported in the FAERS database were consistent with those mentioned in the instructions for its use. This study suggested that physicians need to be more cautious when using atezolizumab clinically. Individuals eligible for atezolizumab treatment should be screened for a personalized treatment, thus promoting the importance of precision medicine.

Compared with cytotoxic T-lymphocyte-associated protein 4-blocking agents, PD-1/PD-L1 inhibitors are generally considered to have minor side effects [20]. However, during the course of PD-1/PD-L1 inhibitor treatment, the use of glucocorticoids to treat irAEs can result in opportunistic infections owing to temporary immunosuppression [21]. In addition, there are currently reported cases of latent/chronic infection reactivation

without irAEs during treatment with PD-1/PD-L1 inhibitors [22]. Therefore, it is necessary to fully evaluate the risks that patients with irAEs may be subject to. It should be considered that the irAEs-related complications can reduce the clinical benefit [23]. Moreover, some ADEs might occur after treatment; therefore, it is important to provide a timely treatment to reduce the risk of ADEs. In addition, some reported ADEs of ICIs might be specific to some ICIs.

At present, further studies are needed to investigate other aspects of the irAEs, including their mechanism, population characteristics, and effect on tumor treatment, as well as whether immunosuppressive therapy might affect tumor treatment efficacy. It has been suggested that cross-antigens, non-specific immune activation, and T cell diversification contribute to the pathogenesis of irAEs [24]. However, there are no prospective studies to support this hypothesis. In addition, it is essential to identify the factors related to irAEs clearly and thus help improve the screening of susceptible patients, thereby reducing the risk of ADRs. Large-scale, multi-center, randomized controlled studies should be encouraged to determine the best medication plan for immunotherapy drugs and provide a basis for the safe and reasonable medication use.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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