Global Scientific JOURNALS
GSJ: Volume 11, Issue 2, February 2023, Online: ISSN 2320-9186
www.globalscientificjournal.com

Pembrolizumab, Nivolumab and Ipilimumab is associated with Anterior Segment, Posterior Segment and Neuro-Ophthalmic Complications: A Systematic Review.

Sampana Fatima[1], Muhamad Abrar[2], Rohama Qubra[3], Delima Maria[3], Rashid Mahmood khan[3], Nasma Wabasa[3]

Correspondence:

Dr. Sampana Fatima

Department of Physiology

[1]Shalamar Medical and Dental College, Lahore, Pakistan.

Email id: sampanasami@gmail.com

[2]National University of Science and Technology, Pakistan

[3]Bahawal Victoria Hospital, Bahawalpur, Pakistan

EOI: 10.11216/gsj.2023.02.213604

Abstract:

Introduction:

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that deactivate inhibitory receptors of immune system and restore the antitumor immunity.[2] ICIs provides novel alternative treatment for high prevalence cancers like, melanoma, lung cancer, lymphoma, metastatic prostate carcinoma and renal tumors.

Methodology:

Systemic review was conducted according to the Cochrane handbook of systemic reviews and ophthalmology book of systemic reviews and reported based on PRISMA. Articles from August 2017-August 2022.Total 57 articles were obtained. Out of which only 25 were selected discussing Ophthalmic ICIs related adverse effects in previously normal patients.

Results:

Ipilimumab is commonly observed in inducing optic neuropathy, anterior uveitis, and graves ophthalmopathy in previously normal patient. Anterior uveitis and pan uveitis, ocular hypotony and complete visual loss were most reported with pembrolizumab. Most common ocular complications associated with Nivolumab is uveitis. Degree of uveitis and its presentation varied in different cases.

Conclusion:

ICI's are frequently associated with neuro-ophthalmic complications, though reversibility of complications is observed upon ICI's stoppage. If ICI's are given in monitored doses and multidisciplinary approach is made, rate of incidence of such complications can be minimized.

***Key words**:* Pembrolizumab, Ipilimumab, Nivolumab, Immune checkpoint inhibitors, Adverse effects of ICIs, Neuro-ophthalmic complications.

Introduction:

The 21st century is bringing new challenges with expected rapid changes in disease process, formulation of new and better pharmaceutical agents. From past a decade, Immuno-oncology has been an important talk, but its associated adverse effects and complication has become a point of major concern in recent years.[1]

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that deactivate inhibitory receptors of immune system and restore the antitumor immunity.[2] ICIs provides novel alternative treatment for high prevalence cancers like, melanoma, lung cancer, lymphoma, metastatic prostate carcinoma and renal tumors.[3,4] These monoclonal antibodies are targeting programmed death-1 receptor(PD-1), programmed death lgand-1 (PD-L1) and cytotoxic T-lymphocyte associated antigen-4(CTLA-4).[4] several ICIs has been approved by FDA, but most commonly prescribed and effective are pembrolizumab, Ipilimumab and Nivolumab.[1] PD-1/PD-L1work in association as PD-L1 bind to its cell surface receptor on immune host cells and causes inactivation or apoptosis of T cells. CTLA-4 receptors, in addition to CD28 receptors are also present on plasma membrane of activated T cells. When antigen-presenting cells (APCs) recognize the foreign body and present it to T cell, at this moment CTLA-4 attaches to B7 of APCs instead of normal interaction between CD28 and CTLA-4.[5] Activation of CTLA-4 inhibits the NF-kB signaling and leads to decreased IL-2 production and hence attenuate T cell activity, thus preventing damage to host tissue.[3]

Their excessive use in treating such carcinomas is beneficial on one side but their post-treatment adverse effects, are also a hallmark.[5] Immune-related adverse events (IRAEs), which can affect any organ system and occur in 70-90% of patients.[3,2]

These ICIs are responsible for maintaining immune homeostasis and prevention of autoimmunity.[2,3] Pembrolizumab, formerly lambrolizumab, is a selective, humanized IgG4 kappa monoclonal antibody superiorly prescribed for melanoma and non-small cell lung carcinoma(NSCLC).[6] Incidence of IRAEs with pembrolizumab is approximately 10%.[6,7] Nivolumab is used for treatment of metastatic malignancies. IRAEs associated with Nivolumab includes anterior uveitis, macular edema, vitreous opacity and serious retinal detachment.[8] Ipilimumab, in combination or alone, is associated with less than 1% of ophthalmic IRAEs.[1] Neuro-ophthalmic complications can vary from efferent or afferent or seldom together.[3,2,5]

Currently, there are systematic reviews that cover either neuro-ophthalmic or anterior segment and posterior segment complications, alone but no systematic review covers all of them together. So, this study will cover all of the concerned risks and incidence of IRAEs for early screening and timely management to avoid visual threats.

Aim of this study is to asses all of the reported ophthalmic complications of Pembrolizumab, Ipilimumab and Nivolumab treatment and their prevalence in order to early diagnose and manage ophthalmic IRAEs as per departmental protocol.

Methodology

This systematic review was started in March 2022 under heading of "Pembrolizumab, Nivolumab and Ipilimumab is associated with Anterior Segment, Posterior Segment and Neuro-Ophthalmic Complications: A Systematic Review".

Duration:

March 2022 till August 2022

We included articles from August 2017-August 2022.Total 57 articles were obtained. Out of which only 25 were selected discussing Ophthalmic ICIs related adverse effects in previously normal patients.

Data selection:

Quantitative or qualitative studies, particularly case reports, describing neuro-ophthalmic, anterior segment and posterior segment IRAEs in previously normal subjects were included.

Inclusion criteria:

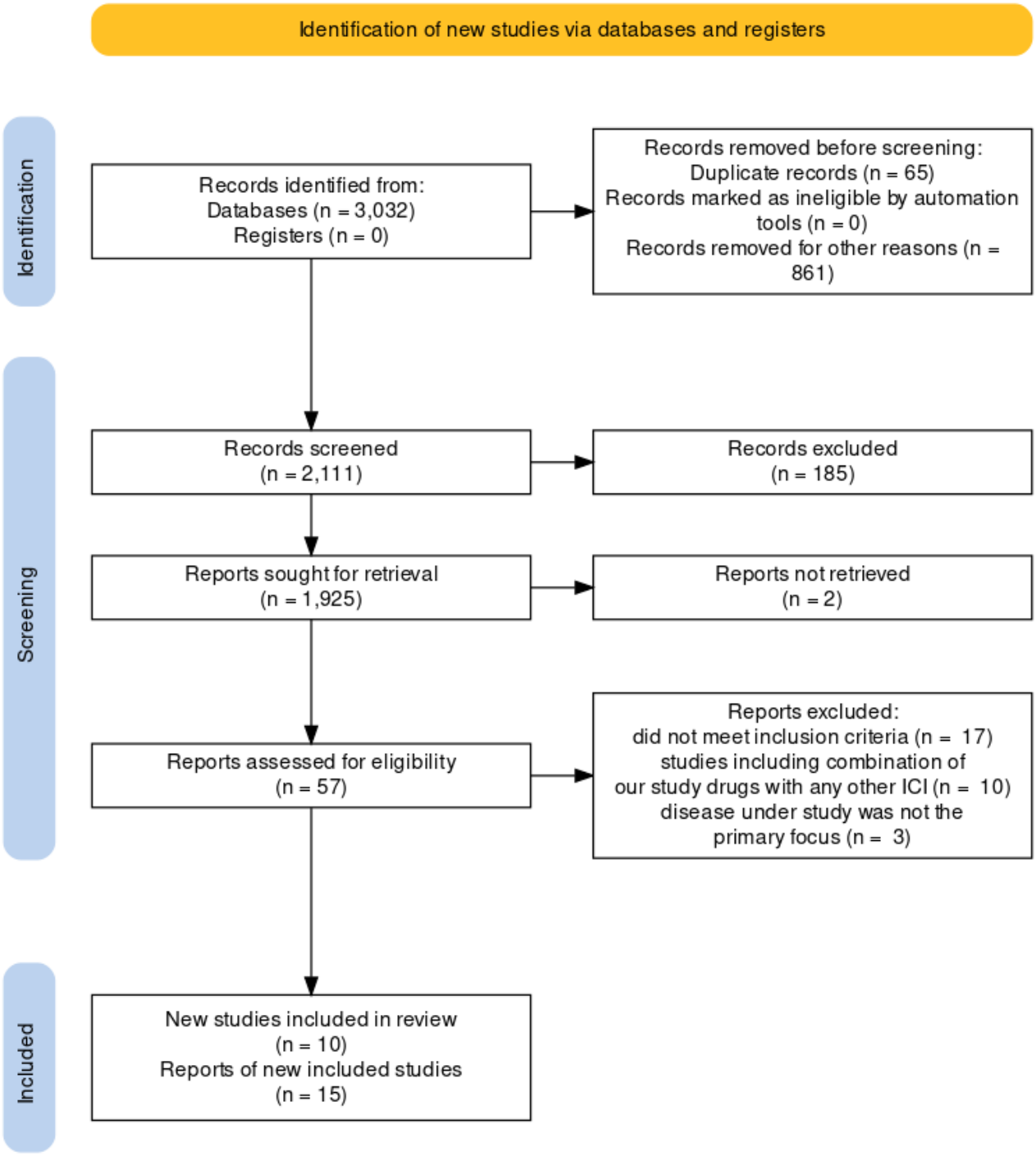
1. Studies including IRAEs in previously healthy individual.
2. Studies providing data for administration of any or all of the ICIs of concern.

Exclusion criteria:

1. Studies involving patients with ailments that can predispose to early development of Neuro-ophthalmic complications or uveitis, such as Diabetes, Vitamin A deficiency.
2. Studies involving patients, who are on drugs other than ICIs.

Study Protocol

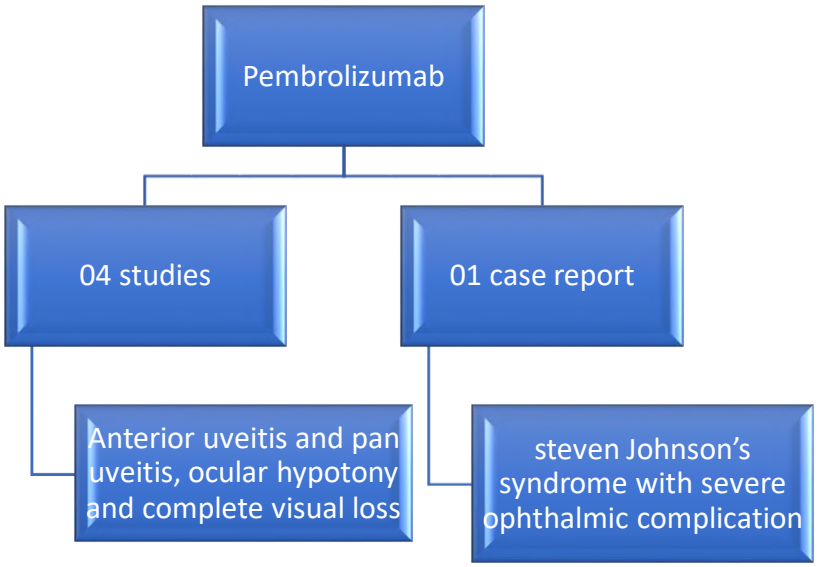
Systemic review was conducted according to the Cochrane handbook of systemic reviews and ophthalmology book of systemic reviews and reported based on PRISMA.[9]



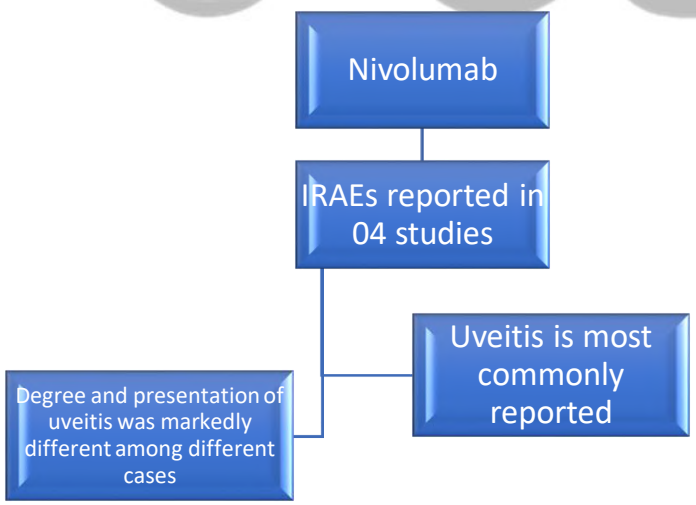
Results

Total 04 studies solely reported Ophthalmic IRAEs due to Pembrolizumab. Anterior uveitis and pan uveitis, ocular hypotony and complete visual loss were most commonly reported IRAE's.

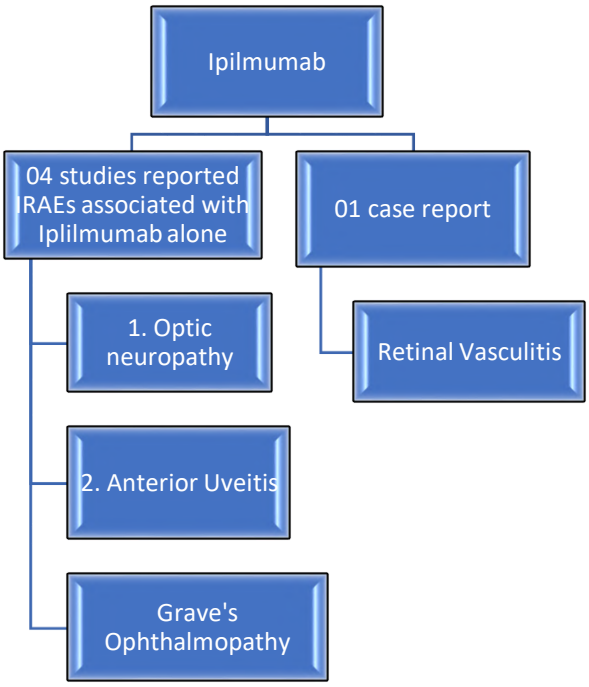
[4,11,12,6,10] 01 case report study mentioned development of steven Johnson's syndrome with severe ophthalmic complication.[11]



04 studies reported ocular IRAEs with Nivolumab. Most common ocular complications include uveitis. Degree of uveitis and its presentation varied in different cases.[8,12,13,14,17,18]



While 04 studies reported Ipilimumab associated ocular complications. Ipilimumab is commonly observed in inducing optic neuropathy, anterior uveitis and graves ophthalmopathy in previously normal patient.[13] 01 case report stated post ipilimumab treatment retinal vasculitis.[14]



While rest of 12 studies reported combined ICI's ocular complications. These studies included case reports and case series, that included uveitis and neuro-ophthalmic complications. All of the ophthalmic IRAE's included in this study are tabulated below.

Table 1: Ophthalmic IRAE's when single ICIs were administered.

Sr. #	Study	ICI	IRAEs	Disease	Treatment
1.	Reid G (2019) Case report[15]	pembrolizumab	Ocular hypotony, choroidal effusion, B/L optic disc swelling, Ant. Uveitis	Metastatic melanoma	Ocular viscoelastic device injection cured hypotony. IOP was stabilized
2.	Ryu S (2021) Case report[11]	pembrolizumab	Blurred vision with mild eyelid ulceration. Ant. Uveitis	Urothelial cancer	Improved after cessation of pembrolizumab

3.	Mori S[4] (2018)	Pembrolizumab	Optic Neuritis	NSCCL	IV methylprednisolone resolved disc pallor and edema
4.	Nguyn M[10](2019)	Pembrolizumab	Ocular hypotony with near complete vision loss	Advanced melanoma	Cessation of pembrolizumab improved vision
5.	Dang T[6] (2016)	pembrolizumab	Optic neuritis and uveitis	NSCLC	Pembrolizumab cessation improved the IRAE's
6.	Yoshida M[8] (2019)	Nivolumab	Ant. Uveitis, vitreous opacity	Renal cell carcinoma	Vitrectomy improved the vision. Steroid therapy remained unaffective.
7.	Dow ER[12] (2021)	Nivolumab	Ant. Uveitis, post. Uveitis, pan uveitis	Metastatic melanoma	Topical, I/v steroids significantly improved the IRAE's
8.	Lee JC[13] (2020)	Nivolumab	Acute bilateral anterior uveitis	Clear cell renal carcinoma	Topical and I/v steroids
9.	Karlin J [16](2018)	Nivolumab	Bilateral ant. uveitis	NSCLC	Did not respond to steroid theraph
10.	Lee JC[13] (2020)	Ipilimumab	Acute bilateral anterior uveitis	Clear cell renal carcinoma	Topical and I/v steroids

11.	Miyakubo T [17] (2019)	Ipilimumab	Retinal detachment	Metastatic melanoma	NA
12.	Dow ER[12] (2021)	Ipilimumab	Ant. Uveitis, post. Uveitis, pan uveitis	Metastatic melanoma	Topical, I/v steroids significantly improved the IRAE's
13.	**Tsui E[14] (2020)**	Ipilimumab	Cystoid macular edema with retinal vasculitis	Chronic myeloid leukemia	0.7mg Intravitreal injection of Dexamethasone resolved the IRAEs
14.	Yeh OL [18](2018)	Ipilimumab	Bilateral optic neuropathy with disc edema	Left thigh melanoma	Steroids improved the IRAE's

Table 2: Ophthalmic IRAE's when more than one ICIs were administered.

	study	**cases**	**ICIs administered for:**	**Ophthalmic IRAEs**	**Management**	**Recovery status**
1.	Thurau S[5]Retrospective case series(2021)	54 ICI (45)	Cutaneous melanoma (18),uveal melanoma,(4) lung cancer(2),Hodgkin's lymphoma(1), Myeloid leukemia(1)	Anterior uveitis (15) Posterior uveitis (9)	Topical steroids (12,), topical and regional (4) I/v ±Topical/regional (8)	11, 2, 4 patients recovered respectively

2.	Braun D[19]. Retrospective cohort (2020)	4,695,669	9.9% diagnosed with cancer (2.8% with melanoma)	Uveitis341.8/100,000	Treatment plan was not observed	-
3.	Kaur A[20]	220	Melanoma + NSCLC	Out of 59 patients with IRAE's, 1 developed Optic neuritis	High dose steroids with ICI continuation	Symptoms improved
4.	Kim JM[21](2019) Case series	Single site case series	Cutaneous melanoma	Anterior uveitis, vitritis, optic disc swelling	Topical and systemic steroids with cessation of ICIs	Visual acuity improved but chronic uveitis and disc pallor.
5.	Omuro[22](2018)	40	Recurrent glioblastoma	Optic N. disorder	-	-
6.	Zhou L[23](2021)	79	NSCLC, Lung cancer, SCLC, Lung adenoma	Uveitis, ophthalmoplegia, optic neuritis	Only few patients received steroids while rest discontinued ICI's.	Complete recovery
7.	fortress[24](2021)	996	Single Centre study including all tumor patients receiving ICIs	28 developed ophthalmic complications of Dry eye, uveitis,	Steroids in 27, ICIs cessation in 01 patient of panuveitis	Complete recovery

8.	Fang T[25](2019)	113	Multi Centre study in US on patients receiving ICI's.	Uveitis, ocular myasthenia, dry eye	-	-
9.	Michel M[26] (2020)	3123	Retrospective register study on patients receiving ICIs	112 presented with IRAEs Ant. Uveitis, papilledema	-	-
10.	Mukharesh L[27](2021)	5 individual case reports	Lung, bladder and renal carcinoma and malignancies	Optic neuritis	Corticosteroids initially and if patient didn't respond, then ICIs were discontinued.	Patients recovered after treatment
11.	Garibaldi M[28](2020)	Case study	Not mentioned	Ocular ophthalmoplegia	corticosteroids	Progressive improvement
12.	Bitton K[29](2019)	745, single Centre cohort study.	Not specified	3 developed dry eye and optic neuritis	Steroids in 2 and discontinuation of ICIs in 01	Complete recovery
13.	Zhou y[30](2022)	Case series	Not mentioned	uveitis	corticosteroids	Symptoms alleviated in majority
14.	gumusay[31](2022)	-	Breast cancer	Uveitis, optic	-	-

				neuritis, retinal choroidal disease		

Discussion

ICIs provide an emerging immunotherapy, that activates body's own immune cells to target cancer cells. There are numerous ICIs, but currently almost 7 has been approved by FDA. Most commonly prescribed ICIs include pembrolizumab, Nivolumab and ipilimumab. These drugs target different receptors and proteins present on T- cells of immune system. These target proteins are either CTLA-4, PD-L1or PD-1 which normally function as immunological checkpoint signaling pathways that typically prevent autoimmune host damage by decreasing T-cell activation. But they are repurposed by cancer cells to avoid T-cell identification in the tumor microenvironment. Administration of ICI's is almost always associated with development of IRAE's. Literature has shown that almost 1% of patients receiving ICIs develop ocular IRAE's.

Our systematic review included 25 articles, based on inclusion criteria. PD-1/PD-L1 inhibitors have been shown to be more effective in treating tumors as compared to CTLA-4. Pembrolizumab is most commonly prescribed in treatment of melanomas and NSCCL. It is associated with development of pan uveitis, anterior uveitis and optic disc edema, interfering with visual acuity.[4] more than 50 percent of patients had anterior uveitis, few patients were having pan-uveitis and almost none was reported to be having intermediate-uveitis. Ocular hypotony was also commonly reported along with uveitis. One case presented with steven Johnson eye. Most of the cases with uveitis and optic neuritis were bilateral and symmetric. Some patients reported unilateral optic disc edema. Patients on average presented within 4- 8 weeks of receiving ICIs for ophthalmology related complaints. Most of the patients received topical steroid initially and if not treated, I/V corticosteroid were administered that showed marked improvement in vision and resolution of inflammation. In almost 20 percent of patients, discontinuation of ICIs was recommended.

Management of ocular IRAEs of ICIs has been proposed by American Society of clinical oncology (ASCO) and society of immunotherapy of cancer (SITC), depending upon Grading of immune related ocular adverse effects (IROAE).[32,33] IROAE has been categorized into 4 grades. Grade 1 states anterior uveitis with trace cells, Grade II shows anterior uveitis with +1 and +2 cells, Grade III tell about anterior uveitis with +3 or +4 cells, pan uveitis and posterior uveitis, while Grade IV denotes Best corrected visual acuity (BCVA).[34]

Table 3: SITC and ASCO recommendations different Grades of IROAE of ICI's

Grades	ASCO	SITC
Grade I	Continue ICIs with Artificial Tears.	Continue ICIs with artificial tears
Grade II	Stop ICIs and start I/V corticosteroids.	Stop ICIs and start P/O Corticosteroids with increasing dose unless Grade I is achieved and then taper over next 4-6 weeks.
	And continue ICIs, one steroid has been tapered off	
Grade III	Stop ICIs and start steroids	Stop ICIs permanently
Grade IV	Permanently stop ICIs	Permanently stop ICIs and start systemic steroids.

Choice for re-continuation of ICIs is a challenging decision, as literature has reviewed that patient who continued therapy after tapering off steroid again developed ocular infections, particularly uveitis. But the rate of BCVA was much better than uveitis. Minority of such patients even presented with recurrence of pan uveitis of greater severity. It does not matter, at which point one discontinue the ICIs after IROAE as clinical data shows same rate of recurrence, if occurs.

Our systematic review was based on the current guidelines for cancer management and adverse effects related to ICIs.

Conclusion:

Ipilimumab is commonly observed in inducing optic neuropathy, anterior uveitis, and graves ophthalmopathy in previously normal patient. Anterior uveitis and pan uveitis, ocular hypotony and complete visual loss were most reported with pembrolizumab. Most common ocular

complications associated with Nivolumab is uveitis. Degree of uveitis and its presentation varied in different cases. ICI's are frequently associated with neuro-ophthalmic complications, though reversibility of complications is observed upon ICI's stoppage. If ICI's are given in monitored doses and multidisciplinary approach is made, rate of incidence of such complications can be minimized.

Limitations

Limitations of our study were non availability of data on gender distribution of disease pattern.

Conflict of Interest:

The Authors declare no Conflict of Interest.

REFERENCES

1 Hou YL, Wang DY, Hu JX, Tian RY, Wang W, Su Q *et al.* Risk of Ophthalmic Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. *Ocul Immunol Inflamm* 2021; **00**: 1–11.

2 Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M *et al.* Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 2019; **16**: 563–580.

3 Yu CW, Yau M, Mezey N, Joarder I, Micieli JA. Neuro-ophthalmic Complications of Immune Checkpoint Inhibitors: A Systematic Review. *Eye Brain* 2020; **Volume 12**: 139–167.

4 Mori S, Kurimoto T, Ueda K, Enomoto H, Sakamoto M, Keshi Y *et al.* Optic Neuritis Possibly Induced by Anti-PD-L1 Antibody Treatment in a Patient with Non-Small Cell Lung Carcinoma. *Case Rep Ophthalmol* 2018; **9**: 348–356.

5 Thurau S, Engelke H, McCluskey P, Symes RJ, Whist E, Teuchner B *et al.* Uveitis in Tumor Patients Treated with Immunological Checkpoint- and Signal Transduction Pathway-Inhibitors. *Ocul Immunol Inflamm* 2021; **00**: 1–7.

6 Dang TO, Ogunniyi A, Barbee MS, Drilon A. Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer. *Expert Rev Anticancer Ther* 2016; **16**: 13–20.

7 Feng S, Coward J, McCaffrey E, Coucher J, Kalokerinos P, O'Byrne K. Pembrolizumab-Induced Encephalopathy: A Review of Neurological Toxicities with Immune Checkpoint Inhibitors. *J Thorac Oncol* 2017; **12**: 1626–1635.

8 Yoshida M, Kunikata H, Nakazawa T. Intraocular Concentrations of Cytokines and Chemokines in a Unique Case of Nivolumab-Induced Uveitis. *Ocul Immunol Inflamm* 2020; **28**: 850–853.

9 Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020 : An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Syst Rev* 2022; **18**. doi:10.1002/cl2.1230.

10 Nguyen M, Islam MR, Lim SW, Sahu A, Tamjid B. Pembrolizumab Induced Ocular Hypotony With Near Complete Vision Loss, Interstitial Pulmonary Fibrosis and Arthritis. *Front Oncol* 2019; **9**. doi:10.3389/fonc.2019.00944.

11 Ryu S, Jun I, Kim TI, Seo KY, Kim EK. Pembrolizumab-induced Stevens–Johnson Syndrome with Severe Ocular Complications. *Ocul Immunol Inflamm* 2021; **00**: 1–3.

12 Dow ER, Yung M, Tsui E. Immune Checkpoint Inhibitor-associated Uveitis: Review of Treatments and Outcomes. *Ocul Immunol Inflamm* 2021; **29**: 203–211.

13 Lee JC, Al-Humimat G, Kooner KS. Acute Bilateral Uveitis, Hypotony, and Cataracts Associated with Ipilimumab and Nivolumab Therapy: Optical Coherence Tomography Angiography Findings. *Case Rep Ophthalmol* 2020; **11**: 606–611.

14 Tsui E, Gonzales JA. Retinal Vasculitis Associated with Ipilimumab. *Ocul Immunol Inflamm* 2020; **28**: 868–870.

15 Reid G, Lorigan P, Heimann H, Hovan M. Management of Chronic Hypotony Following Bilateral Uveitis in a Patient Treated with Pembrolizumab for Cutaneous Metastatic Melanoma. *Ocul Immunol Inflamm* 2019; **27**: 1012–1015.

16 Karlin J, Gentzler R, Golen J. Bilateral Anterior Uveitis Associated with Nivolumab Therapy. *Ocul Immunol Inflamm* 2018; **26**: 283–285.

17 Miyakubo T, Mukai R, Nakamura K, Matsumoto H, Akiyama H. A Case Of Ipilimumab-

Induced Unusual Serous Retinal Detachment In Bilateral Eyes. *Int Med Case Rep J* 2019; **Volume 12**: 355–361.

18 Yeh OL, Francis CE. Ipilimumab-Associated Bilateral Optic Neuropathy. 2013; **4**: 4–7.

19 Braun D, Getahun D, Chiu VY, Coleman AL, Holland GN, Yu F *et al.* Population-Based Frequency of Ophthalmic Adverse Events in Melanoma, Other Cancers, and After Immune Checkpoint Inhibitor Treatment. *Am J Ophthalmol* 2021; **224**: 282–291.

20 Kaur A, Doberstein T, Amberker RR, Garje R, Field EH, Singh N. Immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. *Medicine (Baltimore)* 2019; **98**: e17348.

21 Kim JM, Materin MA, Sznol M, Kluger HM, Weiss S, Chow J *et al.* Ophthalmic Immune-Related Adverse Events of Immunotherapy: A Single-Site Case Series. *Ophthalmology* 2019; **126**: 1058–1062.

22 Omuro A, Vlahovic G, Lim M, Sahebjam S, Baehring J, Cloughesy T *et al.* Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143. *Neuro Oncol* 2018; **20**: 674–686.

23 Zhou L, Wei X. Ocular Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors in Lung Cancer. *Front Immunol* 2021; **12**. doi:10.3389/fimmu.2021.701951.

24 Fortes BH, Liou H, Dalvin LA. Ophthalmic adverse effects of immune checkpoint inhibitors: the Mayo Clinic experience. *Br J Ophthalmol* 2021; **105**: 1263–1271.

25 Fang T, Maberley DA, Etminan M. Ocular adverse events with immune checkpoint inhibitors. *J Curr Ophthalmol* 2019; **31**: 319–322.

26 Sun MM, Kelly SP, Mylavarapu, BS AL, Holland GN, Coleman AL, Yu F *et al.* Ophthalmic Immune-Related Adverse Events after Anti-CTLA-4 or PD-1 Therapy Recorded in the American Academy of Ophthalmology Intelligent Research in Sight Registry. *Ophthalmology* 2021; **128**: 910–919.

27 Mukharesh L, Chwalisz BK. Neuro-ophthalmic Complications of Immune-Checkpoint Inhibitors. *Semin Ophthalmol* 2021; **36**: 241–249.

28 Garibaldi M, Calabrò F, Merlonghi G, Pugliese S, Ceccanti M, Cristiano L *et al.* Immune checkpoint inhibitors (ICIs)-related ocular myositis. *Neuromuscul Disord* 2020; **30**: 420–423.

29 Bitton K, Michot J-M, Barreau E, Lambotte O, Haigh O, Marabelle A *et al.* Prevalence and Clinical Patterns of Ocular Complications Associated With Anti-PD-1/PD-L1 Anticancer Immunotherapy. *Am J Ophthalmol* 2019; **202**: 109–117.

30 Zhou Y-W, Wang Y, Xia R-L, Liu J-Y, Ma X-L. Immune checkpoint inhibitor-associated ophthalmic adverse events: current understanding of its mechanisms, diagnosis, and management. *Int J Ophthalmol* 2022; **15**: 646–656.

31 Gumusay O, Callan J, Rugo HS. Immunotherapy toxicity: identification and management. *Breast Cancer Res Treat* 2022; **192**: 1–17.

32 Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R *et al.* Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017; **5**: 95.

33 Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM *et al.* Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018; **36**: 1714–1768.

34 Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. CTCAE versión 5.0. Evaluación de la gravedad de los eventos adversos dermatológicos de las terapias antineoplásicas. *Actas Dermosifiliogr* 2021; **112**: 90–92.