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Research Article

Pulmonary Immune-Related Adverse Events of PD-1 Versus PD-L1 Checkpoint Inhibitors: A Retrospective Review of Pharmacovigilance

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ABSTRACT

Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapeutics. However, immune-related adverse events (irAEs) increase morbidity and mortality and thereby limit therapeutic utility. The real-world incidence of the entire spectrum of pulmonary irAEs has not been systematically described. The objective of this study is to assess the risk of developing pulmonary irAEs (pneumonitis, pleural events [i.e., effusion and pleurisy], exacerbations of airway disease [i.e., bronchitis and bronchiectasis], and sarcoidosis) with exposure to five commonly used ICIs: nivolumab, pembrolizumab, durvalumab, avelumab, and atezolizumab. **Methods:** We conducted a retrospective review of the Food and Drug Administration Adverse Events Reporting System (FAERS) pharmacovigilance database. We collected data from 2012 to 2021 to assess the risk of pulmonary irAEs and performed a disproportionality analysis using Open-Vigil, a software package used for analysis of pharmacovigilance data, to calculate reporting odds ratios (RORs). We used 95% CIs to evaluate the precision of RORs. An ROR greater than 1 and the upper limit of the 95% CI indicated statistical significance. **Results:** A total of 17,273,403 events were reported in FAERS between 2012 and 2021. Of these, 88,099 (0.5%) were attributed to the PD-1 (programmed cell death protein 1) inhibitors and 21,905 (0.1%) to PD-L1 (programmed death ligand 1) inhibitors of interest. The most common indication for using the ICIs of interest was lung cancer: a total of 2832 (46.70%) for the PD-1 inhibitors and 1311 (70.9%) for the PD-L1 inhibitors. In the anti–PD-1 group, 2342 (38.6%) patients were hospitalized, and 1962 (32.4%) patients died from the lung adverse event. In the PD-L1 group, 744 (40.3%) patients were hospitalized, and 520 (28.1%) patients died from the event. Nivolumab resulted in the highest statistically significant risk (ROR, 10.5; 95% CI, 10.1–10.9) for pneumonitis. Avelumab had a lesser risk for pneumonitis (ROR, 0.2; 95% CI, 0.2–0.3). The risk for pleural events was highest with nivolumab (ROR, 3.6; 95% CI, 3.4–3.9), followed by pembrolizumab (ROR, 1.8; 95% CI; 1.6–2.0) ($p < 0.001$), with the lowest risks from durvalumab, atezolizumab, and avelumab. For ICI-related sarcoidosis, the risk was most significant with pembrolizumab (ROR, 3.6; 95% CI, 2.8–4.7), followed by nivolumab (ROR, 2.5; 95% CI, 1.9–3.5) ($p < 0.001$). The RORs for all five ICIs were less than 1 for exacerbations of airway diseases as compared with other drugs. **Conclusion:** Using a pharmacovigilance database, we found an increased risk of multiple pulmonary irAEs after ICI therapy, particularly with PD-1 inhibitors. Further work is needed to investigate the incidence of pulmonary irAEs other than pneumonitis.

Keywords: ROR, PD-1, PD-L1, adverse events

INTRODUCTION

The development of immune checkpoint inhibitors (ICIs) has transformed the treatment of cancer. One of the ways by which cancer cells evade immunosurveillance is the activation of immune checkpoint pathways. ICIs block the interaction between PD-1 (programmed cell death protein 1 (PD-1) and PD-L1 (programmed death ligand 1), thus promoting T-lymphocyte–mediated immune destruction of cancer cells. ICIs are given as monotherapy or alongside chemotherapy, surgery, or radiation therapy to treat different cancers regardless of stage.[1–3]

Checkpoint inhibitors are efficacious and generally well tolerated in patients. However, in any organ system these drugs can produce toxicities, known as *immune-related adverse events* (irAEs).[4–7] ICI-induced pulmonary toxicities, particularly pneumonitis, are the leading cause of ICI-related fatality and account for 35% of ICI-related deaths during treatment.[2,4,8,9]

To understand the incidence of pulmonary irAEs, including but extending beyond pneumonitis, we conducted a retrospective study from the United States Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) database, an open-access international database used to perform postmarketing surveillance on FDA-approved drugs. The FAERS database is a system that contains reports on adverse events, medication errors, and product quality of therapeutic biologic drugs. In addition, the FDA performs further investigations on medications of concern to make decisions to improve medications and protect public health. The FAERS database is available to healthcare professionals, consumers, and manufacturers globally; however, most adverse events reports come from countries in North America (i.e., United States) and Northeast Asia (Japan).[10]

The data in this study were collected from 2012 to 2021 to assess immune adverse pulmonary events in the following five common ICI monotherapies: nivolumab and pembrolizumab, which target PD-1; and durvalumab, avelumab, and atezolizumab, which target PD-L1. The pulmonary toxicities assessed in this study include pneumonitis, pleurisy, pleural effusion, exacerbations of airway disease (bronchitis and bronchiectasis), and sarcoidosis. In addition, the study aims to assess the risk of developing the described pulmonary irAEs with exposure to each ICI described above, as compared with other drugs reported in the FAERS database from 2012 to 2021. There are limited real-world data on ICI-related pulmonary adverse events because most data on ICIs come from clinical trials or single centers. Thus, this pharmacovigilance study provides an avenue to provide real-world information on the risks of developing ICI-associated pulmonary toxicities.[3,10,11]

METHODS

This study was exempt from institutional review board approval. The FAERS is a public database that is available to clinicians courtesy of the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.[12]

We analyzed pneumonitis, organizing pneumonia, and interstitial lung disease in combination, since they likely reflected the same disease process but were reported in different ways. Similarly, we analyzed pleurisy and pleural effusion in combination. We also analyzed the incidence of pulmonary sarcoidosis related to ICI exposure. Finally, we evaluated the incidence of ICI-related exacerbations of airway diseases (i.e., bronchitis and bronchiectasis).

We categorized the raw data into the following: indication for use, nature of the event (i.e., serious versus non-serious), reported date of the event, sex (male, female, or unknown), patient outcome, median age, reporter (healthcare professional, consumer, manufacturer, or others), and country for the event. Next, we calculated a reporting odds ratio (ROR) to assess the risk of developing the selected lung irAEs due to each ICI; we performed ROR calculations by using OpenVigil 2.1 (developed by Dr. Ruwen Böhm), a software package used for data mining and analysis of pharmacovigilance data.

Disproportionality analyses detect a signal in a database or investigate hypotheses based on clinical signs of a drug risk.[13,14] A disproportionality analysis in this study aims to assess the possibility of an association between a drug (checkpoint inhibitors) and an adverse reaction (pulmonary irAEs). An advantage of disproportionality analysis is that it is a cost-effective method of providing valuable information on adverse drug reactions and the safety of checkpoint inhibitors that clinical trials may not evaluate. Another strength of this disproportionality analysis is that it can represent real-life patient populations and situations.[13–15] The interpretations of ROR are as follows. A ROR equal to 1 represents a lack of signal, which means the pulmonary irAE of interest is similarly reported with the checkpoint inhibitor of interest as with other drugs in FAERS. A ROR less than one also shows a lack of signal, which means the pulmonary irAE of interest is not commonly reported with the checkpoint inhibitor of interest, compared with other drugs in the database. There is a signal for ROR greater than 1, which means that more cases of pulmonary irAE are reported with the checkpoint inhibitor of interest, compared with other drugs. The same concept applies to the 95% CI; if the lower end of the CI is less than 1, it is interpreted as a lack of signal. Conversely, a statistically significant signal exists when the lower end of the 95% CI is greater than 1; this means that the pulmonary irAE is ROR times reported with the ICI of interest than with other drugs.[13]

RESULTS

The total number of events reported in FAERS between 2012 and 2021 was 17,273,403. Of these, 88,099 (0.5%) were attributed to the PD-1inhibitors (nivolumab and pembrolizumab) and 21,905 (0.1%) to PD-L1 inhibitors

Table 1. Data from 2012 to 2021 from FAERS

Parameters	Number of Events Reported
Total AEs due to all drugs in FAERS	17,273,403
Total AEs with PD-1 of interest	88,099
Total AEs with PD-L1 of interest	21,905
Total AEs with PD-1 or PD-L1 inhibitors of interest	110,004
Total lung-related AEs of interest in FAERS	130,130
Lung-related AEs due to the PD-1 inhibitors of interest	6064
Lung-related AEs due to the PD-L1 inhibitors of interest	1848
Other AEs by reaction group in patients treated with the PD-1 or PD-L1 of interest	
Generalized disorders and administration site conditions	21,498
Gastrointestinal disorders	15,397
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	12,892
Nervous system disorders	12,325
Skin and subcutaneous tissue disorders	8452
Metabolism and nutrition disorders	4673
Musculoskeletal and connective tissue disorders	3678
Blood and lymphatic system disorders	3961
Hepatobiliary disorders	3673
Renal and urinary disorders	3579
Cardiac disorders	3513
Endocrine disorders	2936
Vascular disorders	2188
Psychiatric disorders	1376
Immune system disorders	1951

AEs: adverse events; FAERS: Food and Drug Administration Adverse Events Reporting System; PD-1: programmed cell death-1; PD-L1: programmed cell death ligand-1.

(atezolizumab, avelumab, and durvalumab). A total of 110,004 adverse events due to PD-1 or PD-L1 inhibitors were reported in FAERS. Of those, 7912 (7.2%) were from the pulmonary events of interest. Other adverse events with exposure to PD-1 or PD-L1 are summarized into reaction groups in Table 1.

Ninety-three percent of the adverse events reported in FAERS during this time were by healthcare providers, 0.3% by others (i.e., manufacturing companies), and 7.2% by consumers. In terms of sex, 59.6% and 57.9% in males for PD-1 and PD-L1 inhibitors, respectively; 25.7% and 32.5% in females for PD-1 and PD-L1 inhibitors, respectively (Supplemental Table S1, available online). The most common regions for the pulmonary irAEs associated with five ICIs were Japan (31.8%) and the United States (25.4%).

During this time frame, 130,130 patients developed the pulmonary irAEs of interest, including pneumonitis, pleural events (effusion and pleurisy), exacerbations of airway disease (bronchitis, bronchiectasis), and sarcoidosis. Among those patients, 6064 (4.7%) events were due to the PD-1 inhibitors, and 1848 (1.4%) were due to the PD-L1 inhibitors (Table 1). The median age for the cohort of patients was 66 years (Supplemental Table S1).

Table 2. Total adverse events of interest reported in FAERS from 2012 to 2021

Adverse Events	Total Events in FAERS
Pneumonitis	41,224
Pleural events (pleural effusion, pleurisy)	36,997
Exacerbations of airway disease (bronchitis, bronchiectasis)	49,344
Sarcoidosis	2565

FAERS, Food and Drug Administration Adverse Events Reporting System.

In the PD-1 exposure group, 5944 cases were serious (grades 3, 4, and 5), and 120 (grades 1 and 2) were nonserious. On the other hand, 1830 adverse events were serious (grades 4 and 5) and 18 (grades 1 through 3) were associated with the PD-L1inhibitors. Regarding the reported lung irAEs from PD-1 inhibitors, there were 2342 (38.6%) hospitalized patients, while 1962 (32.4%) patients died from the adverse event. In the PD-L1 group, there were 44 (40.3%) hospitalized patients, and 520 (28.1%) patients died from pulmonary irAEs (Supplemental Table S1).

A total of 41,224 pneumonitis events were reported in the FAERS database between 2012 and 2021 (Table 2). Nivolumab had the greatest pneumonitis events, followed by pembrolizumab. Durvalumab and atezolizumab produced similar pneumonitis events, with avelumab having the least. Nivolumab had the highest number of airway diseases and pleural events, followed by pembrolizumab. Avelumab produced the least exacerbations. In the sarcoidosis group, 2565 were reported during this time frame. Pembrolizumab had the greatest sarcoid events, followed by nivolumab, with avelumab producing the least events (Supplemental Table S2).

Table 3 shows the ROR and CIs for each selected lung irAE with each drug exposure from 2012 to 2021. Nivolumab resulted in the highest statistically significant risk (ROR, 10.5; 95% CI, 10.1–10.9) for pneumonitis, followed by pembrolizumab. Although not as high in magnitude as the PD-1 inhibitors, durvalumab and atezolizumab had a statistically significant risk for pneumonitis. Avelumab had a lesser risk for pneumonitis. The risk for pleural events was highest with nivolumab (ROR, 3.6; 95% CI, 3.4–3.9), followed by pembrolizumab (ROR, 1.8; 95% CI, 1.6–2.0) ($p < 0.001$), with the lowest risks from durvalumab, atezolizumab, and avelumab. For ICI-related sarcoidosis, the risk was greatest with pembrolizumab (ROR, 3.6; 95% CI, 2.8–4.7), followed by nivolumab (ROR, 2.5; 95% CI, 1.9–3.5) ($p < 0.001$). The RORs for all five ICIs were less than 1 for exacerbations of airway diseases as compared with other drugs.

The most common indication for the use of the checkpoint inhibitors was lung cancer: a total of 2832 (46.70%) for the PD-1 inhibitors and 1311 (70.9%) for the PD-L1 inhibitors. Other common indications for the use of the PD-1 inhibitors included malignant melanoma

Table 3. ROR for adverse events of interest versus full database from 2012 to 2021

Drug	ROR (95% CI)	*p*-value
Pneumonitis		
Pembrolizumab	8.0 (7.6–8.3)	< 0.001
Nivolumab	10.5 (10.1–10.9)	< 0.001
Atezolizumab	2.7 (2.51–2.9)	< 0.001
Durvalumab	2.7 (2.5–2.9)	< 0.001
Avelumab	0.2 (0.2–0.3)	< 0.001
Exacerbations of airway diseases (bronchitis, bronchiectasis)		
Pembrolizumab	0.2 (0.1–0.2)	< 0.001
Nivolumab	0.6 (0.5–0.7)	< 0.001
Atezolizumab	0.1 (0.1–0.2)	< 0.001
Durvalumab	0.1 (0.0–0.1)	< 0.001
Avelumab	0.00 (0.0–0.0)	< 0.001
Pleural events (effusion and pleurisy)		
Pembrolizumab	1.8 (1.6–2.0)	< 0.001
Nivolumab	3.6 (3.4–3.9)	< 0.001
Atezolizumab	0.7 (0.6–0.8)	< 0.001
Durvalumab	0.5 (0.4–0.6)	< 0.001
Avelumab	0.1 (0.0–0.3)	< 0.001
Sarcoidosis		
Pembrolizumab	3.6 (2.8–4.7)	< 0.001
Nivolumab	2.5 (1.9–3.5)	< 0.001
Atezolizumab	1.4 (0.93–2.1)	0.2–0.1
Durvalumab	0.4 (0.2–0.8)	0.02–0.01
Avelumab	0.4 (0.2–0.8)	0.02–0.01

ROR, reporting odds ratio.

(837 [13.8%]), renal cancer (443 [7.3%]), and head and neck cancers (153 [2.5%]). Other indications for the PD-L1 inhibitors include hepatocellular cancer (134 [7.3%]), pancreatic cancer (63 [3.4%]), bladder cancer (65 [3.5%]), and triple-negative breast cancer (98 [5.3%]). Figures 1 and 2 show a breakdown of the yearly indications for using the PD-1 and PD-L1 inhibitors of interest, respectively; lung cancer was the most common indication regardless of the year. Supplemental Tables S3 and S4 show a more detailed organization of pulmonary irAEs by year. Supplemental Tables S5 and S6 show the dates of first approval for each indication by the FDA for the ICIs.

DISCUSSION

In this pharmacovigilance study, we evaluated the odds of developing pulmonary irAEs (pneumonitis, pleural events [pleurisy and pleural effusion], exacerbations of airway diseases [bronchiectasis and bronchitis], and sarcoidosis) from exposure to the ICIs pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab. The study uses a disproportionality analysis on the FAERS to assess the magnitude of risk in developing the select pulmonary irAEs with exposure to checkpoint inhibitors. In this study, the definition of the pneumonitis adverse event includes reports of interstitial lung disease and organizing pneumonia in FAERS. The outcomes of the study showed the risk of the pulmonary irAEs (pneumonitis and pleural events) to be the greatest for nivolumab, followed by pembrolizumab. In terms of ICI-related sarcoidosis, pembrolizumab produced the greatest risk followed by nivolumab. The study found minimal risk for ICI-related exacerbations of airway diseases. In this study, serious adverse events are defined as life-threatening and prolonged hospitalization (grade 3 and 4), and death (grade 5).

Data on the safety of newly marketed drugs are limited to clinical trials, which may not be representative of events that occur in real-world clinical situations and patient populations. In addition, clinical trials may lack long-term drug surveillance of clinical trials; thus, rare adverse events are not identified.[16,17] Pharmacovigilance databases and analysis are essential because they provide information regarding rare and long-term safety profiles of newly approved drugs.[15,16] The availability of pharmacovigilance reporting systems helps clinicians, manufacturers, and regulatory agencies make decisions about the medication (e.g., withdrawal, relabeling).[16] A retrospective study on VigiBase (the World Health Organization [WHO] pharmacovigilance database) analyzed pneumonitis events associated with FDA-approved checkpoint inhibitors from 1967 to 2018.[18] The study showed a higher incidence of ICI-related pneumonitis with the anti–CTLA-4 (ipilimumab) and the anti–PD-1. Other pharmacovigilance studies have used FAERS from a literature review.[18–23] These studies report individual lung events associated with a specific checkpoint inhibitor and have established a risk of pneumonitis with ICIs. To our knowledge, our study is the first to assess ICI-associated pulmonary irAEs for clinical groups in which patients typically present in real-world situations instead of using classifiers in the FAERS database, as previous pharmacovigilance studies have done.

The exact mechanisms by which checkpoint inhibitors induce pulmonary toxicities are not fully understood. PD-1 proteins are expressed on T cells, whereas its ligands, PD-L1, and PD-L2, are expressed in tumor cells, normal tissues, and antigen-presenting cells. The interaction between PD-1 and its ligands downregulates T-cell activation by stimulating the differentiation of Th1 cells into Tregs.[9,23,24] Inhibition of PD-1 or PD-L1 with immunotherapy leads to T-cell activation and proliferation with downregulation of Tregs, thus, stimulating humoral autoimmunity. This inhibition also leads to the subsequent release of proinflammatory cytokines such as TNF-α, IL-1Ra, and CXCL10.[24,25] An explanation of the development of irAEs results from the cross-reactivity of antitumor T cells (PD-1) with antigens (PD-L1 or PD-L2) on healthy cells. Our study showed a higher incidence of pulmonary irAEs (pneumonitis, pleural events, and sarcoidosis) with the anti–PD-1 than the anti–PD-L1.[24] A hypothesized theory for this difference, as seen in murine models, is that blockade of PD-1 leaves PD-L2 open to bind and interact with repulsive guidance molecule B. This membrane-associated glycoprotein may play a role in developing pneumonitis and possibly other lung irAEs.[21]

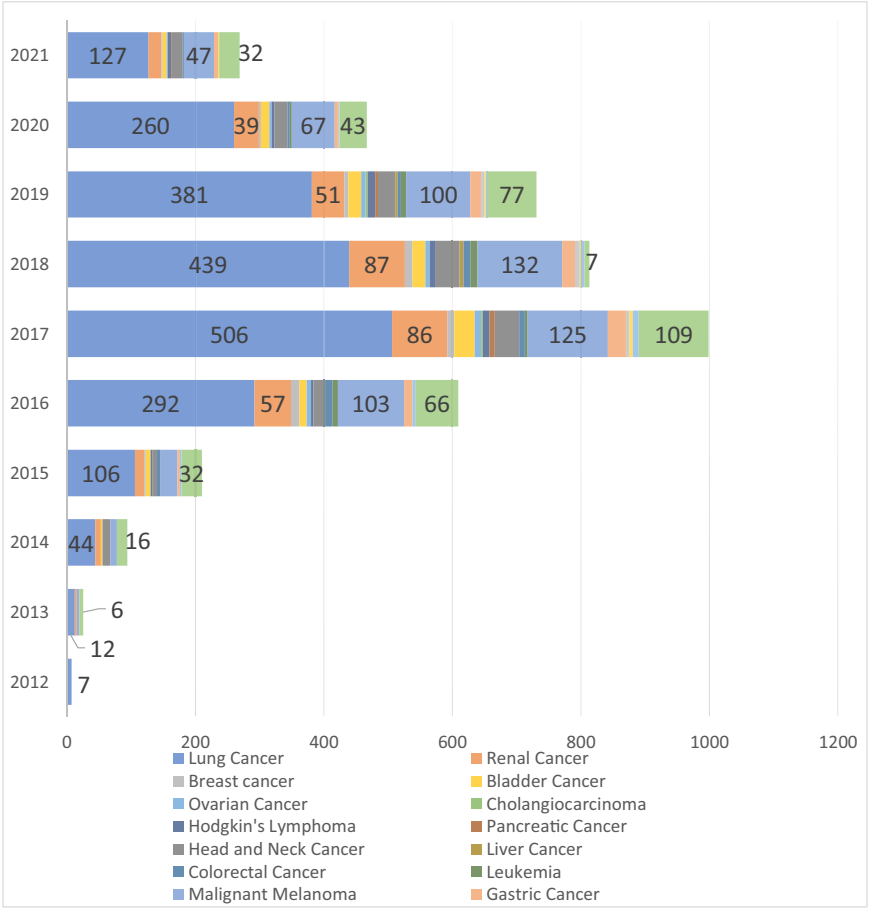

Figure 1. FAERS indications for the PD-1 inhibitors by year. FAERS: Food and Drug Administration Adverse Events Reporting System; PD-1: programmed cell death protein 1.

Our study found a significant association between ICI-related sarcoidosis and PD-1 inhibitors. Others have shown a relationship between ipilimumab, a CTLA-4 inhibitor, and ICI-induced sarcoidosis.[26] The study on the WHO pharmacovigilance database identified 103 patients with ICI-induced sarcoidosis between 1967 to 2018; the main culprit was ipilimumab.[22] Sarcoidosis-like reactions related to PD-1 inhibitors are rare. Braun et al[26] showed that the peripheral blood and bronchoalveolar lavage samples from patients with pulmonary sarcoidosis express high numbers of PD-1+ CD4+ T cells. It is hypothesized that Th17 cells play a role in the pathogenesis of ICI-related sarcoidosis; Th17 cells differentiate into Th1-like cells, which are known as Th17.1 cells.[27,28] Previous studies in patients with melanoma showed that patients who develop sarcoid-like events had increased levels of Th17.1 cells prior to initiating checkpoint inhibitors. The Th17.1 cells produce IFN-γ and IL-17, which play a role in forming granulomas seen in sarcoidosis.[28] Another group of T cells hypothesized to facilitate germinal cell centers and pathogenesis of sarcoidosis is CXCR5hiPD1hi T follicular helper (Tfh) cells.[26,29] Thus, anti-PD-1 drugs may increase Tfh and Th17.1, making patients susceptible to pulmonary sarcoidosis. We did not find a significant association between checkpoint inhibitors and airway exacerbations (bronchitis and bronchiectasis). ICI-induced exacerbations of airway disease are limited to case reports or case series.[17,30] However, research on checkpoint-inhibitor–induced exacerbations of airway disease is limited. Reporting bias may also play a role in the lack of significant association between the ICIs and exacerbations of airway disease because more severe adverse reactions are reported more frequently in the FAERS database. We could not demonstrate an association between checkpoint blockade and pulmonary airway disease.

We found that male sex and older age were risk factors for developing pulmonary irAEs associated with all the combined ICIs assessed in this study. An explanation for the differences in risk of ICI-related pulmonary irAEs is the possible variations in immune responses between both sexes.[20] The female sex is hypothesized to mount a stronger innate and adaptive immunity, resulting in less susceptibility to ICI-related irAEs than the male sex.[31–33] A retrospective study on ICI-related pneumonitis in patients with acute myeloid leukemia found it to be most remarkable in the male than in the female sex. However, another study in patients with melanoma showed a higher risk of pneumonitis in female patients than in male patients treated with ipilimumab.[32] Other

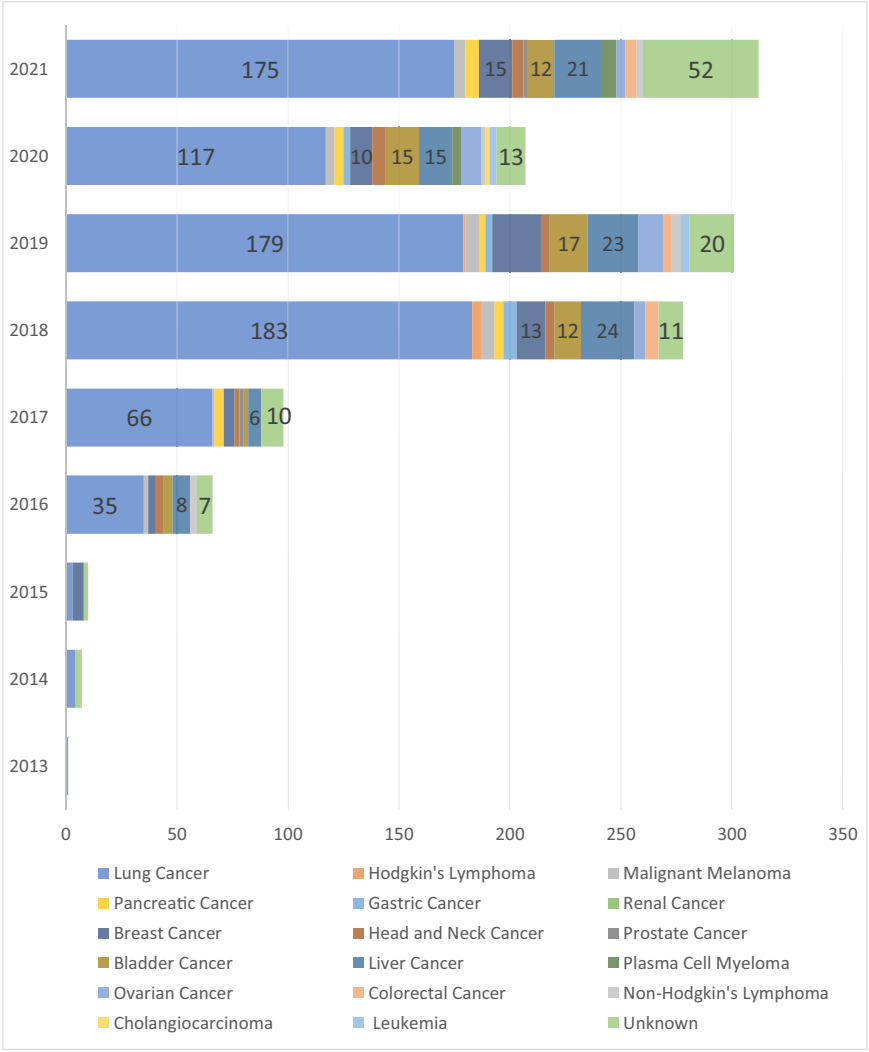

Figure 2. FAERS indications for the PD-L1 inhibitors by year. FAERS: Food and Drug Administration Adverse Events Reporting System; PD-L1: programmed death ligand 1.

retrospective studies have shown no differences in sex regarding irAEs. More prospective studies are needed to assess a clinically significant risk of pulmonary irAEs with ICIs.[31] It is unclear why older patients might have a higher incidence of irAEs. One possibility is that aging leads to increased inflammation ("inflammaging"),[34] which makes older adults more susceptible to ICI-induced toxicities. Another possibility might be the increased risk of interstitial lung disease (a form of pneumonitis) with advanced age, which is also associated with higher rates of pneumonitis.

This study has limitations and biases; thus, interpretation of the results of this study should be made cautiously. Limitations include potential underreporting of minor adverse events and overreporting of serious adverse events (i.e., pneumonitis).[14,15] This overreporting can be seen in our study, especially with anti–PD-1; the PD-1 inhibitors were first approved in 2017 for cancer therapeutics. Most pulmonary irAEs were reported in 2017–2019 and 2021. Thus, this may result in exaggerated signals in the ROR and overestimation of the severity of irAEs. In addition, it is vital to be aware that the anti–PD-1 agents were approved years before anti–PD-L136. Thus, this contributes to overestimation of the RORs in the anti–PD-1s compared with the anti-PD-L1s. There is no known phenomenon to control for these biases. To assess the extent of reporting bias, we performed an era-restricted analysis using the FAERS database to compare the ROR for the pulmonary irAEs with the anti–PD-1s and the anti-PD-L1s in 2017 and 2021. In 2017, the anti–PD-1s had a statistically significant risk (ROR, 8.6; 95% CI, 7.9–9.4) ($p <$ 0.001) for developing pulmonary irAEs when compared with the anti–PD-L1s (ROR, 1.1; 95% CI, 1.0–1.5) ($p = 0.2$–0.1). Similar to 2021, there was a statistically significant greater risk (ROR, 6.5; 95% CI, 5.9–7.0) of developing the pulmonary irAEs when compared with anti–PD-L1s (ROR, 3.3; 95% CI, 2.9–3.7) ($p < 0.001$), although with a lesser magnitude than in 2017.

Confounders include variations in the experience of reporters, leading to differing reporting patterns and lack of

uniformity in reporting.[16] Additionally, some adverse events may not be accounted for owing to reporting in different categories. For example, some sarcoidosis events may be reported as lymphadenopathy, or pneumonitis events may be reported as dyspnea. Other confounders that may influence the ROR in this study include presence of other medical comorbidities such as autoimmune conditions; the FAERS database is lacking because this information on cases reported is missing. Another confounder is the role concurrent chemotherapy or radiation therapy plays in the extent of the risk for developing the pulmonary irAEs when combined with the ICIs. We did not evaluate the ROR when the checkpoint inhibitors are combined with chemotherapy or radiotherapy, thus, this is a limitation of the study. Previous studies have associated increased incidence of CTLA-4 inhibitors with anti–PD-1 agents. Thus, our data focused on ICIs.[35]

As with other pharmacovigilance studies, this study lacks a denominator for the number of patients that received the ICIs. However, RORs are a validated method to calculate the relative odds of a given adverse event using pharmacovigilance data.[13,36,37]

This study is subject to channeling bias whereby patients exposed to the ICIs have other risk factors (i.e., autoimmune conditions, patient risk behaviors, comedications) that make them more susceptible to pulmonary irAEs, potentially leading to false-signal detection.[13–15] Finally, the choice of immunotherapy for a patient differs according to cancer type; therefore, the rate of a pulmonary irAE will differ by cancer type.[13] The relevance of this pharmacovigilance study is to alert clinicians that ICI-related pulmonary risks are more commonly associated with checkpoint inhibitor therapies, but cannot prove a causal relationship between checkpoint inhibitor therapy and pulmonary toxicities.

CONCLUSION

This retrospective review shows increased risk of pulmonary irAEs, except for bronchitis and bronchiectasis, with exposure to checkpoint inhibitors. The risk is greater for PD-1 inhibitors than PD-L1 inhibitors. Early detection is essential by frontline healthcare providers to initiate management, thus minimizing patient morbidity and mortality from the event. This pharmacovigilance study provides real-world information on pulmonary toxicities related to ICIs. The future of pharmacovigilance studies should look towards better use of digital health technologies to provide more refined, accurate, and personalized data, thus allowing clinicians to make informed decisions about immunotherapy use in patients.

Supplemental Material

Supplemental materials are available online with the article.

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