Observational Study

Medicine

OPEN

The association of hypophysitis with immune checkpoint inhibitors use

Gaining insight through the FDA pharmacovigilance database

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Abstract

The use of immune checkpoint inhibitor (ICI) marked a revolutionary change in cancer treatment and opened new avenues for cancer therapy, but ICI can also trigger immune-related adverse events (irAEs). Here, we investigated the publicly available US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database to gain insight into the possible association between immune checkpoint inhibitors and hypophysitis. Data on adverse events (AEs) due to hypophysitisfor nivolumab, pembrolizumab, ipilimumab, and atezolizumab were collected from the US FDA Adverse Event Reporting System from the first quarter of 2004 to the second quarter of 2021, and the signals for hypophysitis associated with the four drugs were examined using the reporting odds ratio (ROR) method. The number of reported hypophysitis events ≥ 3 and the lower limit of the 95% confidence interval (CI) of the ROR > 1 were considered positive for hypophysitis signals. A total of 1252 AE reports of hypophysitis associated with nivolumab, pembrolizumab, ipilimumab, and atezolizumab were collected, including 419, 149, 643, and 41 cases, respectively. The RORs of hypophysitis were 289.58 (95% CI 258.49–324.40), 171.74 (95% CI 144.91–203.54), 2248.57 (95% CI 2025.31–2496.45), and 97.29 (95% CI 71.28–132.79), respectively. All four drugs were statistically correlated with the target AE, with the correlation being, in descending order, ipilimumab, nivolumab, pembrolizumab, and atezolizumab. Nivolumab, pembrolizumab, ipilimumab, and atezolizumab have all been associated with hypophysitis, which can negatively impact quality of life, and early recognition and management of immune checkpoint inhibitor-related hypophysitis is critical.

Abbreviations: AEs = adverse events, CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte antigen 4, FAERS = FDA Adverse Event Reporting System, FDA = Food and Drug Administration, ICI = immune checkpoint inhibitor, irAEs = immune-related adverse events, PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1, PT = preferred term, ROR = reporting odds ratio.

Keywords: adverse events, FDA adverse event reporting system, hypophysitis, immune checkpoint inhibitors, signal processing

1. Introduction

Since their first Food and Drug Administration (FDA) approval in 2011, immune checkpoint inhibitors (ICIs) have rapidly become an integral part of several cancer treatment options.[1,2] By inhibiting the negative regulators of T-cell activation, it can start anti-tumor immune responses and significantly affect how well tumors are removed.[3,4] Immune checkpoint inhibitors include antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death 1 receptor (PD-1) and anti-programmed cell death ligand 1 (PD-L1).[5] These monoclonal antibodies (MAB) combat cancer by break immune checkpoints and release T cells. Immune checkpoints, however, are crucial for preserving immunological self-tolerance and preventing autoimmune disease, so ICIs can trigger autoimmune adverse reactions, called immune-related adverse events (irAEs).[6] Unlike toxicity induced by cytotoxic or molecularly targeted drugs, the onset of toxicity may be delayed rather than following a cyclic pattern as with traditional cytotoxic drugs, it is yet unknown how toxicity works, and even with the same medicine, toxicity in different patients may vary.[7] Immune-related endocrine diseases are one of the major irAEs, including hypophysitis, hypothyroidism, hyperthyroidism, primary adrenal insufficiency and autoimmune diabetes mellitus.[8] The pituitary is one of the main targets of ICI-induced irAEs,

This research was supported by Jining City Science and Technology Bureau key research and development plan (2020YXNS011)

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

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How to cite this article: Tang Q, Han Y, Song M, Peng J, Zhang M, Ren X, Sun H. The association of hypophysitis with immune checkpoint inhibitors use: Gaining insight through the FDA pharmacovigilance database. Medicine 2024;103:13(e37587).

Received: 24 October 2023 / Received in final form: 2 January 2024 / Accepted: 22 February 2024

http://dx.doi.org/10.1097/MD.0000000000037587

and ICI-related hypophysitis can trigger pituitary dysfunction, which may result in a worse quality of life for patients with advanced cancer and may be life-threatening in severe cases. Therefore, early diagnosis of hypophysitis and initiation of appropriate treatment are crucial.[9]

As a publicly available database of spontaneous adverse event reports submitted to the FDA by healthcare professionals, consumers and manufacturers, the FDA Adverse Event Reporting System (FAERS) database enables early detection of safety signals, prompt characterization of safety profiles that necessitate reevaluation of risks and benefits, and interim drug-to-drug comparisons between drugs in the same therapeutic class.[10] To this end, with nivolumab, pembrolizumab, ipilimumab, and atezolizumab serving as the target drugs, we analyzed the relationship between these drugs and adverse events in hypophysitis (including lymphocytic hypophysitis), using relevant data from the FAERS database.

2. Materials and methods

2.1. Data Sources

Retrieve the FAERS database, download all data from the first quarter of 2004 to the second quarter of 2021 (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html), build the local database using Postgresql database, apply Python for natural language processing, and data cleaning and normalization. Eliminate reports with names of food, medical devices, cosmetics and uncertain names, and screen drug-related AE reports. The standard nomenclature of clinical drugs (RxNorm) (https://lhncbc.nlm.nih.gov/MOR/RxTerms/) was used to standardize the names of drugs in the local database, and the anatomical therapeutic chemical (ATC) classification system of the WHO drug dictionary was used to classify the drugs in the local database so that different varieties of the same class of drugs could be retrieved. The target drugs were nivolumab, pembrolizumab, ipilimumab, and atezolizumab, which were classified as "immune checkpoint inhibitors" by the ATC drug classification, and the AE reports with the target drug as the primary suspect (PS) or secondary suspect (SS) were screened. The preferred term (PT) in the International Medical Dictionary for Regulatory Activities (MedDRA) v24.0 (https://www.meddra.org/) was used to standardize AEs and drug indications, with hypophysitis and lymphocytic hypophysitis as target AEs, and the AE reports of PT for hypophysitis and lymphocytic hypophysitis were screened from the 4 target drug-related AE reports. A self-designed Excel data extraction form was applied to record recorded data (available data) on patient age, gender, clinical outcome (resulting in hospitalization or prolonged hospitalization, disability, life-threatening, death, and other serious AEs), reporter occupation, reporting country, year of reporting, and time of AE occurrence for statistical analysis.

2.2. Analysis of risk signals for immunosuppression-related hypophysitis

Based on the disproportionality analysis, the target AE signal was calculated using the reporting odds ratio (ROR) method, and the ROR and 95% CI values were calculated based on a four-grid table of ratio imbalance measures (Table 1), the calculation formula going as follows

$$\mathrm{ROR} = \mathrm{ad}/\mathrm{c}/\mathrm{b}$$

$$95\%\ \mathrm{CI} = \mathrm{e}^{\ln(\mathrm{ROR})\ \pm\ 1.96(1/\mathrm{a}+1/\mathrm{b}+1/\mathrm{c}+1/\mathrm{d})\ \hat{}\ 0.5}$$

2.3. Statistical analysis

R language was used for data processing and analysis. Those that did not follow a normal distribution were represented as M (Q1, Q3), and count information was expressed as frequency (%). Assessment of the correlation between the target drug and the target AE using the ROR method, and the ROR was calculated using a two-by-two columnar table of the counts of reported events for the specific drug and other drugs. When using the full database as a control, imbalance can be calculated from the reported ROR when comparing different drug strategies. For ROR, if the lower limit of the 95% confidence interval (ROR_{025}) exceeds 1 and the number of reports is at least 3 cases, the target drug is statistically correlated with the target AE.[11] A larger ROR represents a stronger correlation between the drug and AE.

3. Results

3.1. Basic information for AE reports of the four immune checkpoint inhibitors-related hypophysitis

Using FAERS data to establish a local database, a total of 33007665 AE reports were obtained, and 224053 AE reports were screened for 4 drugs as PS or SS, including 1252 AE reports for PT as hypophysitis and lymphocytic hypophysitis. 419, 149, 643, and 41 AEs associated with nivolumab, pembrolizumab, ipilimumab, and atezolizumab were reported, respectively. Table 2 describes the basic information of the four immune checkpoint inhibitors-related hypophysitis reports. Data available by patient age show that hypophysitis caused by nivolumab, ipilimumab, and atezolizumab occurs more often in people aged 45 to 65 years, and hypophysitis caused by pembrolizumab occurs more often in people aged 65 to 80 years. A higher proportion of males than females were found in patients with all four drug-associated hypophysitis. Hypophysitis caused by nivolumab, ipilimumab, and atezolizumab was reported predominantly by physicians, while pembrolizumab was reported by the highest proportion of consumers. Among the clinical outcomes of AEs associated with nivolumab, pembrolizumab, ipilimumab, and atezolizumab, the number of hospitalizations or prolonged hospital stays was 265 (63.25%), 88 (59.06%), 298 (46.36%), and 16 (41.03%) times, respectively, and the number of cases resulting in death was 30 (7.16%), 10 (6.71%), and 31 (4.82%), and 5 (12.82%) cases. 28.64%, 28.86%, 56.45%, and 25.64% respectively were reported by the United States. The number of reported cases per year for nivolumab, pembrolizumab, and ipilimumab showed an upward and then downward trend from launch to the second quarter of 2021, while the trend for atezolizumab has been on the rise.

The time from initiation of nivolumab, pembrolizumab, ipilimumab, and atezolizumab to the onset of hypophysitis ranged from 1 to 1196, 1 to 975, 1 to 1065, and 1 to 726 d, respectively, with median onset times of 63, 84.5, 50, and 141.5 d, respectively (Table 3).

3.2. The signal analysis of the four immune checkpoint inhibitors-related hypophysitis

The number of hypophysitis associated with nivolumab, pembrolizumab, ipilimumab, and atezolizumab reported were 419,

Table 1

Ratio imbalance measurement method 4-compartment table.

Drug	Number of target AE reports	Number of non-target AE reports	Total
Immune checkpoint inhibitors	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

AE = adverse events; target AE: hypophysitis (including lymphocytic hypophysitis); non-target AE: all AEs except target AE; Immune checkpoint inhibitors: nivolumab, pembrolizumab, ipilimumab, atezolizumab.

Table 2

The basic information of the four immune checkpoint inhibitors-related hypophysitis reports.

Basic parameters analysis	Nivolumab n = 419	Pembrolizumab n = 149	Ipilimumab n = 643	Atezolizumab n = 39‡
Age group				
Adult	34 (8.11)	12 (8.05)	45 (7.00)	1 (2.56)
Middle aged	148 (35.32)	41 (27.52)	225 (34.99)	12 (30.77)
Aged	136 (32.46)	52 (34.90)	161 (25.04)	9 (23.08)
Aged, 80 and over	22 (5.25)	12 (8.05)	23 (3.58)	NA
Missing	79 (18.85)	32 (21.48)	189 (29.39)	17 (43.59)
Gender				
M	227 (54.18)	81 (54.36)	312 (48.52)	12 (30.77)
F	149 (35.56)	54 (36.24)	189 (29.39)	8 (20.51)
Missing	43 (10.26)	14 (9.40)	142 (22.08)	19 (48.72)
Reporter				
Physician	171 (40.81)	49 (32.89)	238 (37.01)	20 (51.28)
Pharmacist	10 (2.39)	4 (2.68)	15 (2.33)	1 (2.56)
Other health-professional	127 (30.31)	26 (17.45)	223 (34.68)	4 (10.26)
Consumer	40 (9.55)	54 (36.24)	119 (18.51)	1 (2.56)
Lawyer	2 (0.48)	NA	NA	NA
Missing	69 (16.47)	16 (10.74)	48 (7.47)	13 (33.33)
Outcome*				
Hospitalization – initial or prolonged	265 (63.25)	88 (59.06)	298 (46.36)	16 (41.03)
Disability	9 (2.15)	9 (6.04)	13 (2.02)	NA
Life-threatening	48 (11.46)	12 (8.05)	36 (5.60)	NA
Death	30 (7.16)	10 (6.71)	31 (4.82)	5 (12.82)
Other important medical events	319 (76.13)	87 (58.39)	400 (62.21)	23 (58.97)
Country				
United States of America	120 (28.64)	43 (28.86)	363 (56.45)	10 (25.64)
Japan	66 (15.75)	27 (18.12)	64 (9.95)	8 (20.51)
France, French Republic	51 (12.17)	15 (10.07)	37 (5.75)	3 (7.69)
United Kingdom of Great Britain & Northern Ireland	9 (2.15)	3 (2.01)	15 (2.33)	1 (2.56)
Canada	5 (1.19)	1 (0.67)	3 (0.47)	NA
Germany, Federal Republic of	61 (14.56)	16 (10.74)	52 (8.09)	3 (7.69)
Australia, Commonwealth of	22 (5.25)	4 (2.68)	28 (4.35)	NA
China, People's Republic of	1 (0.24)	4 (2.68)	NA	3 (7.69)
Other countries	84 (20.05)	35 (23.49)	80 (12.44)	11 (28.21)
Missing	NA	1 (0.67)	1 (0.16)	NA
Reporting year				
2011			23 (3.58)	
2012	1 (0.24)		39 (6.07)	
2013	3 (0.72)		30 (4.67)	
2014	15 (3.58)	7 (4.70)	37 (5.75)	
2015	13 (3.10)	17 (11.41)	74 (11.51)	1 (2.56)
2016	45 (10.74)	15 (10.07)	81 (12.60)	2 (5.13)
2017	75 (17.90)	19 (12.75)	75 (11.66)	5 (12.82)
2018	90 (21.48)	34 (22.82)	179 (27.84)	1 (2.56)
2019	91 (21.72)	32 (21.48)	48 (7.47)	8 (20.51)
2020	59 (14.08)	15 (10.07)	28 (4.35)	8 (20.51)
2021†	27 (6.44)	10 (6.71)	19 (2.95)	14 (35.90)
Indication				
Malignant melanoma	155 (36.99)	25 (16.78)	342 (53.19)	4 (10.26)
Metastatic malignant melanoma	65 (15.51)	29 (19.46)	154 (23.95)	2 (5.13)
Non-small cell lung cancer	38 (9.07)	23 (15.44)	7 (1.09)	10 (25.64)
Lung adenocarcinoma	5 (1.19)	3 (2.01)	NA	2 (5.13)
Renal cell carcinoma	22 (5.25)	NA	25 (3.89)	2 (5.13)
Other indications	112 (26.73)	55 (36.91)	73 (11.35)	18 (46.15)
Missing	22 (5.25)	14 (9.40)	42 (6.53)	1 (2.56)

*1 AE may have multiple outcomes.

†Data for quarters 1 and 2; NA: data not available in the database.

‡Because there were only 2 cases of atezolizumab-induced lymphocytic hypophysitis, relevant data were not extracted from this study.

149, 643, and 41 cases, respectively, with RORs of 289.58 (95% CI 258.49–324.40), 171.74 (95% CI 144.91–203.54), 2248.57 (95% CI 2025.31–2496.45), and 97.29 (95% CI 71.28–132.79) for hypophysitis, respectively. All four drugs showed a statistically association with the hypophysitis, with the correlations being ipilimumab, nivolumab, pembrolizumab, and atezolizumab, in decreasing order (Table 4).

4. Discussion

The results of this study showed that nivolumab, pembrolizumab, ipilimumab, and atezolizumab were all associated with hypophysitis, with ipilimumab having the strongest correlation. Prior studies have demonstrated that CTLA-4 inhibitors have a higher prevalence of hypophysitis than PD-1/PD-L1 inhibitors.[12] The incidence of hypophysitis associated with pembrolizumab and nivolumab was reported to be less than 1%, while the incidence of hypophysitis associated with ipilimumab ranged from 0% to 17%.[13] A significant dose-dependent relationship has been reported for hypophysitis associated with ipilimumab, with a higher incidence of hypophysitis in patients treated with higher doses of ipilimumab (10 mg/kg) compared to those treated with lower doses (3 mg/kg), with an approximately 2-fold increased risk.[14,15] These different types of drugs have different mechanisms of action; CTLA-4 is a surface receptor protein that inhibits T-cell proliferation during the early stages of the immune response to malignant tumors, whereas PD-1 and PD-L1 work downstream of the pathway that prevents T-cells from activating and functioning normally in peripheral tissues.[16]

There is a higher incidence of typical autoimmune lymphocytic hypophysitis among women, while immune checkpoint inhibitor-related hypophysitis is more prevalent in men.[17] Ryder reported a male to female incidence ratio of approximately 1.4:1.[18] The male to female prevalence ratio in this study was approximately 1.7:1, which is higher than previously reported. Previous research has suggested that the higher incidence of melanoma in men than in women and the frequent use of ICIs therapy, particularly ipilimumab, may be the cause of the male predominance in immune checkpoint inhibitor-associated hypophysitis; however, even after accounting for ICIs, the incidence of immune checkpoint inhibitor-associated hypophysitis still appears to be higher in men.[6] The data available by patient age showed that the age of onset of immune checkpoint inhibitor-related hypophysitis was mostly after 45 years of age, which is consistent with Mikami's report that the mean age of PD-1, PD-L1, and CTLA-4 inhibitor-related hypophysitis was 64.4, 63.4, and 58.7 years, respectively.[10] Hypophysitis occurred at 2 to 3 months with CTLA-4 inhibitors and was prone to occur at 3 to 5 months with PD-1/PD-L1 inhibitor therapy.[19] The Dillard study showed that the median time to onset of hypophysitis associated with ipilimumab was 11 weeks,[20] but previous studies have found onset reported as early as 4 weeks after initiation of treatment.[21] The median time to onset of pembrolizumab and nivolumab-related hypophysitis was similar, at 10 and 11 weeks, respectively.[1] In this study, the median time to occur was, from shortest to longest, ipilimumab, nivolumab, pembrolizumab, and atezolizumab.

The tendency for the number of AE reports to peak and then decline in the face of steadily increasing drug prescriptions is known as the "Weber effect,"[22] the phenomenon of increased reporting of AEs due to attention is known as the "notoriety bias," and the phenomenon of increased reporting of the same AEs for the same drug is known as the "ripple effect."[23,24] The results of this study show that since FDA approval in 2014, there has been an upward and then downward trend for nivolumab, consistent with the "Weber effect." Pembrolizumab and ipilimumab were approved by the FDA in 2014 and 2011, respectively, and the number of reported cases has trended up, then

Table 3

Time to onset of four immune checkpoint inhibitors-related hypophysitis.

	Distribution of time between initiation of ICI and onset of hypophysitis [case (%)]							
Immune checkpoint inhibitors	**≤30 d**	**31–90 d**	**91–180 d**	**181–270 d**	**271–360 d**	**361–720 d**	**721–1800 d**	**Median time to occur [d, M (Q_1, Q_3)]**
Nivolumab	89 (28.62)	101 (32.48)	66 (21.22)	25 (8.04)	14 (4.50)	12 (3.86)	4 (1.29)	63 (21, 130.5)
Pembrolizumab	23 (31.94)	16 (22.22)	17 (23.61)	7 (9.72)	6 (8.33)	2 (2.78)	1 (1.39)	84.5 (19.25, 169.75)
Ipilimumab	82 (27.61)	171 (57.58)	32 (10.77)	5 (1.68)	2 (0.67)	2 (0.67)	3 (1.01)	50 (24, 70)
Atezolizumab	2 (11.11)	3 (16.67)	5 (27.78)	6 (33.33)	0 (0)	1 (5.56)	1 (5.56)	141.5 (91.25, 230.75)

The data in the table were obtained from the US FAERS database for the period from the first quarter of 2004 to the second quarter of 2021; the shortest time between the start nivolumab drug use and the onset of hypophysitis was 1 d and the longest time was 1196 d.

Table 4

Correlation of adverse events in hypophysitis with the four immune checkpoint inhibitors.

Immune checkpoint inhibitor	Case	Non-case	ROR	ROR_{025}	ROR_{975}
Nivolumab	419	114284	289.58	258.49	324.40
Pembrolizumab	149	57928	171.74	144.91	203.54
Ipilimumab	643	28420	2248.57	2025.31	2496.45
Atezolizumab	41	22169	97.29	71.28	132.79

Case: number of cases of hypophysitis; Non-case: number of cases of non-hypophysitis; ROR: reporting odds ratio; ROR_{025}: lower limit of the ROR 95% confidence interval; ROR_{975}: upper limit of the ROR 95% confidence interval.

down, then up and down again. Atezolizumab has shown an upward, then downward, then upward trend since it received FDA approval in 2016.

Immune checkpoint inhibitor-related hypophysitis is a secondary pituitary inflammation that can trigger pituitary dysfunction, usually resulting in a deficiency of one or more hormones produced by the anterior pituitary gland, such as central hypothyroidism, central adrenal insufficiency, and hypogonadotropic hypogonadism.[16,25] However, diabetes insipidus due to posterior pituitary hormone dysfunction is rare, and therefore it is considered that the main site of pituitary-related adverse events is the anterior pituitary rather than the posterior pituitary.[26] Symptoms and signs of immune checkpoint inhibitor-related hypophysitis are nonspecific, with headache, fatigue, and weight loss being common.[6,27] Visual disturbances and polyuria and polydipsia are less common.[28] Pituitary MRI is a sensitive imaging method. More than 30% of patients can demonstrate a moderately enlarged pituitary gland with a convex shape, which is significantly enhanced and partially inhomogeneous, sometimes accompanied by thickening of the pituitary stalk.[6,19] Pituitary imaging changes can precede clinical and biochemical evidence of pituitary inflammation.[29] However, a normal MRI may not entirely rule out the diagnosis of hypophysitis. Its treatment includes replacement therapy depending on the hormone deficiency, as well as symptomatic supportive therapy.[30] Endocrinologists and oncologists should be familiar with the clinical signs of ICI-related endocrine disorders because endocrine irAEs can lead to serious consequences.[1] As ICI is increasingly used in cancer treatment, multidisciplinary cooperation is essential to improve prognoses.[31,32]

Both baseline autoantibody and new autoantibody production during ICI therapy may predict the development of endocrine immune-related adverse events, particularly the presence of TPO-Ab which is a marker of primary thyroid disease. A prospective study showed that,[33] in the 14 patients who had at least one endocrine-related antibody detected at baseline or during follow-up, 12 (85.7%) experienced adverse events related to the endocrine system. In contrast, endocrine adverse event occurred in only 2 (4.3%) of the 46 patients in the antibody-negative group. Two patients who developed immune checkpoint inhibitor-related hypophysitis were positive for anti-TPO antibodies at baseline, presumably, due to cross-reactivity of autoimmune risks, patients with TPO-Ab may have generalized endocrine autoimmunity, putting them at an increased risk for hypophysitis. To enable timely diagnosis and treatment of endocrine disease in patients undergoing ICI, it is recommended that endocrine autoantibodies be tested prior to starting ICI therapy and that they be reviewed regularly after the start of treatment.

The most obvious advantage of this study is the large sample size, which will provide a unique opportunity to study potential immune-related adverse events in the real world. Other advantages such as high sensitivity, early detection of signals, and easy calculation and understanding of signal values.[34] However, the present study also has some limitations.[34–36] First, the FAERS database is voluntary and has inherent limitations, including underreporting, false reporting, arbitrary reporting, and incomplete reporting. Second, the current study only provides an association between immune checkpoint inhibitors and corresponding adverse reactions, not a causal relationship, and validation studies are needed. Third, data mining techniques do not adequately reflect all clinical information about patients, and it also need to be validated by detailed message from clinical follow-up and other investigations.

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