Original Article

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PD-1/PD-L1 inhibitors associated hypophysitis: An analysis from the FAERS database and case reports

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SUMMARY To get a thorough understanding of PD-1/L1 inhibitor-related hypophysitis (PD-1/L1-irH), we utilized a combination of disproportionality analysis and case analysis to comprehensively characterize the clinical features of PD-1/L1-irH. Significant signals of hypophysitis were detected for all PD-1/PD-L1 inhibitors in the FAERS (FDA Adverse Event Reporting System). As revealed by both FAERS and the case analysis, PD-1/L1-irH occurred more commonly in males, PD-1 inhibitors users and patients older than 65 years. The median onset time was 101 days in FAERS and 8 cycles in the case analysis. In the case analysis, eight late-onset PD-1/L1-irHs occurred even after a discontinuation of several months (4-15 months). As revealed in FAERS, the outcome of PD-1/L1-irH tended to be poor, generally resulting in 64.66% hospitalization and 12.59% death. Fatigue was the most prominent symptom of PD-1/L1-irH, followed by anorexia, hyponatremia, and hypotension, as revealed by the analysis of 84 cases. Meanwhile isolated adrenocorticotropic (ACTH) deficiency was particularly prevalent for PD-1/L1-irH (85.71%), while gonadal hormones or posterior pituitary hormones deficiencies were rare. Glucocorticoids were administered to almost all cases (81/84), with a physiologic or stress dosage in 61.9% of cases, and a high-dose in 26.2% of cases. Most cases (58.3%) showed a favorable tumor response before diagnosis of PD-1/L1-irH. PD-1/L1-irH may occur throughout the whole therapy period even after discontinuation. Clinicians should pay more attention to PD-1 inhibitor users, males and older patients. Early diagnosis and prompt managements are crucial for PD-1/L1-irH as its potentially life-threatening nature.

Keywords PD-1/PD-L1 inhibitors, hypophysitis, disproportionality analysis, characteristic, managements

1. Introduction

Immunotherapy has revolutionized the field of cancer treatment over the past decade. Immune checkpoint inhibitors (ICIs), a novel class of medications in cancer therapy, have quickly gained traction in the treatment of various types of cancer (*1*). Currently, ICIs include antibodies that target certain immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1) or its ligand (PD-L1), resulting in T-cell activation and antitumor activity. Despite the significant potential of ICIs, their success has been somewhat limited by a diverse spectrum of immune-related adverse events referred to as irAEs, which may affect every system (*2,3*).

Hypophysitis, characterized by inflammation of the pituitary gland, can result in the impairment of pituitary function and lead to irreversible hypopituitarism. If left untreated, it can also potentially lead to adrenal crisis, a life-threatening condition. Many reports have focused on immune-related hypophysitis induced by anti-CTLA-4 monoclonal antibodies (mAbs) like ipilimumab (*4*), while relatively fewer existed for anti-PD-1 mAbs, and even fewer for anti-PD-L1 mAbs. The underlying high rates of ipilimumab-mediated hypophysitis is thought to be related to expression of CTLA-4 in the pituitary (*5,6*). However PD-1/L1-irH may be a clinical entity distinct from CTLA-4 inhibitors related hypophysitis (*7*). Given the widespread use of PD-1/PD-L1 inhibitors in clinical practice and the potentially life-threatening nature of hypophysitis if not promptly recognized and treated, it is essential for clinicians to have a thorough understanding

of the clinical manifestations and management of PD-1/L1-irH.

In the study, we firstly performed a disproportionality analysis leveraging a large pharmacovigilance database (FAERS) to characterize and evaluate PD-1/L1-irH. As pharmacovigilance data may lack detailed clinical information, we subsequently conducted a systematic search of cases to gather additional information on clinical features, management and outcomes for PD-1/L1-irH.

2. Methods

2.1. Pharmacovigilance study procedures

We performed a retrospective pharmacovigilance study from Quarter 1 (Q1) in 2004 to Q3 in 2022 using the FAERS database (Figure 1A). Data downloaded from FAERS database were deduplicated following the strategy described by the database. Our study included six approved PD-1/PD-L1 inhibitors: nivolumab, pembrolizumab, camrelizumab, atezolizumab, avelumab, and durvalumab. Both generic and brand names from Drugbank were used as keywords for the database retrieval (Table S1, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=187*). Adverse events (AEs) reported in FAERS were coded by preferred terms (PTs) from the Medical Dictionary for Drug Regulatory Activities (MedDRA). All hypophysitis-relevant PTs (immune-mediated hypophysitis, hypophysitis, secondary adrenocortical insufficiency, secondary hypogonadism, secondary hypothyroidism, hypopituitarism) from MedDRA 24.0 were searched in REAC files of the database. Exposure assessment was considered when PD-1/PD-L1inhibitors were recorded as 'primary suspect'. We also collected information such as reporting source, gender, age, treatment regimen, start and end dates of therapy, onset time, and outcomes of adverse events. The anti-CTLA-4 mAbs are often used in combination with PD-1/PD-L1 inhibitors for the therapy of melanoma or hepatocellular carcinoma. To eliminate any potential interference from ipilimumab or tremelimumab, reports solely involving PD-1/PD-L1 inhibitors were selected for further analysis. Disproportionality analyses were conducted by reporting odds ratio (ROR) (*8*). The calculation formulas of ROR was listed in (Tables S2, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=187* and S3, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=187*). An AE signal was generated when both the ROR value was greater than 2 and the lower limit of the 95% CI of the ROR was greater than 1, and at least three cases were required to define a signal. Usually speaking, the higher the value, the stronger the association between the PD-1/PD-L1 inhibitors and PD-1/L1-irH.

2.2. Descriptive study

A systematic search regarding PD-1/L1-irH of multiple electronic databases was conducted up to March 30, 2023, including PubMed, Web of science, Wanfang, and China National Knowledge Infrastructure (CNKI) , with no language restrictions (Figure 1B). The search strategy and terms were listed in Table S4 (*http://www.ddtjournal.com/action/getSupplementalData.php?ID=187*). Case reports and case series were included, and reviews, mechanistic studies, animal studies, and articles without available full text were all excluded. To avoid potential interference, cases involving the concomitant use of ipilimumab or tremelimumab were also excluded from the analysis. Data including the baseline characteristics of patients (age, sex, tumor type), therapy(regime, start time and end time of the treatment, efficacy on tumor) and AEs (onset time, outcomes) were extracted. Two authors independently screened references for eligibility of data extraction and consulted a third author to resolve

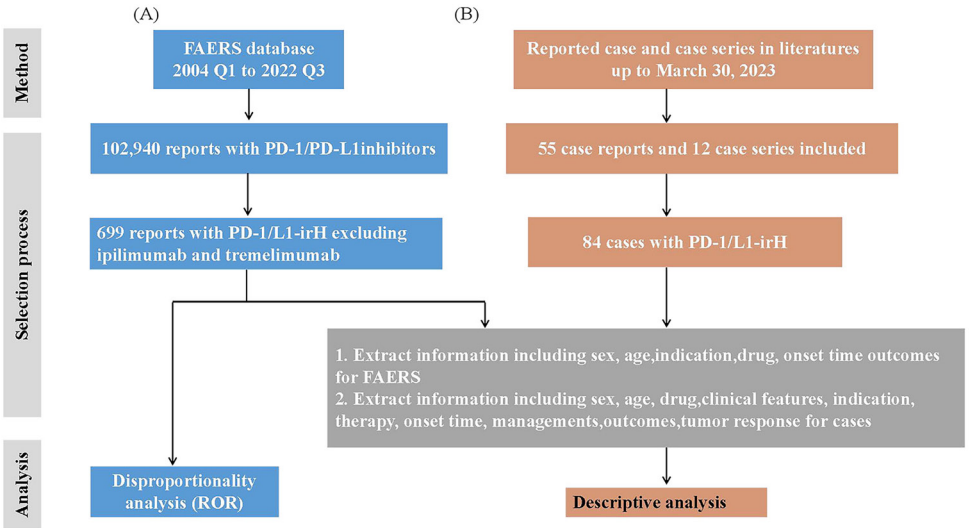

Figure 1. The flow diagram of (A) the pharmacovigilance study and (B) the descriptive study.

Table 1. Characteristics of patients with PD-1/L1-irH in FAERS

Drug	All (*n* = 699)	Nivolumab (*n* = 345)	Pembrolizumab (*n* = 262)	Atezolizumab (*n* = 70)	Avelumab (*n* = 6)	Durvalumab (*n* = 16)
Gender						
Male	421 (60.23%)	218 (63.19%)	143 (54.58%)	45 (64.29%)	3 (50.00%)	12 (75.00%)
Female	189 (27.04%)	92 (26.67%)	73 (27.86%)	18 (25.71%)	3 (50.00%)	3 (18.75%)
Unknown	89 (12.73%)	35 (10.14%)	46 (17.56%)	7 (10.00%)	0 (0.00%)	1 (6.25%)
Age						
Mean (SD)	66.6 ± 11.0	66.0 ± 11.4	66.7 ± 11.0	68.3 ± 8.6	61.7 ± 15.0	70.3 ± 7.5
Median (IQR)	68 (60-74)	68 (60-74)	68 (60-74)	68 (63-74)	66 (52-72)	67 (65-76)
≥ 65 y	371 (53.08%)	175 (50.72%)	145 (55.34%)	35 (50.00%)	4 (66.67%)	12 (75.00%)
< 65 y	222 (31.76%)	115 (33.33%)	74 (28.24%)	27 (38.57%)	2 (33.33%)	4 (25.00%)
Unknown	106 (15.16%)	55 (15.94%)	43 (16.41%)	8 (11.43%)	0 (0.00%)	0 (0.00%)
Indications						
Melanoma	147 (21.03%)	91 (26.38%)	54 (20.61%)	2 (2.86%)	/	/
Lung cancer	238 (34.05%)	90 (26.09%)	108 (41.22%)	26 (37.14%)	/	14 (87.50%)
Gastric cancer	43 (6.15%)	42 (12.17%)	/	/	1 (16.67%)	/
Renal cancer	56 (8.01%)	42 (12.17%)	12 (4.58%)	/	2 (33.33%)	/
Head and neck cancer	35 (5.01%)	24 (6.96%)	11 (4.20%)	/	/	/
Other & Unspecified cancer	180 (25.75%)	56 (16.23%)	77 (29.39%)	42[a] (60.00%)	3 (50.00%)	2 (12.50%)
Outcomes						
DE	88 (12.59%)	45 (13.04%)	29 (11.07%)	9 (12.86%)	/	5 (31.25%)
LT	87 (12.45%)	54 (15.65%)	27 (10.31%)	1 (1.43%)	/	5 (31.25%)
HO	452 (64.66%)	224 (64.93%)	172 (65.65%)	46 (65.71%)	5 (83.33%)	5 (31.25%)
DS	36 (5.15%)	17 (4.93%)	17 (6.49%)	2 (2.86%)	/	/
CA	2 (0.29%)	/	2 (0.76%)	/	/	/
OT	513 (73.39%)	276 (80.00%)	183 (69.85%)	37 (52.86%)	3 (50.00%)	14 (87.50%)
Unknown	59 (8.44%)	15 (4.35%)	38 (14.50%)	5 (7.14%)	/	1 (6.25%)

[a]:19 Hepatocellular cancer in 42 cases. DE: Death; LT: Life-Threatening; HO: Hospitalization - Initial or Prolonged; DS: Disability; CA: Congenital Anomaly; RI: Required Intervention to Prevent Permanent Impairment/Damage; OT: Other Serious (Important Medical Event).

disagreements.

2.3. Ethical considerations

The study was conformed to the provisions of the Declaration of Helsinki (as revised in 2013, https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki)

2.4. Statistical analysis

Data was dealt with SPSS 23.0. Quantitative variables were expressed by the mean, standard deviation, median, and interquartile range (IQR), while qualitative variables were represented using numerical values and rates.

3. Results

3.1. Disproportionality analysis

During the study period, a total of 102,940 PD-1/PD-L1inhibitors associated AEs were documented in the FAERS database: 57,620 for nivolumab, 28,068 for pembrolizumab, 11,066 for atezolizumab, 1,513 for avelumab, 4,673 for durvalumab. After excluding ipilimumab and tremelimumab, 699 reports of PD-1/L1-irH were consisted of 345(49.36%) for nivolumab, 262 (37.48%) for pembrolizumab, 70 (10.01%) for atezolizumab, 6 (0.86%) for avelumab, 16 (2.29%) for durvalumab. Camrelizumab was not included in our analysis as only one relevant case was found.

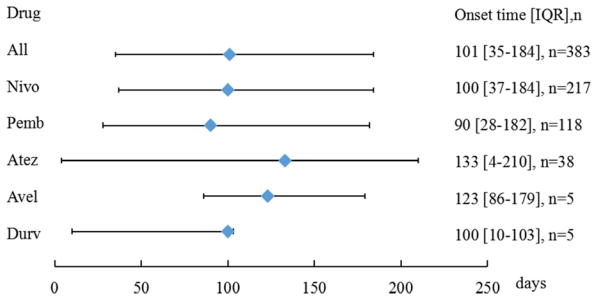

Figure 2. The median onset time of PD-1/L1-irH. Nivo: Nivolumab; Pemb: Pembrolizumab; Atez: Atezolizumab; Avel: Avelumab; Durv: Durvalumab.

The patients' characteristics were summarized in Table 1. Males were presented a larger proportion of PD-1/L1-irH than females, accounting for 60.23%. The average age at diagnosis of PD-1/L1-irH was 66.6 years, which did not differ significantly among each PD-1/PD-L1inhibitors. Lung cancer was the most common indication (34.05%), followed by melanoma (21.03%). While renal cancer was the most common indication for avelumab (33.33%). In our analysis, we found the outcome of PD-1/L1-irH tended to be poor, generally resulting in 64.66% hospitalization and 12.59% death. Among all PD-1/PD-L1inhibitors, the highest fatality proportion occurred in durvalumab (31.25%, 5 death out of 16 cases). As revealed in Figure 2, the overall median

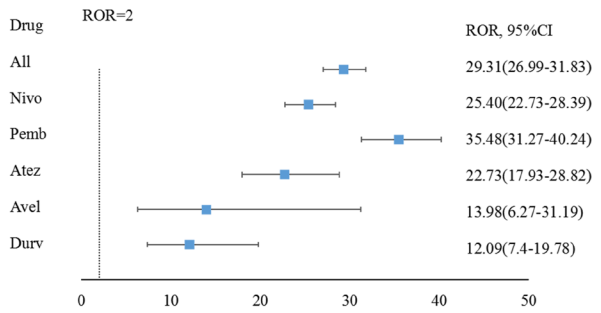

Figure 3. RORs of PD-1/L1-irH. Nivo: Nivolumab; Pemb: Pembrolizumab; Atez: Atezolizumab; Avel: Avelumab; Durv: Durvalumab.

onset time was 101 days (IQR: 35-184). There were also 28 reports with an onset time even longer than one year.

The signals of hypophysitis were detected significantly for each PD-1/PD-L1inhibitor, with an overall ROR 29.31 (95% CI, 26.99-31.83), 25.4 (95% CI, 22.73-28.39) for nivolumab, 35.48 (95% CI, 31.27-40.24) for pembrolizumab, 22.73 (95% CI, 17.93-28.82) for atezolizumab, 13.98 (95% CI, 6.27-31.19) for avelumab and 12.09 (95% CI, 7.4-19.78) for durvalumab, as shown in Figure 3.

3.2. Descriptive analysis

A total of 84 PD-1/L1-irH cases were extracted from 55 case reports (9-63) and 11 case series 64-74). The patients' information were summarized in Table 2. Males seemed to develop hypophysitis more probably than females (male:female, 65:19) as revealed in FAERS. The mean age for PD-1/L1-irH was 65 years old. Furthermore hypophysitis seemed to be induced by PD-1 inhibitors more likely than PD-L1inhibitors (92.86% *vs.* 7.14%). Nivolumab and pembrolizumab emerged as the predominant culprits in these cases, with prevalence rates of 61.9% and 22.62%, respectively. The primary indication of PD-1/PD-L1inhibitors was lung cancer (37 cases, 44.1%), followed by malignant melanoma (20 cases, 23.8%), renal cancer (10 cases, 11.9%). It is widely recognized that patients with PD-1/L1-irH may develop other irAEs concurrently. In our study, thyroiditis (9 cases) and type I diabetes (5 cases) were emerged as the most prevalent concomitant irAEs. Additionally, other irAEs including hepatitis, pancreatitis, pneumonia, pericarditis, as well as cerebritis and Guillain-Barré syndrome, were also found to occur concurrently with hypophysitis. The majority of patients (49 cases, 58.3%) exhibited a favorable tumor response including CR, PR or SD before diagnosis of PD-1/L1-irH.

The clinical features of PD-1/L1-irH were summarized in Table 3. The time between administration and symptom onset varied from two cycles to fifty cycles, with a median period of eight cycles. Interestingly, eight cases had developed hypophysitis even after discontinuing PD-1/PD-L1 inhibitors for several months (4-15 months) in our study. Fatigue (80.95%) emerged as the most prominent symptom, followed by anorexia (52.38%), hypotension (32.14%), and nausea/vomiting (30.95%). Weight loss (11.90%) and disorders of consciousness (11.90%) might also be presented in patients with PD-1/L1-irH. Headache (5.95%) and visual disturbances (1.19%) were rarely observed. As for endocrine, almost all patients exhibited central adrenal insufficiency (81/84, 96.4%), among which central hypothyroidism was coexisted in six cases, and central hypogonadism was coexisted in two cases. Furthermore, a simultaneous involvement of all three aforementioned pituitary axes occurred in one patient. Rarely, only one case was presented as central hypothyroidism, hypogonadism and central diabetes

Table 2. Demographics and baseline characteristics of 84 cases with PD-1/L1-irH

Parameter	*n*	Percentage (%)
Gender		
Male	65	77.38
Female	19	22.62
Age (years) at diagnosis, mean ± SD	65.42 ± 9.74	
Age (years) at diagnosis, medium (IQR)	65(59-73)	
Types of PD-1/PD-L1 inhibitors:		
PD-1 inhibitors	78	92.86
Nivolumab	52	61.90
Pembrolizumab	19	22.62
Camrelizumab	4	4.76
Sintilimab	1	1.19
Sintilimab+tislelizumab	1	1.19
HX008	1	1.19
PD-L1 inhibitors	6	7.14
Atezolizumab	3	3.57
Durvalumab	2	2.38
Avelumab	1	1.19
Cancer type		
Lung cancer	37	44.05
Melanoma	20	23.81
Renal cancer	10	11.90
Ureteral cancer	5	5.95
Liver and biliary tract cancer	2	2.38
Head and neck tumor	5	5.95
Breast cancer	2	2.38
Colon cancer	1	1.19
Neuroendocrine tumor	2	2.38
Additional irAEs		
Thyroiditis	9	10.71
Hepatitis	1	1.19
Pancreatitis	1	1.19
Pneumonia	2	2.38
Cerebritis	1	1.19
Type I diabetes	5	5.95
Pericarditis	1	1.19
Skin exfoliative dermatitis	1	1.19
Guillain-Barré syndrome	1	1.19
Tumor response		
PD	12	14.28
SD	20	23.81
PR	25	29.76
CR	4	4.76
Unknown	23	27.38

PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.

Table 3. The clinical features of PD-1/L1-irH (*n* = 84)

Parameter	*n*	(%)
Symptoms		
Fatigue	68	80.95
Anorexia	44	52.38
Hypotension	27	32.14
Nausea/vomiting	26	30.95
Weight loss	10	11.90
Disorders of consciousness	10	11.90
Headache	5	5.95
Visual disturbances	1	1.19
Median cycles to onset NO. (range)	8 (2-50)	
Pituitary hormone disturbance		
ACTH	72	85.71
ACTH+TSH	6	7.14
ACTH+FSH/LH	2	2.38
TSH+FSH/LH+DI	1	1.19
ACTH+TSH+FSH/LH	1	1.19
FSH/LH	1	1.19
DI	1	1.19
Other disturbance		
Hyponatremia	46	54.76
MRI findings (*n* = 74)		
Normal	56	75.68
Enhancement of the pituitary gland or Pituitary stalk	11	14.86
Heterogeneous enhancement	2	2.70
Atrophy	4	5.41
Abnormal of posterior pituitary	3	4.05

ACTH: isolated adrenocorticotropic deficiency; ACTH+TSH: adrenocorticotropic deficiency concurrent with central hypothyroidism; ACTH+FSH/LH: adrenocorticotropic deficiency concurrent with central hypogonadism; TSH+FSH/LH+DI: central hypothyroidism, hypogonadism, and diabetes insipidus; FSH/LH: isolated hypogonadism; DI: central diabetes insipidus; MRI: magnetic resonance imaging.

Table 4. Managements and outcomes of PD-1/L1-irH (*n* = 84)

Parameter	*n*	(%)
PD-1/L1 discontinuation		
NO	21	25.00
YES, temporarily	15	17.86
YES, permanently	27	32.14
Unknown	21	25.00
Hormonal replacement (HRT)		
Glucocorticoids	81	96.43
High-dose[a]	22	26.19
Physiologic or stress dose[b]	52	61.90
Unspecified dose	7	8.33
Other hormone		
Thyroid hormone[c]	5	5.95
Testosterone	1	1.19
Desmopressin	1	1.19
Unspecified treatments	1	1.19
Outcomes		
Improved after HRT	47	55.95
Unknown	37	44.05
Hormonal recovery (*n* = 24)		
Follow-up (months), median (range)	6 (3-12)	
ACTH (*n* = 24)	2	8.33
TSH (*n* = 3)	1	33.33

[a]A high-dose refers to 0.5-2 mg/kg/day methylprednisolone or equivalent. [b]A physiologic or stress dose steroid refers to a dose of hydrocortisone less than 100 mg or equivalent. [c]Meant that thyroid hormone was given concurrently with steroids.

insipidus while maintaining normal in pituitary-adrenal axis. Additionally, one case had isolated hypogonadism, and one had isolated central diabetes insipidus. Hyponatremia was observed in the majority of cases (54.8%). MRI was taken in 74 patients, with the majority of cases showing normal pituitary imaging (75.68%). Enhancement of the pituitary gland or stalk thickening was only presented in 11 cases (14.86%). Abnormal imaging of posterior pituitary occurred in only three cases. Meanwhile only one of three cases had a clinical symptom of central diabetes insipidus.

The managements and outcomes of PD-1/L1-irH were listed in Table 4. Among 84 cases, 21 cases did not mention information about PD-1/PD-L1inhibitors discontinuation in the reports. PD-1/PD-L1inhibitors were continued for 21 cases, temporarily discontinued for 15 cases, and permanently discontinued for 27 cases. Glucocorticoids was usually initiated promptly at diagnosis, including methylprednisolone, prednisone or hydrocortisone. Nearly all patients (81/84) received glucocorticoids, with five also receiving thyroid hormone concurrently. Apart from seven cases where the dose was not mentioned, the majority of patients (52 /84, 61.90%) initiated a physiologic or stress dose of steroids, while thirteen cases (22/84, 26.19%) received high-dose steroids. A physiologic or stress dose steroid refers to a dose of hydrocortisone less than 100 mg or equivalent other glucocorticoids while a high-dose refers to 0.5-2 mg/kg/day methylprednisolone or equivalent. Furthermore, it is worth noting that one case with isolated hypogonadotropic hypogonadism was treated by testosterone, and desmopressin was given to one with central diabetes insipidus. A total of 24 patients were followed up for a median duration of 6 months (range: 3-12 months). Significant improvements in symptoms were observed following hormone treatments. One of three cases with pituitary-thyroid deficiency experienced a full recovery. However, the restoration of the pituitary-adrenal axis was uncommon. Only two cases (2/24) demonstrated recovery after two and three months respectively.

4. Discussion

Undoubtedly, ICIs such as PD-1/PD-L1 inhibitors have become a game changer in cancer treatment following the unprecedented and satisfactory response rate in recent years. However, a series of unique irAEs accompanied by the increased usage of PD-1/PD-L1 inhibitors also bother the clinicians. Initially as a specific irAE of ipilimumab (*75*), hypophysitis has also been reported to be associated with PD-1/PD-L1 inhibitors though less frequently. To the best of our knowledge, our study is, as of today, the first and largest case-analysis and disproportionality analysis, specifically focused on PD-1/

L1-irH, rather than encompassing all immune checkpoint inhibitors-related hypophysitis.

Hypophysitis associated with PD-1 inhibitors seemed to be reported more frequently than PD-L1 inhibitors whether from the case analysis or FAERS. The trend was presented similarly in a meta-analysis conducted in 2019 (PD-1 inhibitors *vs.* PD-L1 inhibitors 1.2% *vs.* 0.8%) (*76*). The male preponderance of anti-CTLA-4 mAbs-induced hypophysitis was confirmed by a recent meta-analysis of de Filette *et al.* (*77*) which kept the same trend even after adjusting sex difference caused by primary tumor *i.e.* melanoma (*78*). It has not studied whether PD-1/L1-irH also had the same sex difference. Our study had firstly shown that males had a higher reporting rate of PD-1/L1-irH than females. Moreover the male preponderance was observed for each PD-1/PD-L1 inhibitor as evidenced by FAERS. The phenomenon may be explained by the indication of PD-1/PD-L1 inhibitors, in particular lung cancer, kidney cancer and melanoma which affect men more than women (*79-81*).

PD-1/L1-irH was found with a higher reporting rate in patients older than 65 years old, especially revealed in FAERS regardless the type of PD-1/PD-L1 inhibitors. A similar median age (66 years old) was revealed in a retrospective study including all ICIs from VigiBase (*82*). The onset time of PD-1/L1-irH had been varied from one month to over a year, as revealed in both database and case analysis. This might be explained by different exposure of PD-1/PD-L1 inhibitors which might be influenced by factors such as sex, baseline eGFR, age, race *etc.* (*83,84*). A notable finding in the case analysis was that eight patients (nivolumab: 5 cases; pembrolizumab: 3 cases) had the late-onset hypophysitis even after discontinuing the offender-drugs for several months, with the longest interval as fifteen months (*30,36,37,49,51,60,64*). The interesting phenomenon could be explained by the pharmacokinetics and pharmacodynamics of PD-1/PD-L1 inhibitors to some degree. A pharmacodynamics analysis of nivolumab demonstrated that even after a single infusion, a mean occupancy of > 70% for PD-1 molecules on circulating T cells was sustained for a period of 2 months, regardless of dose (*85*). This indicated that nivolumab could block PD-1-mediated signaling even when it is undetectable in serum. T-cell memory for tumor antigens may also be reactivated by ICIs, with the resulting antitumor effect being maintained for several months. Indeed, a long-term antitumor action was observed in patients with non-small cell lung cancer (NSCLC) or melanoma even after discontinuation (*86,87*), suggesting that irAEs might also occur even after nivolumab withdrawal.

The nonspecific symptoms presented by PD-1/L1-irH, such as fatigue, anorexia, nausea, vomiting, could be confused with chemotherapy or other irAEs or cancer itself. So it may pose a challenge for diagnosis of hypophysitis in these particular patients in the absence of abnormal pituitary MRI findings (*88*). Hypotension and hyponatremia might be another two common features of PD-1/L1-irH. Hyponatremia was even be reported as a powerful predictor of the acute development of isolated ACTH deficiency caused by anti-PD-1/PD-L1mab (*71*). Visual disturbances were uncommon, occurring in only 1% PD-1/L1-irH in our study. And the incidence of headaches was approximately 6% in patients with PD-1/L1-irH, which demonstrated a much lower prevalence compared to anti-CTLA-4 hypophysitis (13/15, 86.7%) (*89*). This could potentially be attributed to a heightened prevalence of pituitary enlargement in anti-CTLA-4 hypophysitis (12/15, 80.0%) (*89*), while lower for PD-1/L1-irH accounting for 21.4% and even lower in our study, accounting for 14.86%. Unlike the hypervascular state observed in the early stage, pituitary atrophy and empty sella might be present as the final outcome of PD-1/L1-irH (*90*).

As revealed in 84 cases, PD-1/L1-irH mainly involved ACTH deficiency (96.4%) especially isolated ACTH deficiency (85.7%), as opposed to whole hypophysitis caused by anti-CTLA4 (*91*). The multiple hormonal abnormalities were not common in these cases accounting for 12%. Other pituitary-endocrine axis might be affected alone without ACTH deficiency like one case concurrently presented as central hypothyroidism, hypogonadism and diabetes insipidus, one as central diabetes insipidus, and one as isolated hypogonadotropic hypogonadism (*25*). Mechanistically, the "ectopic" expression of PD-1 on corticotrophs cells could potentially elucidate the exquisite predilection for ACTH-deficiency in PD-1/L1-irH (*92*). Conversely, the "ectopic" expression of CTLA-4 on adenohypophyseal cells may partially account for the whole hypophysitis induced by anti-CTLA4 (*5*). The recovery of ACTH is typically challenging, often requiring lifelong hormone supplementation. In contrast, the restoration of gonadotropic hormone and thyroid-stimulating hormone is relatively straightforward. The predictors of immunotherapy related hypophysitis had also drawn researchers' interests. In one case-control study, anti-pituitary cell antibody was positive for most hypophysitis induced by ICIs including anti-CTLA-4 mAbs and anti-PD1/L1 mAbs. Furthermore, different human leukocyte antigen (HLA) types were found between isolated ACTH and ICI-induced hypophysitis (*93*). However only one of four cases tested positive for anti-pituitary cell antibodies in our study. Additionally, due to the limited sample size of six cases, we were unable to determine the specific type(s) of HLA that may be associated with PD-1/L1-irH.

The discontinuation of anti-PD-L1/PD-L1 mAbs did not come to agreement now which might depend on the severity of hypophysitis and the special condition of patients. In cases of mild or moderate hypophysitis, it is advisable to continue anti-PD-L1/PD-L1 mAbs , while the option to suspend or discontinue treatment may be warranted for severe hypophysitis (*94*). For example,

a NSCLC patient manifested moderate hypophysitis following 33 administrations of nivolumab, while subsequently managing to sustain an additional 50 courses concurrent with hormone replacement (*10*).

Glucocorticoids remain the primary therapy for PD-1/L1-irH until now. Generally, a physiologic regimen was recommended for mild hypophysitis whereas a high-dose protocol for severe cases (*95*). However the dosage of glucocorticoids for severe cases varied widely, ranging from 50 mg of hydrocortisone to 1 mg/kg/day of prednisolone in our study (*14,17,22*). While a high dose of glucocorticoids has been reported to be correlated with a reduced survival in ipilimumab-induced hypophysitis (*96,97*). Therefore, it's urgent to gather more evidence regarding the appropriate dosage of glucocorticoids for immunotherapy related hypophysitis. Isolated hypogonadotropic deficiency was uncommon for PD-1/L1-irH (*58*), which could be corrected by synthetic sex hormones in order to prevent bone loss and osteoporotic fractures in women, and muscular mass loss in men. Posterior hypophysitis, such as diabetes insipidus, was extremely rare and could be treated with oral desmopressin in mild cases (*59*).

A prospective study revealed that hypophysitis accompanied by ACTH deficiency was associated with improved overall survival in patients with NSCLC and melanoma who were treated with physiological doses of hydrocortisone (*98*). In our study, most patients with PD-1/L1-irH showed a positive tumor response before the diagnosis of hypophysitis. However, further information and evidence are required to fully understand the relationship between immunotherapy-related hypophysitis and the efficacy of immunotherapy.

In conclusion, clinicians should pay attention to patients treated by PD-1/L1 inhibitors especially for PD-1 inhibitor users, males, and older patients during the whole therapy period, even for several months after discontinuation. Early diagnosis and prompt managements are crucial for PD-1/L1-irH as its potentially life-threatening nature. Further studies should focus on the proper dosage of glucocorticoids and the predictors for PD-1/L1-irH.

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