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Original research

Ocular adverse events with immune checkpoint inhibitors

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Abstract

Purpose: To quantify the risk of ocular adverse events with immune checkpoint inhibitors (ICIs) as reported to the Food and Drug Administration (FDA).

Methods: Disproportionality analysis using data from U.S. FDA's Adverse Events Reporting System (FAERS) database 2003 to 2018. Data from pharmaceutical manufacturers, healthcare providers, consumers in the U.S., and post-marketing clinical trial reports from U.S. and non-U.S. studies. All cases of uveitis, dry eye syndrome, ocular myasthenia and eye inflammation with use of the following ICIs: atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab and pembrolizumab. Reported odds ratios (RORs) and corresponding 95% confidence intervals (CIs) were computed for all drugs as a group or as individual agents.

Results: We identified 113 ocular adverse events for all ICIs of interest including uveitis, dry eye, ocular myasthenia and eye inflammation. Nivolumab had the highest number of adverse events (N = 68) associated with use of the ICI. Nivolumab had the highest association with ocular myasthenia [ROR = 22.82, 95% CI (7.18–72.50)] followed by pembrolizumab [ROR = 20.17, 95% CI (2.80–145.20)]. Among all ICIs approved in North America, atezolizumab had the highest association with eye inflammation [ROR = 18.89, 95% CI (6.07–58.81)] and ipilmumab had the highest association with uveitis [ROR = 10.54, 95% CI (7.30–15.22)].

Conclusion: The results of this disproportionality analysis suggest use of ICIs is associated with an increase risk for ocular adverse reactions. Future epidemiologic studies are needed to better quantify these adverse events.

Keywords: Immune checkpoint inhibitors; Immunotherapy; Drug-induced; Uveitis; Eye inflammation; Disproportionality analysis

Introduction

Immune checkpoint inhibitors (ICIs) are a relatively new class of immunotherapy used for the approved treatment of different types of cancers. Currently, the latest landscape of the Food and Drug Administration (FDA) approved ICIs for cancer therapy include atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab.[1] ICIs fundamentally induce the body's inflammatory response by preventing the immune system's ability to prevent autoimmunity using immune checkpoint proteins including cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death 1 (PD-1).[2] Malignant cells take advantage of CTLA-4 and PD-1 checkpoint proteins to evade and suppress the human body's immune response against cancer cells.[2] ICIs overcome this by allowing the immune system to target otherwise poorly immunogenic tumor antigens.[2] As a result, ICIs have revolutionized the treatment of a number of cancers and have demonstrated efficacy in multiple promising trials

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such as against breast cancer, colorectal cancer, follicular lymphoma, gastric cancer, ovarian cancer, pancreatic cancer, sarcoma, prostate cancer and uterine.[3] ICIs have also been linked to a number adverse events including colitis, pneumonia, hepatitis and neurotoxicities.[4]

Immune-related adverse events are toxicities caused by non-specific activation of the host's own immune system resulting in inflammation. It is thought that ICIs may expose pre-existing organ-specific inflammation through the development of inflammatory toxicity, the same mechanism responsible for the therapeutic effects.[4] One meta-analysis proposed that immune-related adverse events were triggered by a mechanistic-driven hypothesis such that CTLA-4 inhibition on T cells would induce a higher incidence of adverse events compared to PD-1 inhibition on tumor cells. The group found that the incidence for CTLA-4 inhibition monotherapy and PD-1 inhibition monotherapy were 53.8% and 26.5%, respectively, out of 3418 patients.[5] The broad range of adverse events shown in these studies, highlight the need to consider other areas of potential adverse drug reactions, for example, ocular adverse events.

Ophthalmological adverse events are well-recognized and occur less frequently, yet vision-threatening if not identified early. The current understanding of ocular adverse events have been reported with ICIs mostly in the form of case-reports and case-series.[6] A recent review of ocular adverse events cases found several neurologic adverse events occurring at a median onset of 35 days after ICI therapy including optic neuritis and myasthenia gravis.[7] Another review of ophthalmic side effects found that the most frequent ICI side effects included uveitis, dry eye and myasthenia gravis with ocular involvement.[8]

Given the rarity of ocular adverse events with ICIs, large population-based studies using Big Data are the ideal study design to quantify these risks. Recently a prospective cohort study attempted to examine the association between ICIs and ocular adverse events in 745 patients.[9] This study found five cases of intraocular inflammation, two with ocular surface disease and one with orbital myopathy.[9] However, due to a small sample size and short follow-up, not all adverse events could be ascertained, and thus relative risks could not be computed.[9] With a limited number of epidemiologic studies that specifically examine ocular adverse events secondary to ICIs, we undertook a disproportionality analysis. This technique uses the Food and Drug Administration Adverse Events Reporting System (FAERS) databases to examine the frequency of these reported events to the FDA with ICIs compared to the reported events with all other drugs.[10] As ICIs have a delayed onset and prolonged duration compared to adverse events from chemotherapy, early recognition with immunomodulatory strategies are urgently needed to identify, report and manage organ-specific toxicities until data from large epidemiological studies are available to inform clinical decision-making. Ultimately, this information will assist ophthalmologists and other health care providers to better recognize specific ocular adverse events that may be more frequently associated with each individual ICI.

Methods

We used a disproportionality analysis using the FAERS as the main study design for this study.[11] FAERS captures reported spontaneous adverse drug reactions for all drugs reported to the FDA. Cohort studies may underestimate the prevalence of ocular complications, as mild ocular manifestations may be overlooked, and ophthalmologic examination is only performed upon the request of the patient's complaints.[9] On the other hand, FAERS is a powerful and comprehensive database whereby reports can be sent by pharmaceutical manufacturers, healthcare providers, consumers in the United States, and post-marketing clinical trial reports from U.S. and non-U.S. studies. FAERS data is available to the public. For this study, ICI data was collected from Quarter 4 (Q4) 2003 to Quarter 3 (Q3) 2018 in the FAERS database.

Disproportionality analyses compute the reported rate of a specific adverse drug reaction with a specific drug and compares this rate to the rate reported with all other drugs to the FAERS.[10] This technique has been used by the FDA as part of the drug safety assessment of drugs when issuing warnings to physicians.[12,13]

For this study, we included the following adverse events – uveitis, dry eye, ocular myasthenia and eye inflammation. Although eye inflammation is a broad search term which includes uveitis, endophthalmitis and other ocular inflammatory diseases, we opted to include uveitis as a separate outcome to better elucidate the risk of uveitis compared to all eye inflammation. These adverse events were initially chosen based on their frequency of reporting in the current literature.[8,14] Many other ocular complications including orbital myopathy or optic neuritis at the time did not have any hits. Exact phrasing was used according to structured query language in the OpenVigil 2.1 software for the FAERS data.[15] An initial search included all ICI drugs of interest atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab with all adverse events of interest. Avelumab, cemiplimab, and duvalumab were not included in future searches as the FAERS database did not contain any reports associated with the three ICI drugs. We then performed a search including each individual ICI drug of interest with all adverse events of interest. OpenVigil 2.1 pharmacovigilance analytical tool was used to count all unique cases involving the drug (s) of interest with adverse event (s) of interest and to calculate reporting odds ratios (RORs).[15] It quantifies the number of cases with checkpoint inhibitors and compares it to the same events with all other drugs using the FAERS database. Since this database is a reporting database and not a population-based database a prevalence on the use of these drugs could not be calculated. The ROR is a measure of association between an exposure and an outcome. The ROR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Each ROR value was considered statistically significant if the lower bound value of the 95% CI was above 1.0.

Results

We identified 113 ocular adverse events between all ICI drugs of interest and all ocular adverse events of interest including uveitis, dry eye, ocular myasthenia and eye inflammation (Table 1). Nivolumab had the highest number of adverse events (N = 68), associated with use of the ICI. Nivolumab also had the highest association with ocular myasthenia [ROR = 22.82 95% CI (7.18–72.50)] and pembrolizumab was also highly associated with ocular myasthenia [ROR = 20.17, 95% CI (2.80–145.20)]. Additionally, use of nivolumab showed a strong signal with uveitis [ROR = 8.73, 95% CI (6.25–12.20)] and a moderate signal with eye inflammation [ROR = 2.68, 95% CI (1.34–5.36)]. Of all FDA-approved ICIs, atezolizumab had the highest association with eye inflammation [ROR = 18.88, 95% CI (6.07–58.81)] and ipilmumab had the highest association with uveitis [ROR = 10.53, 95% CI (7.30–15.22)]. No cases were reported for the newly FDA-approved ICIs including avelumab, cemiplimab, and durvalumab.

Discussion

This is the first study using a signal disproportionality analysis that has quantified the risk of ICIs using the FAERS database. The results of this disproportionality analysis suggest an increased association between ICIs and ocular adverse events (Table 1). Our study demonstrated an overall increase risk of uveitis with use of ipilimumab, nivolumab, pembrolizumab and atezolizumab while an increased risk of dry eye was associated with use of ipilimumab, nivolumab and pembrolizumab. Ocular myasthenia risk was only associated with nivolumab and pembrolizumab, and eye inflammation risk was associated with ipilimumab, nivolumab and atezolizumab. We found a stronger signal with use of nivolumab and pembrolizumab and the reporting of ocular myasthenia compared to the other ICI reports in the FAERS database.

Although the pathogenesis of adverse events is not well understood with use of ICIs, one study has shed light on the putative autoimmune mediated mechanisms as seen with ocular adverse events such as uveitis, dry eye, ocular myasthenia and eye inflammation.[16] CTLA-4 inhibitors, such as ipilimumab, impair survival and function of T regulatory cells which lead to known autoimmune disorders such as inflammatory bowel disease.[16] On the other hand, PD-1 inhibitors, such as avelumab, atezolizumab, cemiplimab, durvalumab, nivolumab and pembrolizumab, perform similarly to CTLA-4 inhibitors, but also produce pathological autoantibodies as seen in patients treated with nivolumab.[16] The synthesis of pathological autoantibodies with PD-1 inhibitors may give rise to the increased incidence of inflammatory adverse events as compared to CTLA-4 inhibitors as seen in our results whereby only anti-PD-1 ICIs were highly associated with myasthenia gravis and anti-CTLA-4 ICIs such as ipilimumab had no reports. This suggests that each ICI may be associated with individualized adverse events that need to be further investigated.

Autoimmune adverse events with anti-CTLA-4 regimens were also noted to be dose-dependent, but not with anti-PD-1 monotherapy.[7] This may lend to the higher number of ocular adverse events associated with anti-PD-1 ICIs including nivolumab, pembrolizumab and atezolizumab compared to the only FDA-approved ICI that targets CTLA-4, ipilimumab

Table 1
Reported odds ratios (RORs) for ocular adverse events with use of immune checkpoint inhibitors (ICIs) in the Food and Drug Administration Adverse Event Reporting System (FAERS) database from 2003 to 2018.

Drug name (s)	Adverse event (s)	Events with specific ICI	ROR[a]
All ICIs of interest[b]	All adverse events of interest[c]	113	2.52 (2.06–3.08)
Atezolizumab	All adverse events of interest[c]	4	3.79 (1.42–10.14)
Atezolizumab	Uveitis	1	4.60 (0.65–32.76)
Atezolizumab	Eye inflammation	3	18.89 (6.07–58.81)
Ipilimumab	All adverse events of interest[c]	17	2.65 (1.91–3.68)
Ipilimumab	Uveitis	15	10.54 (7.30–15.22)
Ipilimumab	Dry eye	1	0.34 (0.11–1.05)
Ipilimumab	Eye inflammation	1	1.95 (0.73–5.20)
Nivolumab	All adverse events of interest[c]	68	2.73 (2.09–3.57)
Nivolumab	Uveitis	45	8.73 (6.25–12.20)
Nivolumab	Dry eye	11	0.62 (0.32–1.24)
Nivolumab	Ocular myasthenia	3	22.82 (7.18–72.50)
Nivolumab	Eye inflammation	9	2.68 (1.34–5.36)
Pembrolizumab	All adverse events of interest[c]	24	2.47 (1.56–3.93)
Pembrolizumab	Uveitis	22	10.80 (6.60–17.68)
Pembrolizumab	Dry eye	1	0.21 (0.03–1.50)
Pembrolizumab	Ocular myasthenia	1	20.17 (2.28–145.20)

ROR: Reported odds ratios; ICI: Immune checkpoint inhibitor.
Drugs with no reported adverse events of interest were not included in the table.
[a] RORs with 95% confidence intervals.
[b] All ICIs of interest include: atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab.
[c] All adverse events of interest include uveitis, dry eye, ocular myasthenia and eye inflammation.

(Table 1). We can appreciate that anti-CTLA-4 therapy may have a lower incidence of ocular adverse events compared to anti-PD-1 therapy as dosing may have been more conservative to avoid adverse events.

Strengths and limitations of this study include those associated with disproportionality analysis studies. One of the strengths of this study include quantifying ICI's ocular adverse events which can better inform ophthalmologists about these risks in the absence of data from large epidemiologic studies. Results produced can only demonstrate correlations and not causation. Use of the FAERS database also includes limitations such as overreporting and underreporting. For example, the highest number of reported events with nivolumab does not necessarily translate to this drug having the highest risk among all ICIs but rather, is probably related it being the most commonly used ICI. Reporting bias can be seen whereby those who report adverse events are more likely to report more often. To overcome overreporting, we searched only for unique cases associated between our ICI drug of interest and the ocular adverse event of interest. However, underreporting due to missing data or lack of voluntary reporting would underestimate the true risk of these rare ocular adverse events. Additionally, our data analysis does not include dosing, which may affect the difference in adverse events signals between the different ICIs. Furthermore, limitations of a disproportionality analysis compared to epidemiological studies include the lack of data on detailed risk factors and confounders such as patient demographics, comorbidities and past medical conditions. The analysis was not corrected for temporal trends or potential confounding factors including age or sex. Our study demonstrates that further research into ICIs and ocular adverse events is warranted to better understand these associations.

Results of our disproportionality analysis of adverse drug reaction data from FAERS reveals an increased association between ICIs and ocular adverse events. With the evolving understanding of ICIs and their increase in use for different types of cancer, there will be an increase use of ICIs. The incidence of ocular adverse events may not lead to the cessation of ICI prescriptions when benefits overcome side effects and there is no superior alternative. Findings in this study emphasize the need for ophthalmologist's vigilance in the identification and examination of potential adverse events. The need to further investigate ocular adverse events associated with ICIs using large, well-designed epidemiologic studies will help shed light on the risk of ocular adverse events secondary to ICIs.

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