Ocular adverse events due to PD-1 and PD-L1 checkpoint inhibitors: A retrospective review of FDA adverse events reporting system (FAERS)

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Introduction:

- Immune checkpoint inhibitors (ICIs) targeting program cell death protein 1 (PD-1) and program cell death ligand 1 (PD-L1) have improved outcomes for many cancer subtypes.
- ICIs are not without toxicity due to immune related adverse events (irAEs) which can affect any organ.
- Case reports and case series in literature have described ocular AEs due to PD-1/PD-L1 inhibitors.
- We queried FAERS (a pharmacovigilance database) to find out rate of ocular toxicity due to ICIs targeting PD-1 and PD-L1.

Methods:

- We retrospectively queried FAERS from January 1st, 2015 to June 30th, 2020 for "dry eyes", "uveitis", retinal detachment", "ocular myasthenia", "ulcerative keratitis", and "optic neuropathy" due to five FDA approved PD-1/PDl-L1 inhibitors atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab.
- Disproportionality signal analysis was done by calculating reporting odds ratio (ROR) with 95% confidence interval (CI). ROR was considered significant when lower limit of 95% CI was >1.
- Chi-square or fischers exact test was used to calculate p value as appropriate.

Table 1. Details of seven ocular AEs due to PD-1/PD-L1 ICIs

		Dry Eyes	Uveitis	Eye Inflammation	Retinal Detachment	Ocular Myasthenia	Ulcerative Keratitis	Optic Neuropathy
Total Adverse events		75	204	21	49	16	13	11
Indication for ICI use	Total number (n)	68	188	19	46	13	12	11
	Malignant Melanoma	25 (36.7%)	108 (57.44%)	7(36.84%)	25(54.34%)	4(30.76%)	3(25%)	2(18.18%)
	Lung Cancer	15 (22.05%)	40 (21.27%)	6 (31.57%)	10(21.73%)	8(61.53%)	3(25%)	4(36.36%)
	Other Cancers	28 (41.17%)	40 (21.27%)	6 (31.57%)	11(23.91%)	1(7.69%)	6(50%)	5(45.45%)
ICI Used	Nivolumab	51 (68%)	136 (66.66%)	16 (76.19%)	30(61.22%)	7(43.75%)	9(69.23%)	3(27.27%)
	Pembrolizumab	22 (29.33%)	57(27.94%)	1(4.7%)	11(22.44%)	7(43.75%)	1(7.69%)	2(18.18%)
	Durvalumab	1(1.3%)	1(0.49%)	0	0	1(6.25%)	1(7.69%)	1(9.09%)
	Atezolizumab	1(1.3%)	9(4.41%)	4(19.04%)	8(16.32%)	1(6.25%)	2(15.38%)	4(36.36%)
	Avelumab	0	0	0	0	0	0	1(9.09%)
	2ICIs	0	1(0.49%)	0	0	0	0	0
Sex	Total number (n)	60	186	18	47	16	12	11
	Male	31(51.6%)	90(48.38%)	10(55.5%)	26(55.31%)	12(75%)	8(66.66%)	4(36.36%)
	Female	29(48.3%)	96(51.61%)	8(44.44%)	21(44.68%)	4(25%)	4(33.33%)	7(63.63%)
Median Age (years)		62 (N=60)	64.5 (N=154)	58.5 (N=6)	67 (N=39)	72.5 (N=16)	73 (N=13)	65 (N=11)

Results:

- Total adverse events(AEs) reported from all drugs was 10,687,588 out of which 78,081 were due to PD-1/PD-L1 ICIs.
- Details of seven ocular AEs are shown in Table 1.
- Results of disproportionality signal analysis is shown in Table 2.

Table 2. ROR ratios.

Event	ROR	CI	P value
Dry eyes	0.7	95% (0.5-0.9)	0.005
Uveitis	7.6	95% (6.6-8.8)	<0.0001
Eye inflammation	0.9	95% (0.6-1.5)	0.9
Retinal detachment	2.3	95% (1.7-3.1)	<0.0001
Ocular myasthenia	23.1	95% (13.6-39.3)	<0.001
Ulcerative keratitis	1.9	95% (1.1-3.3)	0.01
Optic neuropathy	2.3	95% (1.3-4.3)	0.0085

Conclusions:

- Ocular irAEs are rare due to PD-1/PD-L1 ICIs.
- ROR for ocular myasthenia, optic neuropathy, retinal detachment, ulcerative keratitis and uveitis was elevated due to PD-1/PD-L1 ICIs.
- Oncologists and ophthalmologist should be aware of these irAEs.
- No financial disclosure or conflict of interest.

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