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Mycobacterial infections due to PD-1 and PD-L1 checkpoint inhibitors

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ABSTRACT

Background Immune checkpoint inhibitors that block programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) have improved outcomes for many cancer subtypes but do exhibit toxicity, in the form of immune-related adverse events.

Objective The aim of this study was to investigate the emerging toxicities of PD-1 and PD-L1 inhibitors including acute or reactivation of tuberculosis (TB) and atypical mycobacterial infection (AMI).

Methods This study was completed as a retrospective review using the US Food and Drug Administration Adverse Events Reporting System (FAERS) for incidence of TB and AMI due to PD-1 and PD-L1 inhibitors compared with other FDA (Food and Drug Administration) approved drugs. The statistical methods included disproportionality signal analysis using the reporting OR (ROR) to compare cases. The 95% Wald CI was reported to assess the precision of the ROR.

Results Out of the 10 146 481 adverse events (AEs) reported to FAERS for all drugs between 1 January 2015 and 31 March 2020, 73 886 AEs were due to the five FDA approved PD-1/PD-L1 inhibitors. Seventy-two cases of TB were due to PD-1/PD-L1 inhibitors. Specifically, 45 cases (62.5%) due to nivolumab, 18 (25%) due to pembrolizumab, 5 (7%) due to atezolizumab and 4 (5.5%) due to durvalumab. There were 13 cases of AMI: 9 (69.3%) due to nivolumab, 2 (15.3%) due to pembrolizumab and 1 (7.7%) each due to durvalumab and atezolizumab. Avelumab was not attributed to any AE of TB or AMI. From analysis of the FAERS database, the calculated ROR for TB due to PD-1/PD-L1 inhibitors was 1.79 (95% CI, 1.42 to 2.26) (p<0.0001) and for AMI was 5.49 (95% CI, 3.15 to 9.55) (p<0.0001).

Conclusion PD-1/PD-L1 inhibitors used in the treatment of cancer subtypes is associated with increased TB and AMI risk. Although this complication is rare, clinicians using PD-1/PD-L1 inhibitors should be aware of the risks.

Key questions

What is already known about this subject?

- Case reports and case series suggest programmed-cell death-1/programmedcell death ligand-1 (PD-1/PD-L1) inhibitors are associated with acute tuberculosis (TB) or reactivation of TB.

What does this study add?

- This is the first large systemic effort to quantify the risk of TB due to PD-1/PD-L1 inhibitors through retrospective analysis of FAERS (Food and Drug Administration Adverse Events Reporting System), a pharmacovigilance database. PD-1/PD-L1 inhibitors were not only associated with increased risk of TB compared with other drugs but atypicalmycobacterial infection as well.

How might this impact on clinical practice?

- Although this complication is rare, clinicians using PD-1/PD-L1 inhibitors should be aware of this.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) that block programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) have transformed care for many cancer subtypes and have improved outcomes for patients with PD-L1 overexpression.[1 2] Through blockade of the PD-1/PDL-1 axis, the T-lymphocyte-mediated response against tumour cells is enhanced, resulting in accelerated immune-mediated destruction of cancer cells. However, facilitating immune-mediated activation is not benign, and patients receiving ICIs are known to exhibit unique toxicities that result in organ damage known as immune-related adverse events (irAEs).[3] The most common irAEs with PD-1 and PD-L1 inhibitors are fatigue, pruritus and diarrhoea.[4] Some irAEs can be fatal, with pneumonitis, hepatitis, neurotoxicity and most commonly myocarditis reported.[5] While counterintuitive when the mechanism of action is considered, an emerging and increasingly reported toxicity of PD-1 and PD-L1 inhibitors is acute tuberculosis (TB) and reactivation of TB.[6] The first case of TB due to the PD-1 inhibitor was described in a patient with relapsed Hodgkin's lymphoma who developed pulmonary TB following treatment with pembrolizumab.[7] Since then, there have been other case reports of TB following initiation of PD-1 or PD-L1 inhibitors that make the development of TB a relevant concern.[8–11] In a preclinical mouse study, PD-1 deficient mice were found to be highly susceptible to TB with reduced survival compared with wild-type mice.[12] However,

Table 1 Adverse events of TB and AMI due to PD-1/PDL-1 inhibitors from January 2015 to March 2020 in FAERS

Total AEs due to all drugs in FAERS	10 146 481
Total AEs due to PD-1/PDL-1 inhibitors	73 886
Total AEs due to PD-1 inhibitors	62 823
Total AEs of TB in FAERS	5560
Total AEs of TB due to PD-1/PDL-1 inhibitors	72
Total AEs of AMI in FAERS	336
Total AEs of AMI due to PD-1/PDL-1 inhibitors	13
ROR calculation	
ROR for TB due to PD-1/PDL-1 inhibitors versus full database	1.79 (95% CI, 1.42 to 2.26)
ROR for AMI due to PD-1/PDL-1 inhibitors versus full database	5.49 (95% CI, 3.15 to 9.55)

AEs, adverse events; AMI, atypical mycobacterial infection; FAERS, Food and Drug Administration Adverse Events Reporting System; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; ROR, reporting OR; TB, tuberculosis.

there is no current risk estimate describing the potential risk of developing TB or atypical mycobacterial infection (AMI) from PD-1 and PD-L1 inhibitors. In this study, we retrospectively reviewed the US Food and Drug Administration Adverse Events Reporting System (FAERS), a pharmacovigilance database, for the risk of TB and AMI due to PD-1 and PDL-1 inhibitors compared with other FDA (Foodand Drug Administration) approved drugs.

METHODS

This study is a retrospective analysis that used data queries from the FAERS pharmacovigilance monitoring database. FAERS is a public database that contains nearly 19.7 million adverse event (AE) reports, medication error reports and product quality complaints reported by healthcare professionals, manufacturers and consumers from around the world since 1968. These reports are managed by FDA and evaluated by clinical reviewers in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. Date in each event report, where applicable, include individual case identification numbers for reference, the suspected pharmaceutical agent, treatment indication, adverse reactions, nature of the event (ie, serious), outcomes (eg, hospitalised, death, other outcomes), sex (male, female or unknown), age, weight, event date, initial FDA receipt date, latest FDA receipt date, pharmaceutical company, reporter (eg, healthcare professional, consumer, pharmaceutical company, unknown), concomitant medications, latest manufacturer received date, country where the event occurred and manufacturer control number. Individual names and date of birth are excluded from these lists.

The present study involved data queries of the FAERS database between 1 January 2015 and 31 March 2020, for AEs secondary to PD-1 inhibitors, namely 'pembrolizumab' and 'nivolumab' and PD-L1 inhibitors, namely 'atezolizumab', 'durvalumab' and 'avelumab'. In all AEs due to above five drugs we then searched for three AEs specifically, 'tuberculosis', 'pulmonary tuberculosis' and 'atypical mycobacterial infection'. Tuberculosis and pulmonary tuberculosis were grouped together for analysis. All other events that were reported in patients with TB or AMI were characterised into subcategories, including pulmonary, infectious, endocrine, gastrointestinal, hepatobiliary, dermatological, cardiac, haematological, neurological, vascular, infusion-related, rheumatological and others.

TB and AMI cases among patients treated with PD-1 and PD-L1 inhibitors were compared with all reported TB and AMI events in the database due to other drugs by conducting a disproportionality signal analysis based on the reporting OR (ROR). The ROR is a measure of the magnitude of association between an exposure to a pharmaceutical agent and the odds of a specific outcome occurring. In the setting of an elevated ROR, it can be conferred that there is an elevated risk of an adverse event occurring with a specific medication. The 95% Wald CI was used to assess the precision of the ROR. When lower limit of ROR >1 and CI did not cross 1, ROR was considered significant.[13] The likelihood of association between PD-1/PD-L1 inhibitors and TB/AMI were investigated using two-sided χ^2 or Fisher's exact tests as warranted. All analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, North Carolina, USA) and statistical significance was defined as $p<0.05$.

RESULTS

Between 1 January 2015 to 31 March 2020, a total of 10 146 481 adverse events report cases were generated in FAERS. Out of 10 146 481 AE, there were 73 886 (0.73%) associated with the approved five PD-1/PD-L1 inhibitors. The majority of AEs were reported with nivolumab and pembrolizumab at 62 823 (85%). In FAERS there were 5560 (0.05%) reports of TB with any drug, of which 72 (1.3%) were reported with PD-1/PDL-1 inhibitors. The ROR for TB due to PD-1/PD-L1 inhibitors was elevated at 1.79 (95% CI, 1.42 to 2.26) ($p<0.0001$). For AMI, there were 336 (0.003%) reports associated with all drugs, of which 13 (3.9%) were due to PD-1/PD-L1 inhibitors. The

Table 2 Details of TB AE due to PD-1/PDL-1 inhibitors

Total number of TB AEs	72
PD-1/PDL-1 inhibitor used	
Nivolumab	45 (62.50%)
Pembrolizumab	18 (25%)
Atezolizumab	5 (6.94%)
Durvalumab	4 (5.55%)
Indication for PD-1/PDL-1 use	
Lung cancer	44 (61.11%)
Gastric cancer	6 (8.33%)
Head and neck cancer	6 (8.33%)
Hodgkin's lymphoma	3 (4.16%)
Malignant melanoma	2 (2.77%)
Colon cancer	1 (1.38%)
Neuroendocrine carcinoma	1 (1.38%)
Ovarian carcinoma	1 (1.38%)
Pancreatic carcinoma	1 (1.38%)
Plasma cell myeloma	1 (1.38%)
Renal cell carcinoma	1 (1.38%)
Transitional cell carcinoma	1 (1.38%)
Unknown	4 (5.55%)
Type of reaction	
Serious	72 (100%)
Sex	
Male	49/61 (80.32%)
Female	12/61 (19.68%)
Median age, years (range, min-max)	68.5 (38–88); n=54
Outcome	
Died	13 (18.05%)
Hospitalised	20 (27.77%)
Life threatening	2 (2.77%)
Other outcome	37 (51.38%)
Reporter	
Healthcare professional	68 (94.44%)
Consumer	4 (5.55%)
Year initial report received	
2016	5 (6.94%)
2017	13 (18.05%)
2018	22 (30.55%)
2019	26 (36.11%)
2020	6 (8.33%)
Region of origin of AE	
Asia	51 (70.83%)
Europe	9 (12.5%)
Americas	7 (9.72%)
Africa	4 (5.55%)
Australia	1 (1.38%)
Suspected drug	
PD-1/PDL-1 inhibitor	56 (77.78%)
PD-1/PDL-1 inhibitor + ≥1	16 (22.22%)

AEs, adverse events; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; TB, tuberculosis.

ROR for AMI due to PD-1/PD-L1 inhibitors was elevated at 5.49 (95% CI, 3.15 to 9.55) (p<0.0001) (table 1).

Out of 72 cases of TB due to PD-1/PD-L1 inhibitors, 45 (62.50%) were due to nivolumab followed by 18 (25%) due to pembrolizumab, 5 (6.94%) and 4 (5.55%) due to atezolizumab and durvalumab, respectively. There were no cases reported with avelumab. The most common indication for which PD-1/PD-L1 inhibitor was used was lung cancer (61.11%). Median age of the whole cohort was 68.5 years. Eighty per cent of the patients were men and 20% were women. Out of 72 cases, 13 (18.05%) cases had a reported outcome of death. The most common region of origin in which TB was reported was Asia (70.83%). Sixteen cases (22.22%) had PD-1/PD-L1 inhibitors plus one of more non-checkpoint inhibitor drug listed as a suspect drug leading to AE. (table 2)

Out of 13 cases of AMI due to PD-1/PD-L1 inhibitors, 9 (69.23%) were due to nivolumab followed by 2 (15.38%) due to pembrolizumab and 1 (7.69%) each due to durvalumab and atezolizumab. No report of AMI attributable to avelumab was found. The most common reason for use of PD-1/PD-L1 inhibitor was lung cancer (76.92%). Median age of the entire cohort was 78.5 years. Seventy-three per cent of patients were men and 27% were women. Out of 13 cases, 1 (7.69%) patient died. The most common region in which AMI was reported was Asia (76.92%). One case (7.69%) had PD-1/PD-L1 inhibitors plus one of more non-checkpoint inhibitor drug listed as a suspect drug leading to AE. (table 3)

Patients who had TB due to PD-1/PD-L1 inhibitors also had additional reported pulmonary complications in 19.44% of cases, followed by other infectious complications in 13.88% of cases. Similarly, patients who had AMI attributed to use of PD-1/PD-L1 inhibitors had pulmonary complications in 38.46% of cases followed by endocrine, dermatological and others in 15.38% of the cases. (table 4)

DISCUSSION

In this retrospective pharmacovigilance database review, PD-1/PD-L1 inhibitors had a statistically significant positive signal with TB and AMI, with a proportion of these events associated with mortality. Nivolumab had the highest frequency of reported TB and AMI, whereas avelumab had no reported events. Most commonly affected patients were receiving treatment for lung cancer and the most commonly reported country of origin was Japan.

TB has a high disease burden worldwide with the highest disease associated mortality of any infectious agent. In 2018 there were 10 million new cases globally and 1.5 million reported deaths.[14] AMIs are estimated to occur in approximately 5.7 to 7.2 per 100 000 persons, with an increasing incidence in developed countries.[15 16] There is growing evidence that patients receiving ICIs can develop TB reaction while on treatment.[6] To date, there are reported 16 cases of TB secondary to ICIs, none of which were attributed Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors. Median time to diagnosis from ICI initiation was 6.3 months (range, 1 to 24 months).[17] The mechanism by which a PD-1/PD-L1 inhibitor results in TB is not clear. In a murine study, PD-1 knockout mice had decreased survival compared with wild-type mice following exposure to *Mycobacterium tuberculosis*. Furthermore, PD-1 inhibition is needed to prevent $CD4^+$ T cells from promoting development of TB.[18] PD-1 inhibition mitigates over-production of Interferon gamma (IFN-γ) which is important for host resistance to TB.[19]

Increased risk of TB and AMI is also found in patients on tumor necrosis factor (TNF)-alpha inhibitors and Janus Kinase (JAK) 1/2 inhibitor ruxolitinib.[20 21] Patients treated with infliximab, a TNF-alpha inhibitor, were 5.6 and 3.8 times more likely to develop TB and AMI, respectively.[22] In patients prior to start TNF-alpha inhibitors, screening for latent TB is recommended.[20] If the patient is found to have latent TB, treatment with isoniazid is recommended as it substantially reduces the risk of developing TB reactivation.[23] However, a recent study suggests that PD-1 inhibition induced TB reactivation is actually driven by TNF-alpha and use of TNF-alpha inhibitor could reverse this complication.[24] There are currently no recommended screening guidelines for latent TB prior to starting PD-1/PD-L1 inhibitors. A single institution study in Germany found that 18% of patients had positive test for Quantiferon Gold TB plus (QGT) prior to starting ICIs; however, none of the patients who had a positive QGT test developed TB while on treatment with ICIs.[6] Of the 16 cases of TB reported in literature due to ICIs, treatment with ICIs was stopped in all cases, TB treatment was initiated and seven cases had re-initiation of ICIs. Out of seven who had re-initiation of ICI, five had response to therapy, one had progression and in one case response was not available.[17] As TB reactivation may lead to treatment interruptions or discontinuation, standardised recommendations for TB screening in patients with planned ICI should be considered with substantiation of results from the current study in prospective studies.

This is the first study using FAERS to demonstrate the potential risk of developing TB and AMI in PD-1/PD-L1 inhibitor treated patients. As PD-1/PD-L1 inhibitors use becomes more prevalent on a global scale, including regions with an elevated prevalence of latent TB, clinicians need to consider the risk, benefit and economic impacts of screening for latent TB and treatment initiation if the patient is positive. These questions cannot be answered in this observational signal analysis, and future prospective research studies should be conducted. If a patient develops TB or AMI while on treatment with PD-1/PD-L1 inhibitors, permanent discontinuation of therapy should be avoided if there is clear clinical benefit from ICI and multidisciplinary discussions regarding treatment delay should be conducted with the treating oncologist and infectious disease specialists. A majority

Table 3 Details of AMI AE due to PD-1/PDL-1 inhibitors

Total number of AMI AEs	13
PD-1/PDL-1 inhibitor used	
Nivolumab	9 (69.23%)
Pembrolizumab	2 (15.38%)
Atezolizumab	1 (7.69%)
Durvalumab	1 (7.69%)
Indication for PD-1/PDL-1 use	
Lung cancer	10 (76.92%)
Head and neck cancer	1 (7.69%)
Malignant melanoma	1 (7.69%)
Unknown	1 (7.69%)
Type of reaction	
Serious	13 (100%)
Sex	
Male	8/11 (72.72%)
Female	3/11 (27.27%)
Median age, years (range, min-max)	78.5 (50–88); n=10
Outcome	
Died	1 (7.69%)
Hospitalised	4 (30.76%)
Life threatening	2 (15.38%)
Other outcome	6 (46.15%)
Reporter	
Healthcare professional	13 (100%)
Year initial report received	
2016	1 (7.69%)
2017	3 (23.07%)
2018	4 (30.76%)
2019	4 (30.76%)
2020	1 (7.69%)
Region of origin of AE	
Asia	10 (76.92%)
Europe	2 (15.38%)
Americas	1 (7.69%)
Suspected drug	
PD-1/PDL-1 inhibitor	11 (84.61%)
PD-1/PDL-1 inhibitor + ≥1	2 (15.38%)

AEs, adverse events; AMI, atypical mycobacterial infection; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1.

Table 4 Other AEs grouped into major organ systems in patients treated with PD-1/PDL-1 inhibitors

	TB death events (n=13)	TB alive events (n=59)	TB total (n=72)	AMI death events (n=1)	AMI alive events (n=12)	AMI total (n=13)
Pulmonary	5 (38.46%)	9 (15.25%)	14 (19.44%)	0	5 (41.66%)	5 (38.46%)
Infectious	3 (23.07%)	7 (11.86%)	10 (13.88%)	1 (100%)	0	1 (7.69%)
Endocrine	0	5 (8.47%)	5 (6.94%)	0	2 (16.66%)	2 (15.38%)
Gastrointestinal	2 (15.38%)	3 (5.08%)	5 (6.94%)	0	1 (8.33%)	1 (7.69%)
Hepatobiliary	1 (7.69%)	4 (6.77%)	5 (6.94%)	0	0	0
Cardiac	0	4 (6.77%)	4 (5.55%)	0	0	0
Haematological	0	3 (5.08%)	3 (4.16%)	0	0	0
Dermatological	0	3 (5.08%)	3 (4.16%)	0	2 (16.66%)	2 (15.38%)
Neurological	0	3 (5.08%)	3 (4.16%)	0	0	0
Vascular	1 (7.69%)	1 (1.69%)	2 (2.77%)	0	0	0
Infusion related	1 (7.69%)	0	1 (1.38%)	0	0	0
Rheumatological	0	1 (1.69%)	1 (1.38%)	0	0	0
Others	1 (7.69%)	4 (6.77%)	5 (6.94%)	1 (100%)	1 (8.33%)	2 (15.38%)

AEs, adverse events; AMI, atypical mycobacterial infection; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; TB, tuberculosis.

of patients in whom TB or AMI have reported are those with lung cancer. It is worth pointing out that especially in patients with lung cancer, there is significant difficulty in differentiating immune-pneumonitis or radiation-pneumonitis from pseudoprogression, true disease progression or infectious causes. Prospective studies of irAEs should include testing for TB or AMI in diagnostic work-up.

This study has limitations. This analysis was a retrospective study of reported events in FAERS, and as such, baseline characteristics including presence of latent TB was not known. Moreover, the actual incidence of TB or AMI due to PD-1/PD-L1 inhibitors cannot be determined because FAERS reports patients with AEs, not total number of patients taking the medication. Furthermore, it is likely that not all cases of TB that occur in the clinical setting are reported within FAERS. As such, there are similar limitations in ROR estimate. AE reporting for a drug may be influenced by extent of use, publicity and bias.[25] Although the use of disproportionality analysis through pharmacovigilance databases to determine the increased risk of AEs secondary to particular drug has been shown in various settings,[25 26] it is critical that any hypothesis generated by using pharmacovigilance databases are validated through prospective studies.

CONCLUSION

PD-1/PD-L1 inhibitors used in treatment for cancer is associated with increased risk of TB and AMI. The most common drug in FAERS attributed to TB and AMI is nivolumab. In this study, lung cancer was the most common indication for which use of PD-1/PD-L1 inhibitor leads to TB or AMI. Although this complication is rare, clinicians using ICIs should be aware of this possibility. Currently, there is no additional data available to support or refute the need to screen patients for latent TB prior to initiation of ICIs. Prospective studies are needed to address these questions as well as indications to initiate prophylactic therapy.

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