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Reported Adverse Drug Reactions of Immune Checkpoint Inhibitors in the Eudravigilance Database

Irsida Mehmeti*, Eftiola Pojani

Catholic University "Our Lady of Good Counsel", Tirana, Albania

Abstract

Introduction: Immune checkpoint inhibitors (ICIs) represent a revolution in the treatment of cancer patients. More than 40% of cancer patients in the United States of America (USA) are currently being treated with ICI. Up until now, ICIs approved by the Food and Drug Administration (FDA) for antitumor treatment include pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab, and ipilimumab.

Objectives: The main objective of the study is to identify any potential signal among reported cases of adverse events of immune checkpoint inhibitors in the Eudravigilance database and the factors influencing such as the age of the patient, the outcome of the case, gender ratio, seriousness, and reporter group.

Materials and Methods: In this study, Eudravigilance database has been used to identify potential signals for immune checkpoint inhibitors. Signals of suspected adverse events for immune checkpoint inhibitors have been evaluated using Proportional Reporting Ratio (PRR). Further, Reporting Odds Ratio (ROR) has been used to evaluate the association between the drug and the adverse event.

Results: A total of 19,712 adverse events were reported for ICI during the 2016-2020 period in the Eudravigilance database. The drug associated with most of the events was Nivolumab (7,628),

Address for correspondence: Irsida Mehmeti*, Rr. Dritan Hoxha, Tirana, Albania, 1000. E-mail: i.mehmeti@unizkm.al

followed by Pembrolizumab (6153). PRR values > 1 have been identified for Pembrolizumab for the following System Organ Class (S.O.C) and Preferred Terms (P.T); PRR of 1.26 for cardiac disorders, 1,76 for general disorders and administration site disorders, 2.1 for immune system disorders,1.9 for cytokine storm, 2.32 for drug ineffective, therapeutic response decreased, 2.6 for product issues, 1.2 for drug intolerance or withdrawn.

Conclusion: The real incidence rate of the adverse events cannot be determined with certainty because of the underreporting which is the major disadvantage of passive surveillance systems. Moreover, confounding factors such as genetics, weight, age, gender, comorbidities, combination therapy, and underlying clinical conditions might influence the prevalence of an adverse event reported after an ICI. Specific studies investigating causality must be implemented.

Keywords: immune checkpoint inhibitors, reported events, adverse events, eudravigilance

INTRODUCTION

Immune checkpoint inhibitors (ICIs) represent a revolution in the treatment of cancer patients. More than 40% of cancer patients in the USA are currently being treated with ICI (1). Ipilimumab was the first ICI approved in 2011 for the treatment of melanoma. Pembrolizumab and nivolumab represent the second generation of immune checkpoint inhibitors which target the Programmed Cell Death Protein 1/ Programmed Cell Death Ligand 1 (PD-1/PD-L1) pathway. The ICIs approved by Food and Drug Administration (FDA) for antitumor treatment until 2022 include pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab, and ipilimumab. While the indications of PD-L1 inhibitors are restricted to urothelial carcinoma, non-small-cell lung cancer (NSCLC), and metastatic Merkel cell carcinoma, the inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTL4) are indicated for the treatment of melanoma. The CTL4 inhibitors are indicated for different types of cancers and some of them such as melanoma, and NSCLC, have demonstrated a high response rate (2). Their role in clinical practice is expected to increase.

AntiCTLA-4 agents usually enhance T cell priming, whereas the blockade of PD-1 or PD-L1 reinvigorates pre-existing cytotoxic (CD8+) T cell responses which explains the increased frequency and severity of immune-related adverse events (irAEs) associated with anti-CTLA-4 agents. PD-1:PD-L1 interactions preserve the PD-1:PD-L2 interaction, which may explain the lower

incidence of irAEs with PD-L1 inhibitors (3).

Moreover, CTLA-4 and PD-1/PD-L1 inhibitors demonstrate different patterns of tissue toxicity. While CTLA-4 deficiency is lethal for mice, with multiorgan infiltration by polyclonal T cells, PD-1 deficiency induces less severe autoimmune diseases such as rheumatoid arthritis or dilated cardiomyopathy and it does not have a fatal ending in mice (4). Studies in animals have shown that CTLA-4 deficient mice rapidly develop severe myocarditis and pancreatitis, and die at 3-4 weeks of age (5). ICIs may induce proinflammatory cytokine storms in the heart tissue (6). However there are no standard diagnostic criteria or consistent biomarkers for cardiac toxicity of immune checkpoint inhibitors which limits the diagnosis based on medical history (7).

Anti-CTLA4 and anti–PD–1 primarily act at different stages of the cancer immunity cycle with CTLA4 blockade primarily acting at sites of priming in which CD28-positive co-stimulation is involved (e.g., tumor draining lymph nodes) whereas PD-1 blockade primarily acts in inflamed peripheral tissues (8). Recent findings demonstrate that CD28 co-stimulation is necessary for responses to PD-1 (9). CTLA-4 and anti-PD-1/PD-L1 antibodies have recently been termed ‘immune enhancers’ and ‘immune normalizers’, respectively (9). Studies suggest a correlation between the occurrence of irAEs and the increase in clonal diversity of T cells. This

leads to the conclusion that irAEs may result from a mobilization of large numbers of T cells, some of which are autoreactive (10).

The safety and efficacy of anti-PD-1 or anti-PD-L1 monoclonal antibodies are being evaluated by more than 2000 clinical trials (11). The spectrum of side effects is mainly related to autoimmune and autoinflammatory reactions. Therefore, irAEs are a common complication of checkpoint inhibitors although the exact mechanism is not well known (12).

The irAEs can affect any organ system such as the gastrointestinal tract, skin, and endocrine glands. Severe reactions are associated with pulmonary, cardiac, and neurologic systems (13). The severity of the side effects is classified based on Common Terminology Criteria for Adverse Events (CTCAE). While grade 1 reactions are generally mild, grade 3 or 4 reactions are often severe and/or life-threatening conditions requiring intervention. The majority of irAEs are mild to moderate.

The incidence and severity of irAEs varies from the dose of the CTLA-4 inhibitor, and if there is combination therapy or monotherapy (14).

The incidence of immune-related adverse events varies from 74% in cancer patients treated with PD-1/PD-L1 inhibitors, to 89% in the CTLA-4 inhibitor group, 90% in the ICI combination group, and 89% in the ICI plus chemotherapy group (14).

The incidence of Cardiac complications from immune checkpoint inhibitors is reported as <1% (15). Although ICI-associated cardiotoxicity is uncommon, it has a high fatality rate (16). The cardiac toxicity can manifest as heart failure, cardiomyopathy, conduction abnormalities, myocardial fibrosis, myocarditis, and pericarditis. Myocarditis is the most common adverse event and it is highest with the combination of ipilimumab and nivolumab compared with nivolumab alone (17).

Dermatological toxicities occur early after the initiation of treatment with ICI therapy and are among the most common immune-related side effects occurring in 30–40% of patients treated with PD-1/PD-L1 blockade and in approximately 50% of patients treated with CTLA-4 inhibitors (18). The severity of dermatological adverse events is mild to moderate (grade 1–2) with rash and pruritus being the most common. However, serious toxicities such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and systemic symptoms have been described (19).

Due to factors such as strict diagnosis standards, selection criteria, relatively small sample sizes, and limited duration of follow-ups, the real profile of irAEs cannot be characterized in pre-market clinical trials. Hence, post-marketing monitoring is necessary to assess the real prevalence of irAEs associated with ICIs.

Eudravigilance is a passive pharmacovigilance system for managing the collections and analysis of collecting, managing and analyzing suspected adverse reactions to medicines authorized in the European Economic Area (Eudravigilance | European Medicines Agency (europa.eu).

The main objective of the study is to identify any potential signal among reported cases for adverse events of immune checkpoint inhibitors in the Eudravigilance database using the Proportional Reporting Ratio (PPR) as an indicator. The higher values of PPR have been considered to further evaluate the influencing factors such as age of the patient, outcome of the case, gender ratio, seriousness, and reporter group.

The purpose is to highlight those signals that might be new, serious, and preventable to further suggest the investigation of the causality through profound studies. The analysis of safety data from spontaneous reporting systems has a proven value for signal detection.

The obtained results will be confronted and discussed in relation to the data published in the literature.

MATERIALS AND METHODS

Data resource

In this study, Eudravigilance database has been used to identify potential signals for immune checkpoint inhibitors (20). Data was extracted from individual case safety reports (ICRs).

In the Eudravigilance database, the adverse events are grouped in System Organ Class (S.O.C) which is composed of Preferred Terms (P.T) of reporting. For the same event, there might be several preferred reporting terms. The possibility to report an adverse event is given to the public, healthcare professionals, and the pharmaceutical industry.

We have used only the S.O.C of interest in order to exclude other reported events that might inflate the magnitude of the PRR.

The current study used disproportionality analysis including Reporting odds ratio (ROR) and PRR for signal detection.

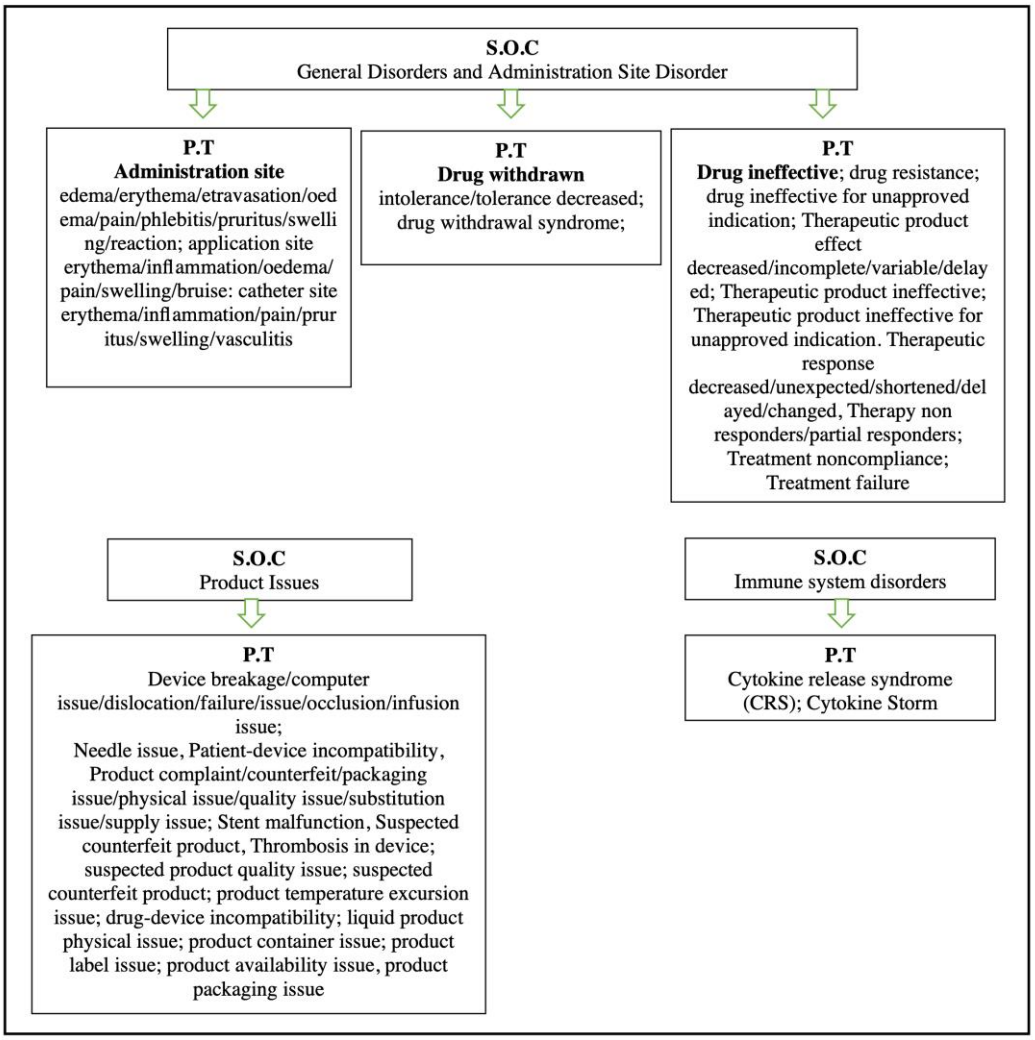
Signals of suspected adverse events for immune checkpoint inhibitors have been evaluated using PRR. Further, ROR has been used to evaluate the association between the drug and the adverse event. We assessed the association between the drug and the adverse event by comparing the proportion of reported cases for the interested adverse events of the target drug with the proportion of the same event reported for other ICIs in the database. Subjects of the study were 6 drugs used in cancer therapy belonging to the group of immune checkpoint inhibitors: avelumab, pembrolizumab, durvalumab, nivolumab, atezolizumab, and ipilimumab. After the identification of higher PRR related to a specific medicine, we have further investigated the possible reasons behind this high value of PRR in terms of reporting group, geographical area, gender ratio, the seriousness of the events, and reported cases over time. The selected age group of patients has been 18-64 years old as this age group has less probability of underlining confounding factors related to concomitant pathologies.

After identifying the drug with higher PRR, we have further confronted the type and number of Adverse Drug Reactions (ADR) reported for that drug.

The selected S.O.C. are Cardiac disorders, General disorders and administration site disorders, product issues, and immune system disorders. Further, in order to calculate the PRR related to specific events such as administration site condition, withdrawal of the drug, cytokine storm, and inefficacy of the treatment, we have separated these events from their SOC. Thus, the following preferred terms (P.T) have been used to analyze the type and number of ADR reported for the specific event. (Figure 1)

The preferred terms have been selected according to their frequency and synonyms.

Based on the number of cases reported for each S.O.C and each group of P.T. we have calculated the PRR in order to evaluate the relative risk of an ADR reported for a specific drug of interest.



S.O.C. (System Organ Class), P.T. (Preferred Terms)

Figure 1. The preferred terms used to search for reported adverse events for immune checkpoint inhibitors

Values of PRR >1 indicate an elevated risk of ADR which is more frequently reported for the drug of interest compared to other drugs. However, values of PRR >1 result also from sample variations, bias of reporting, multiple reporting of the same case, and flawed reports.

Data analysis

Data are expressed in ratios and frequency. The data has been extracted from Eudravigilance and analyzed using the Excel Microsoft Office program.

The PRR has been calculated using the following equation:

a/(a+c)/b/ (b + d)

where a is the reaction of interest to a given drug of interest, b is the reaction of interest to all the other drugs in the class, c are all other reactions to a given drug of interest, d is all other reactions to all the others drugs of the class (21).

Signal definition: PRR ≥ 2, a minimum of three reports/cases for the reaction of interest, X2 ≥ 4. No signal is identified, if PRR is = 1. The duplication of a specific report was manually assessed and excluded from the analysis.

In order to assess the causes of a higher PRR related to the drug of interest, the Line Listing section of the Eudravigilance database has been used in order to identify the responsible mechanisms for such value. The list of ICSRs has been transferred to Excel and filtered for the requested information in terms of year of reporting, monotherapy or multiple therapy, co-administration of other drugs, eventual drug withdraws, and outcome of the case.

Further, ROR has been used to evaluate the strength of the association between the drug of interest and the reported ADR. If a signal is identified (using PRR), the characteristics of the signal will be analyzed in terms of the strength of the signal (using ROR) and type of signal (type of reported event, seriousness).

RESULTS

1. Reported events

A total of 19,712 of adverse events were reported for ICI during the 2016-2020 period in the Eudravigilance database. The drug associated with most of the events was Nivolumab (7,628), followed by Pembrolizumab (6153). The data are presented in table 1.

2. Signal Detection

PRR values > 1 have been identified for Pembrolizumab for the following S.O.C and P.T; PRR of 1.26 for cardiac disorders, 1,76 for general disorders and administration site disorders, 2.1 for immune system disorders,1.9 for cytokine storm, 2.32 for drug ineffective, therapeutic response decreased, 2.6 for product issues,1.2 for drug intolerance or withdrawn. (Figure 2)

PRR values > 1 have been identified also for other drugs for a few events, but pembrolizumab had values >1 for all the reported ADRs.

Table 1. Number of Reported Adverse Events after ICI therapy in the Eudravigilance Database between 2016-2020

IMMUNOLOGICAL DRUG	**N of total ADR of immunologic drug class (a+b) adult 18-64 years old**		**Cardiac Disorders**		**General disorders and administration site conditions**		**PRODUCT ISSUES**		**Immune system disorders**	
Nivolumab	7.628	39%	304	39%	2189	41%	3	27%	160	27%
Pembrolizumab	6153	31%	283	36%	1548	29%	6	55%	287	49%
Durvalumab	756	4%	35	4%	134	2%	0	0%	8	1%
Atezolizumab	1283	7%	60	8%	351	7%	1	9%	31	5%
Avelumab	181	1%	5	1%	52	1%	0	0	5	1%
Ipilimumab	3711	18%	92	12%	1114	21%	1	9%	93	16%
Total	19712	100%	779	100%	5388	100%	11	100%	584	100%

ADR; Adverse Drug Reaction

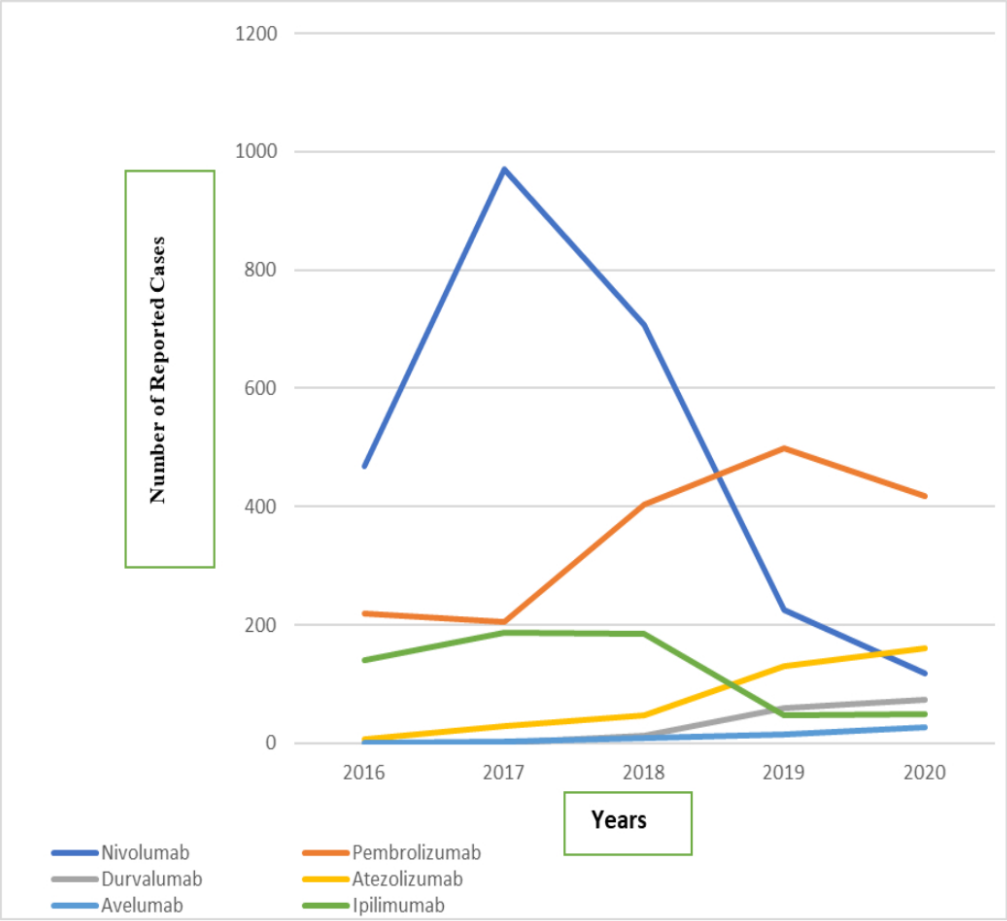


Figure 2. PRR values for Immune Checkpoint Inhibitors

A ROR>2 for Pembrolizumab was reported for the following adverse events: Immune system disorders (2,18), product issues (2.65), cytokine storm (2), treatment failure (2.37).

A ROR> 1 for Pembrolizumab was reported for cardiac disorders (1.26), administration site condition (1.7), drug withdrawal (1.2) .

3. Reporter Group

In the Eudravigilance pharmacovigilance system, the possibility to report an adverse event is offered to all the public: healthcare professionals and patients or non-healthcare professionals.

The table below reports in % the number of cases derived from healthcare professionals (HCP) and non-healthcare professionals (N-HCP). It is observed that the percentage of non-healthcare workers is similar among all the immune checkpoint inhibitors. However, compared to other substances, Pembrolizumab has the highest rate for non-healthcare professionals reporting rates related to general disorders and administration site conditions (23%) as seen in Table 2.

Table 2. No of ADR for each ICI according to the reporting group

SOC	CARDIAC DISORDERS		IMMUNE SYSTEM DISORDERS		PRODUCT ISSUES		GENERAL DISORDERS AND ADMINISTRATION SITE DISORDERS	
REPORTER GROUP	HCP	N-HCP	HCP	N-HCP	HCP	N-HCP	HCP	N-HCP
Nivolumab	91.59%	8.41%	93.70%	6.26%	61.54%	38.46%	91.70%	8.30%
Pembrolizumab	96.34%	3.66%	96.43%	3.57%	70.83%	29.17%	76.75%	23.25%
Durvalumab	90.67%	9.33%	90.00%	10.00%	0.00%	0.00%	94.10%	5.90%
Atezolizumab	94.24%	5.76%	93.58%	6.42%	0.00%	100.00%	86.71%	13.29%
Avelumab	100.00%	0.00%	100.00%	0.00%	0.00%	0.00%	93.53%	6.47%
Ipilimumab	91.53%	8.47%	92.13%	7.87%	100.00%	0.00%	78.96%	21.04%

4. Seriousness of the reported cases

For all the substances the proportion of serious events is considerably greater than that of non-serious ones. Cardiac disorders represent 99% of adverse drug reactions reported as serious for Nivolumab, 98,8% for Pembrolizumab, 98% for Durvalumab, 95,8% for Atezolizumab,100% for Avelumab,99,6 for Ipilimumab. Almost the same % is also observed for other S.O.Cs. The General Disorders and Administration Site Disorders are observed to represent 68.6% of the total reported cases for Avelumab. This % is higher for other substances. There is not observed any significant difference between the medicines in terms of serious reactions.

5. Reported cases over time.

As it is shown in Figure 3 the reported case for each drug rises 1 or 2 years after their first introduction in the market. Nivolumab was introduced in 2014 and a rise in reported ADR was observed in 2016-2017. After this time the cases start to decrease. Atezolizumab was approved by the FDA in 2016. Reported ADR for atezolizumab started to rise in 2018. Pembrolizumab was first approved in 2014.

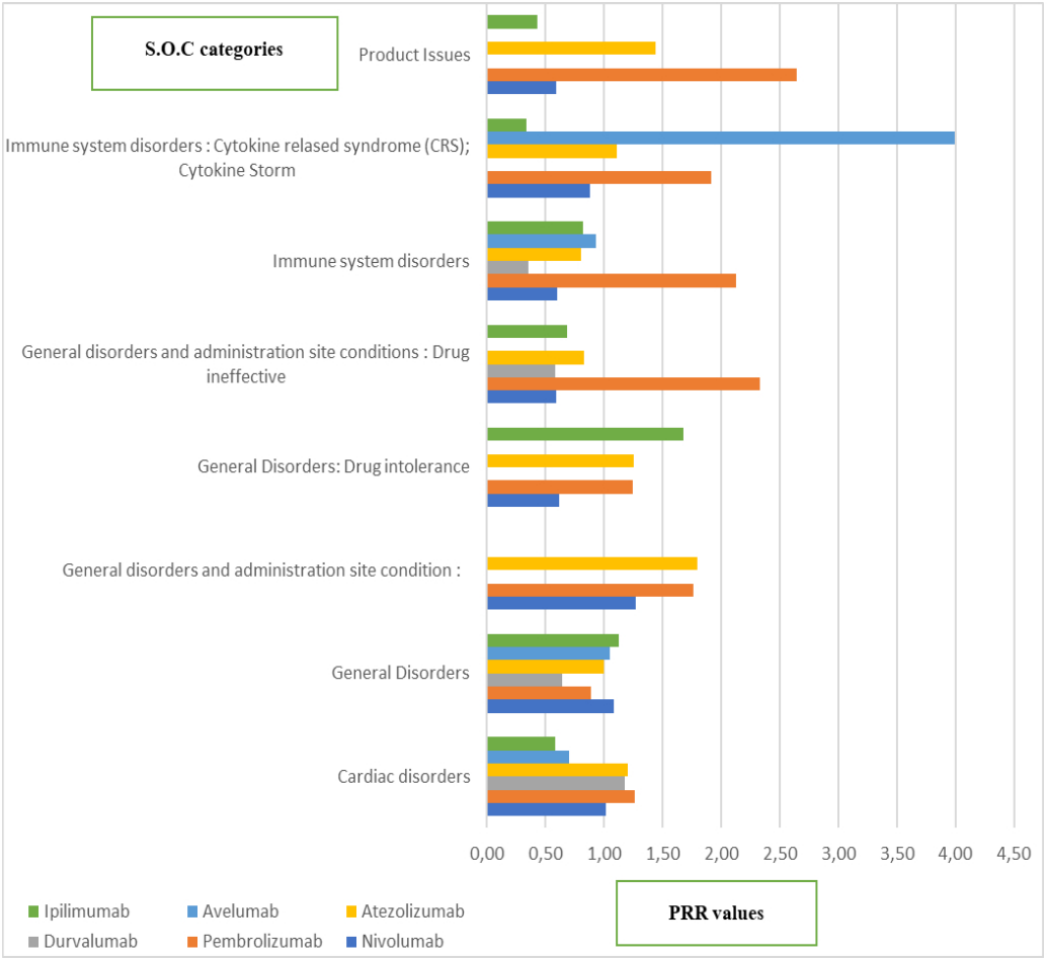


Figure 3. Number of reported cases for each ICI in the last 5 years

However, in 2017 it received a new approvement for any unresectable or metastatic solid tumor with certain genetic anomalies. Therefore, reported cases started to rise in early 2018.

The tendency to report any adverse event after the introduction of a new medicine into the market is known as the Webber effect (22).

6. Reported cases in terms of geographical area

The majority of the cases have been reported from non-European Economic Area. There is no significant difference between the six drugs in terms of % of cases reported from non-European Economic Area.

7. Drug withdrawn proportion during the year 2020

As it is observed from Table 3 below, the highest number of withdrawn cases in 2020 is related to Pembrolizumab. However, a higher % of withdrawn cases is associated with Avelumab and Nivolumab. In more than 50% of the cases, at least one more drug was co-administered by the patient.

DISCUSSION

Associating an adverse event with an ICI treatment is complex due to the absence of prospective clinical studies with defined strategies for the proper monitoring of adverse reactions related to the immune system. This association becomes more difficult because of the multifactorial characteristics of neoplastic diseases and the exposure to different risk factors that influence the different carcinogenic mechanisms. The extent and nature of irAEs are unpredictable and different from patient to patient. However, it has been observed that irAEs

Table 3. Number of withdrawn cases of ICI in 2020

REACTION GROUP: CARDIAC DISORDERS, IMMUNE SYSTEM DISORDERS, GENERAL DISORDERS AND ADMINISTRATION SITE CONDITION, PRODUCT ISSUE		**YEAR:2020**		**AGE:18-64**
SUSPECTED DRUG	TOTAL CASES	WITHDRAWN	% of Withdrawn cases	OTHER SUSPECTED DRUG
Nivolumab	118	49	41.53	Ipilimumab in 43 cases
Pembrolizumab	417	148	35.49	Pemetrexed in 78 cases
Durvalumab	73	22	30.14	
Atezolizumab	160	37	23.13	Bevacizumab in 32 cases
Avelumab	28	12	42.86	Axitinib in 24 cases
Ipilimumab	50	17	34	Nivolumab in 43 cases

resemble classic autoimmune diseases (23). Several factors influence the type and intensity of ICI-related adverse events.

While, clinical studies have reported that immune adverse events are more common and more severe with ipilimumab (24), in this study it is observed that nivolumab has the highest rate of cases reported by non-healthcare professionals compared to other drugs.

This result might partly influence the high rate of adverse events reported with this medication due to the high bias associated with reports derived from non-healthcare workers. It is well known that the familiarity of health workers with the pharmacovigilance system depends on the training received. Although training is essential for health care providers, only 35% of 26 studied European Union countries had developed a training program or manual for nurses on prevention, identification, and treatment of adverse events (25). PRR value for other drugs might be reduced by the over-reporting of ADR for Nivolumab which might result from different factors such as the tendency to report any adverse event for newly introduced drugs. Moreover, we considered also the events reported for product issues which might overrate the adverse events reported for Nivolumab.

However, significant ROR values were found for Pembrolizumab which is in concordance with studies in the literature. There are a few studies that report that pembrolizumab is most associated with adverse events. Wang et al conducted a systematic review of fatal toxic effects from ICI using World Health Organization (WHO) pharmacovigilance database (Vigibase-Vigilyze), international multi-institutional treatment data, and all published clinical trials to characterize more than 750 fatal irAEs (16). PD1/PD-L1 inhibitors in general were associated with lower FAEs compared with either anti-CTLA-4 monotherapy or the combination. However, fatal adverse events occurred with marked distinctions between ICI regimens (26).

The combination of CTLA-4 and PD-1 or PD-L1 inhibitors is known to increase both the incidence and severity of immune-related AEs when compared to single-agent regimens (27). A recently published meta-analysis including 17,197 patients evaluated incidence rates of adverse events (AEs) secondary to combination regimens of one active treatment (chemotherapy, targeted therapy, immunotherapy, or radiation therapy) with PD-1 or PD-L1 inhibitors in 161 prospective trials (28). It was reported that the incidence of AEs following the combination was 86.8% (95% CI = 80.9 – 91.1; I2 = 94%) for all-grade AEs. In this study, most of the reported cases had at least another drug co-administered with the suspected drug for adverse events.

Most of the reported events in the Eudravigilance database are serious. In spontaneous reporting, there is a tendency to not report mild and more predictable reactions such as local reactions, but severe reactions are reported. Thus, spontaneous reporting might have the capacity for early detection when it is properly conducted. However, for the detection of rare events, it might

be necessary to implement contemporaneously ad hoc programs.

A meta-analysis evaluating the fatal adverse reactions of pembrolizumab reported in 11 clinical trials with 3713 patients, concluded that the overall incidence of fatal adverse events with pembrolizumab was 1.2% (29). However, due to the limited number of patients, the overall incidence of Fatal Adverse Events (FAEs) with pembrolizumab in cancer patients is unclear. In another study, using the disproportionality analysis to evaluate 32,441 safety reports based on the Food and Drug Administration Adverse Event Reporting System (FAERS) from January 2004 to December 2019, it was concluded that pembrolizumab had the highest fatality proportion (30).

Another systematic review and network meta-analysis found that pembrolizumab had a higher risk of pneumonitis and arthralgia (31). In a systematic review aiming to evaluate the efficacy and safety of pembrolizumab by analyzing survival outcomes in 3,953 patients, it was reported that the most frequently occurred events included pruritus (OR =1.899, 95% CI: 0.125–8.769) and rash (OR =1.751, 95% CI: 0.863–3.551) (32).

A study characterizing the clinical features of irAEs associated with ICIs using the Japanese Adverse Drug Event Report database reported RORs of 9.08 (8.28-9.97 of pneumonitis associated with pembrolizumab which was higher than the other drugs) (33). In another systematic review including 125 clinical trials, Nivolumab was associated with higher mean incidences of all-grade adverse events compared with pembrolizumab (34). Factors influencing the pathogenesis of irAEs are different. It had been found that anti-PD-1/PD-L1 and anti-CTLA-4 had differences in terms of types, rates, time to onset, and severity of irAEs (35).

IrAEs occur mostly within the first 12–16 weeks of treatment (36).

The clinical activity of PD-1 and CTLA-4 blockade is influenced by the presence of pre-existing T cells before therapy whose density in melanoma patients is positively correlated with good clinical response (37). The more severe the disease and the longer the exposure to the antigen, the more exhausted T cells we have. Recent studies suggest that blockade of the PD-1–PD-L1 axis does not reinvigorate exhausted T cells, as the epigenetic profile of exhausted T cells remains stable after anti-PD-1 therapy (23). Pre-existing autoimmune disorders, baseline circulating cytokine and chemokines levels which may reflect pre-existing inflammatory reactions might be an indicator of the possibility for the occurrence of irAEs (38). A recent meta-analysis revealed that colitis, hypophysitis, and rash were more frequent with anti-CTLA-4 antibodies whereas pneumonitis, hypothyroidism, arthralgia, and vitiligo were more common with anti-PD-1 antibodies (39). Other factors that influence irAEs include age, sex, comorbidities, prior anti-cancer treatment, and the composition of the microbiome (40).

Several studies suggest a positive relationship between the occurrence of immune-mediated toxicities and a favorable tumor immune response. The conclusions of this study lead to the consideration of irAEs as a clinical biomarker for the response of ICIs. In particular, skin irAEs such as vitiligo may be associated with treatment efficacy (41).

An altered balance between Tregs and T effector cells results in a loss of peripheral tolerance, leading to the development of irAEs. PD-1 and CTLA-4 are expressed on the surface of Tregs which have a crucial role in the perseverance of immune homeostasis. Especially CTLA-4 is a key molecule

and ICIs could directly target Tregs (42).

Although, it is well-known that females are at a higher risk of several autoimmune diseases as hormones influence the immune response, in this study no significant difference was found between males and females. A study by Valpione et al reported that females were associated with higher rates of irAEs (43). In a systematic review by Ahmed et al, it was concluded that combined immunotherapy nivolumab plus ipilimumab was associated with a statistically significant higher risk of all grade AEs.

Hence, the exact contribution of nivolumab is not known due to the influence of confounding factors. Moreover, the proportion of serious adverse events varies considerably in national surveillance systems due to different definitions.

AE reporting rates vary among different cultural differences in various countries. Geographical variations in AE reporting are a known phenomenon (44). Joelson et al. (45), showed that adverse events reporting rates fluctuated between 17% and 68% in 13 different countries. This variation should be considered when comparing the safety results from clinical trials with diverse geographical areas. In our study, most of the reported cases were from non-European economic areas. These countries, not being part of the European Union might develop their own case definitions for adverse events, which might be partially different from those of the European Union. Differing case definitions influence the rate of reporting.

A deep insight into the mechanism of action of ICIs, might help to highlight any possible association between the molecular target of these medicines and adverse reactions (46). Although PD-1 (CD279) receptor is expressed broadly on peripheral CD4þ and CD8þ T cells, B cells, and myeloid cells, its ligands; PD-L1 (CD274) and PD-L2 (CD273) are expressed both in hematopoietic cells (dendritic cells, macrophages, T cells, and B cells) and in non-hematopoietic cells (e.g., endothelial cells, pancreatic islet cells, testes, eye, and cardiomyocytes) (47). This differential expression of CTLA-4 (CD152) and PD-1 (CD279) receptors on different cells may explain the different clinical responses and different adverse events related to this agent. Studies in murine models have shown that CTLA-4 and PD-1 do not have the same impact on immune system homeostasis (48). The severity of irAEs is higher

with CTLA-4 inhibitors than with PD-1/PD-L1 inhibitors and even higher with combined immune checkpoint blockade (48).

Although this study is based on real-world data, the analysis of AEs had certain limitations based on the nature of the Eudravigilance database and confounding factors such as potential drug-drug interactions, comorbidities, combination medication, and reporting bias. The results of this study are obtained from Spontaneous reports of adverse events in the Eudravigilance database. The limitations of passive pharmacovigilance systems include inadequate training of health care workers, inappropriate application of standard case definitions, low quality of data, incompleteness of data reported, and inadequate follow-up. Disproportionality measures of PRR and ROR only provide an estimate of the signal strength. They do not quantify the risk or causality.

CONCLUSION

Although, PRR represents a direct measure of the strength of the signal, without systematic review of data, the functions of the passive surveillance system are not valuable. The real incidence rate of the adverse events cannot be determined with certainty because the underreporting which is the major disadvantage of passive surveillance systems. Moreover, confounding factors such as genetics, weight, age, gender, comorbidities, combination therapy and underlying clinical conditions might influence the prevalence of and adverse event reported after an ICI.

Understanding the mechanisms underlying the adverse reactions should be e future objective of the research. Statistical signal detection should be complemented by scientific assessment in order to determine a causal association. More insight should be given to the factors being responsible for the occurrence of adverse events. Specific studies investigating causality must be implemented.

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