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Prevalence and clinical patterns of ocular complications associated with anti-PD-1/PD-L1 anticancer immunotherapy

Short title: ocular complications of anticancer immunotherapy

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## Introduction

In the last decade, the development of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of various advanced cancers. These drugs block inhibitory receptors of the immune system, thus enabling specific antitumor T cell responses. ICIs include monoclonal antibodies directed against programmed death-1 receptor (PD-1), its ligand (PD-L1), and the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Antibodies that interfere with the PD-(L)1 interaction show less toxicity than ipilimumab (CTLA-4-targeting) and are henceforth the most commonly used ICIs, administered either alone or in combination with anti-CTLA-4.<sup>1, 2</sup> While initially given for metastatic malignant melanoma (MM) and non-small cell lung carcinoma (NSCLC), indications for anti-PD-(L)1 have recently been extended to treat renal cell carcinoma, head and neck squamous cell carcinoma, and Hodgkin's lymphoma.

The PD-1 signaling pathway plays a central role in maintaining peripheral tolerance and down-regulating antigen-specific T-cell activation, immunity, and immune-mediated inflammatory disease. When bound by its ligands, PD-L1 and PD-L2, PD-1 inhibits T-cell activation and limits immune effector responses.<sup>3</sup> Tumors can express PD-L1 as one mechanism of inhibiting antitumor T-cell-mediated responses in the tumor microenvironment. Blockade of this receptor/ligand interaction with anti-PD-1 monoclonal antibodies, such as pembrolizumab and nivolumab, or anti-PD-L1 atezolizumab, durvalumab and avelumab increases the immune response against tumor cells.

By the same mechanism, anti-PD-(L)1 can override the suppression of self-targeting immune responses to generate immune-related adverse events (irAEs). The most common irAEs affect the skin (pruritus, rash and vitiligo), the digestive tract (colitis and hepatitis), and endocrine tissues (mainly thyroiditis), in approximately 20% of

patients.<sup>1, 2</sup> Less frequently, irAEs affect lungs, kidneys, or the nervous system.<sup>2</sup> Ophthalmic irAEs, mainly dry eye disease, were reported in early clinical trials.<sup>4</sup> Since then, few small case series have reported incidents of intraocular or orbital inflammation.<sup>5-20</sup> Yet, the prevalence of these complications among anti PD-(L)1-treated patients has not yet been determined. As ocular irAEs may threaten visual function<sup>20</sup> and lead to severe deterioration of the quality of life of patients, further investigation is warranted, and described herein. Using a prospective cohort of ICI-treated patients, we determined the prevalence and the incidence of ocular complications following anti-PD-(L)1 treatment. Furthermore, we studied individual cases reported through a national pharmacovigilance registry of ICI-treated patients. We discuss the clinical patterns in our case series and those reported in the literature and the putative underlying pathophysiological mechanisms.

## **Patients and methods**

This non-interventional study reports the ocular complications associated with anti-PD-1/PD-L1 collected through i) a single-center prospective cohort and ii) a declarative pharmacovigilance registry, which are merged into the REISAMIC registry (Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie). The study protocol was approved by the Ethics Committee of the French Society of Ophthalmology (IRB 00008855 Société Française d'Ophtalmologie IRB#1).

REISAMIC is a pharmacovigilance registry of irAE in ICI-treated patients, set up at the Gustave Roussy Cancer Centre (Villejuif, France). Only irAE of grade  $\geq 2$  (i.e. requiring moderate local noninvasive intervention), according to the Common Terminology Criteria for Adverse Events (CTCAE)<sup>21</sup> are included in REISAMIC. REISAMIC is based on i) a single-centre prospective cohort (initiated in June 2014 at

Gustave Roussy cancer centre) for patients treated in 'real-life' situations, i.e. following marketing authorisation, as part of patient access programmes for unlicensed medications or during compassionate use, and ii) a national pharmacovigilance registry of irAEs occurring in ICI-treated patients. A reference network of organ specialists reviews every irAE declared in REISAMIC during bi-monthly multidisciplinary meetings.<sup>22</sup> Since 2016 the registry is accessible via a mobile application in order to collect irAE data more efficiently. In the present study, we focused on patients with ocular irAE grade  $\geq 2$  following anti-PD-(L)1 immunotherapy to treat malignancy that were included in the REISAMIC registry between June 1<sup>st</sup> 2014, and March 1<sup>st</sup> 2018.

### **Data collection**

For individual patients, cancer history and disease evolution, treatments received, and all irAEs were recorded. There was no systematic ophthalmologic examination planned in the prospective cohort. Consequently, patients of both the prospective cohort and the declarative registry were referred to the ophthalmology department in any case of ophthalmic complaints. In this case, patients underwent comprehensive ophthalmologic assessment by a trained ophthalmologist that included physical examination, and ocular and/or orbital imaging at the discretion of the clinician. Intraocular inflammation was graded according to the Standardization Uveitis Nomenclature Group (SUN) criteria.<sup>23</sup> The severity of adverse events was graded according to the CTCAE version 5.0.<sup>21</sup> Tumoral response to ICI was classified according to revised RECIST guideline (version 1.1).<sup>24</sup> This non-interventional study was conducted in compliance with good clinical practice and the tenets of the Declaration of Helsinki. Constitution of the REISAMIC registry had been authorized by the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés).

## **Statistical analysis**

Patient anonymity was maintained throughout the data collection and statistical analysis phases. Descriptive statistical analysis was performed with Excel for Mac (version 15.16). We estimated the prevalence of ocular complications associated with anti-PD-1/PD-L1 anti-cancer immunotherapy from the prospective patient cohort of the REISAMIC registry alone. We also estimated the incidence of irAEs per patient-months of anti-PD-(L)1 treatment. The cumulative duration of treatment received by all the patients of the prospective cohort has been calculated as follows:  $((\text{date of the last infusion or 03/01/2018}) - (\text{date of first infusion}) / 30.5)$ , where the date 03/01/2018 is the end of the inclusion period, and 30.5 is the average number of days per month. Regarding patients who received a single infusion of treatment, and to avoid their *de facto* exclusion of analysis, we used the value of 0.75 for patients treated with pembrolizumab or atezolizumab (infusion every three weeks), or 0.5 for patients treated with nivolumab (infusion every two weeks).

## **Results**

### **Frequency of ocular complications and systemic characteristics of patients**

Of a total of 745 patients treated with anti-PD-(L)1 included in the prospective cohort during the study period, three were reported as having ocular irAEs, providing a prevalence of anti-PD-(L)1-associated moderate to severe ocular irAEs of 4/1000. Altogether, patients of the prospective cohort were exposed to a total duration of treatment of 4277.4 months. Therefore, the incidence of anti-PD-(L)1-associated moderate to severe ocular irAEs was 0.7 per 1000 patient-months.

An additional five anti-PD-(L)1-treated patients with moderate to severe ocular irAEs were concomitantly declared to the national pharmacovigilance registry, and were reviewed by the reference network ophthalmologist (EB).

When taking all these 8 cases into account, six patients (75%) had received anti-PD-1 monotherapy, two anti-CTLA-4 therapy (ipilimumab, which had been stopped 5 and 46 months earlier), one patient anti-PD-1 as well as anti-CTLA-4 immunotherapy, and the 8<sup>th</sup> patient anti-PD-L1 (atezolizumab). Three patients had non-small cell lung cancer (NSCLC), two cutaneous melanoma, one adenoid cystic carcinoma of the parotid gland, one mesothelioma, and one clear cell renal cell carcinoma (**Table 1**). Five patients (62.5%) experienced an additional extra-ophthalmological irAE. At the end of the follow-up, all patients were considered to respond to the ICI treatment, with four patients being partial responders, three presenting with stable disease, and one complete responder.

Ocular irAEs occurred after the second infusion in half of the patients, but could occur at anytime up to the 36<sup>th</sup> infusion. Ocular irAEs occurred during the treatment or after cessation of the treatment (which could be motivated by cancer remission or serious systemic adverse events). The median time of ocular irAEs occurrence was 29 days  $\pm$  41 (range: 1-120 days) after an infusion of treatment.

### **Ophthalmological features**

Ocular irAEs consisted of ocular surface disease ( $n = 2$ ), intraocular ( $n = 5$ ) and orbital inflammation ( $n = 1$ ). The CTCAE grades of severity were grade 2 (4/8) and grade 3 (4/8). Anti-PD-(L)1 were discontinued in 6/8 patients. In these 6 patients, reason of discontinuation was ocular irAEs in 4/6 patients (in case #7, discontinuation was motivated by concomitant ocular and systemic adverse events); cancer remission in 1 patient (case#4) and extraocular irAE in one patient (i.e. peripheral neuropathy, case#1). Two patients continued ICI treatment despite ocular complications (case #2 and case #8). At the final visit, 4/8 patients had complete resolution of ocular irAEs and 4/8 patients were controlled by treatments. The mean follow-up period was 5.1 months (**Table 2**). Illustrative case reports and video are

provided in supplemental materials.

## **Discussion**

Using a prospective ICI-treated patient cohort we were able to robustly determine that the prevalence of moderate to severe ocular manifestations associated with anti-PD-(L)1 anticancer immunotherapy was 0.4% and the incidence was 0.7 per 1000 patient-months of treatment. Furthermore, data collected through a national pharmacovigilance registry illustrated distinct clinical patterns, including intraocular inflammation, ocular surface inflammation, and orbital neuromuscular disorders that may occur in anti-PD-(L)1 treated patients.

### **Intraocular inflammation**

A few case reports, and short series reported intraocular inflammation associated with anti-PD-(L)1 therapies.<sup>5, 7-9, 11, 13, 17, 18</sup> The spectrum ranged from anterior uveitis, usually non-granulomatous and of variable severity,<sup>8, 11, 18</sup> to panuveitis which may have various non-specific features including vitritis, retinal vasculitis, papillitis, retinal serous detachment, chorio-retinal lesions<sup>5, 7, 9, 17, 25</sup>, and even uveal effusion.<sup>20</sup> More generally, uveitis may occur in the context of ICI-associated systemic diseases, such as sarcoidosis<sup>26, 27</sup> as in case #4. Therefore, systemic work-up may be performed in all patients, both to exclude a differential diagnosis and to look for immune-related systemic conditions.

The prevalence of anti-PD-1-associated symptomatic intraocular inflammation was 0.2% in our current study, which was slightly inferior to that published in a recent systematic review about ocular manifestations of ICIs (0.3% - 0.6%).<sup>28</sup> However, this complete review included patients receiving anti-CTLA-4 treatment, known to induce irAEs more frequently.<sup>2</sup> Thomas *et. al.*, recently hypothesized that intraocular inflammation from ICIs could stem from reprogramming of the cell death pathway in



an immune-privileged tissue.<sup>20</sup> This hypothesis is supported by a case of corneal graft rejection in a patient treated with nivolumab for primary lung cancer.<sup>29</sup> Intraocular inflammation associated with anti-PD-(L)1 can be controlled with topical steroids. However, severe inflammation and posterior segment involvement may require systemic treatment.<sup>9</sup> Diem *et. al.*, recently suggested that uveitis secondary to pembrolizumab, as well as other irAES such as vitiligo, could be surrogate markers for a beneficial MM treatment response.<sup>30</sup> Similarly, in our series, we found that the two pembrolizumab-treated MM patients presenting with uveitis had positive best overall antitumor responses after treatment.

### **Ocular surface diseases**

Dry eye disease (DED) was the first and initially the most frequently reported ocular side effect in ICI-treated patients. In one of the first Phase 1 studies published on anti-PD-(L)1 safety, up to 1% of patients developed dry eye while receiving treatment.<sup>4</sup> Dry eye has also been described as a common complication of all ICI treatments in a recent review.<sup>25</sup> Ocular surface diseases, such as episcleritis and blepharitis have been included in the detailed recommendations for management of ICI adverse effects by the American Society of Clinical Oncology.<sup>31</sup> The peculiar feature of patient #8 was 1) the severity of dry eye, which required specific interventions, and 2) the chronology of symptoms that were exacerbated after infusions. For these reasons, we included patient #8 in this study. However, prevalence of anti-PD-(L)1-induced DED may be difficult to assess due to association with other medications,<sup>32</sup> and due to difficulties in the reporting criteria for DED.<sup>33</sup> Altogether, these issues may contribute to under-reporting of this condition, and more study will be required to determine the connection between ICI and DED. Moreover, anti-PD-(L)1 therapy may induce sicca syndrome as part of a systemic disease like Sjögren's syndrome,<sup>27, 34</sup> or sarcoidosis.<sup>35</sup> Dry eye may also be due to meibomian gland dysfunction arising from

anti-PD-1-induced ocular rosacea.<sup>36</sup> Experimental data suggests that downregulation of corneal epithelial PD-(L)1 amplifies DED-associated corneal inflammation and epitheliopathy.<sup>37</sup> Although DED is in most cases not a blinding condition, it can be associated with severe reduction in quality of life.<sup>38</sup> Case #6 developed DED in the context of lichen planus induced by ICIs. Thus, DED in this case was associated with lesions of cicatrizing conjunctivitis, a complication of involving the basement membrane of the mucosal epithelia.<sup>39</sup>

### **Orbital neuromuscular manifestations**

Anti-PD-(L)1 may induce orbital myasthenia gravis and myositis.<sup>40, 41</sup> Interestingly, we found two reported cases of ophthalmoplegia concomitant with myocarditis associated with anti-PD-1.<sup>14, 42</sup> Both cases were treated with intravenous immunoglobulins and high dose intravenous corticosteroid. Anti-acetylcholine receptor and myositis-associated antibodies were both negative. MRI utilised by Nasr *et al.*, confirmed the diagnosis of myositis of the ocular muscles.<sup>14</sup> Touat *et al.*, reported the clinicopathological features of ten patients with myositis during anti-PD-(L)1 therapy.<sup>43</sup> Electrodiagnostic studies highlighted a myopathic process without decrement pattern, while anti-acetylcholine receptor and myositis-associated antibodies were negative. Interestingly, Suzuki *et al.*, recently reported a series of anti-PD-(L)1-treated patients with concomitant myasthenia gravis and myositis. Some patients had positive anti-acetylcholine antibodies and concomitant myocarditis.<sup>41</sup> Adverse events including diplopia and/or oculomotor paralysis occurring in patients under ICIs should be considered with the greatest precaution, as these conditions can be associated with life-threatening myocarditis.

### **Management and evolution of ocular irAEs**

Most ocular side effects of ICIs are managed with topical or periocular corticosteroids, but advanced cases may require systemic corticosteroids and

cessation of checkpoint inhibitor therapy.<sup>25</sup> In this study, most patients were treated with topical corticosteroids (7/8) and/or systemic corticosteroid (3/8) with resolution of the symptoms. Two patients required increasing doses of corticosteroid or immunomodulatory agents because of the severity of the situation. In this study, there were no prospectively defined criteria for stopping ICI treatment in response to ocular complications. Continuation or discontinuation of treatment was evaluated on a case by case basis, based on the severity and the response to ophthalmological treatment. However, detailed recommendations for management of irAEs have been recently published.<sup>31</sup> In summary, for moderate (CTCAE grade 2, such as anterior uveitis) toxicities, ICI should be held until symptoms revert to grade 1 levels or lower and corticosteroids may be offered. For severe (grade 3, such as posterior uveitis) toxicity, patients should receive systemic corticosteroids. Restarting immunotherapy after a grade 3 toxicity requires extreme precaution. These recommendations include specific recommendations for episcleritis, uveitis and blepharitis but do not address other possible ocular manifestations.

In addition to the variability of the ocular symptoms, the time of onset was variable: symptoms could occur from one day after the second infusion, and after the 36<sup>th</sup> infusion. However, half of the patients developed symptoms after their 2<sup>nd</sup> cycle, i.e. during the early treatment phase.

Limitations of our study included the potential role of other medications in the occurrence of ocular side effects.<sup>44</sup> Anti-CTLA-4 are known to be associated with ocular inflammatory side effects.<sup>6, 28</sup> However, only one patient had concomitant anti-CTLA-4 treatment, and for patients with previous anti-CTLA-4, the chronology of ocular pathology was in favor of anti-PD-(L)1-induced ocular manifestations. Besides, our series may not encompass the whole spectrum of anti-PD-(L)1-associated ocular complications which are rare and pleomorphic, but provides specific data

complementary to those published in a recent comprehensive review on ICIs-associated ocular complications.<sup>6, 25</sup> Finally, the REISAMIC prospective cohort is based on a declarative process. Some mild ocular manifestations may have been overlooked, as ophthalmologic examination was performed only when a patient complained.

To summarize, based on robust epidemiologic data, the prevalence of moderate to severe ocular complications associated with anti-PD-(L)1 can be estimated at 0.4%. Furthermore, anti-PD-(L)1 immunotherapy may be associated with a wide range of orbital/ocular inflammatory complications. The latter may be sight-threatening and/or associated with life-threatening conditions. As ICI treatments are being approved for an increasing number of indications, clinicians should be aware of these complications. Patients complaining of eye problems while receiving ICI treatment should immediately be seen by an ophthalmologist.

**Supplemental data:** illustrative case reports (case #2, #6, #7).

**Supplemental video:** anti-PD-1-associated orbitopathy (Case #7). Oculomotor test demonstrating a complete left ophthalmoplegia with ptosis, partial left ophthalmoplegia with complete deficient adduction (reproduced with written consent of the patient).

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## Tables:

Case #	Age / gender	Cancer	Previous anticancer treatments	Anti-PD-(L)1	Systemic Anti-PD-(L)1 associated complications	Best Overall anti-tumoral Response with ICI
1	77/M	mesothelioma	carboplatine, pemetrexed	nivolumab (combined with ipilimumab)	peripheral neuropathy, lower limbs edema	PR
2	63/F	NSCLC	none	nivolumab	none	PR
3	44/F	MM	dacarbazine	pembrolizumab	vitiligo, hepatitis	SD
4	71/F	MM	dacarbazine, vemurafenib	pembrolizumab	systemic sarcoidosis	PR
5	56/F	CCRCC	sunitinib	nivolumab	none	SD
6	57/F	parotid adenocarcinoma	cyclophosphamide, epirubicine, 5-fluorouracil, docetaxel, létrozole, trastuzumab, vinorelbine	atezolizumab	lichen planus	SD
7	80/M	NSCLC	none	pembrolizumab	myocarditis	CR
8	70/M	lung adenocarcinoma	none	pembrolizumab	none	PR

**Table 1:** Systemic data. M = male, F = female, NSCLC = Non small cell lung carcinoma, MM = malignant melanoma, CCRCC = clear cell renal cell carcinoma, ICI = immune checkpoint inhibitor, PR = partial remission, SD = stable disease, CR = complete remission. Rows highlighted in grey correspond to the cases from the prospective cohort.

Case #	Number of infusion before onset	Delay of onset after infusion (days)	Ongoing ICI treatment when the ocular complication occurred (yes / no)	Ocular anti-PD-(L)1 associated complications	CTCAE grade	Treatment	Ophthalmological Follow-up (months)	Outcome of ocular irAE	Continuation of ICI treatment	Reason for ICI discontinuation	ICI discontinuation for ocular manifestation (yes / no)
1	2	21	yes	bilateral chemosis and nongranulomatous anterior uveitis (1+ cell in both eyes), no posterior synechiae	2	topical DXM (5 drops/day with tapering over 4 weeks)	3	resolution	no	extra ocular manifestation (peripheral neuropathy)	no
2	36	14	yes	bilateral panuveitis including nongranulomatous anterior chamber inflammation (with cyclitic membrane, Descemet's folds, 3+ cell and flare and posterior synechiae in the RE; 1+ cell and flare in the LE), 1+ bilateral vitritis, papillitis, choroidal infiltrates	3	topical DXM (8 drops/day with tapering over 4 weeks in the RE, 6 drops/day with tapering over 4 weeks in the LE) + 5 DXM subconjunctival injections in the RE	1	controlled	yes	NA	NA
3	18	3	yes	bilateral nongranulomatous anterior uveitis (1+ cell in both eyes), no posterior synechiae	2	topical DXM (6 drops/day with tapering over 4 weeks)	2	resolution	no	ocular manifestation	yes
4	8	120	no	bilateral nongranulomatous anterior uveitis (1+ cell in both eyes), no posterior synechiae	2	topical DXM (6 drops/day with tapering over 4 weeks)	7	resolution	no	cancer remission	no
5	2	15	yes	bilateral panuveitis with nongranulomatous anterior chamber inflammation (2+ cell and flare in both eyes), 1+ bilateral vitritis, bilateral serous retinal detachment, infero-macular retinal pigment epithelial detachment in the left eye	3	systemic CS (IV methylprednisolone 500mg / day for 3 days followed by prednisone 1mg/kg with tapering over 3 months) + topical DXM (6 drops/day with tapering over 4 weeks)	9	initial improvement with relapse on re-challenge	no	ocular manifestation	yes
6	10	60	yes	bilateral cicatrizing conjunctivitis with bilateral Oxford grade 4 SPK, bilateral inferior fornix shortening + upper and lower tarsal conjunctival fibrosis, Schirmer test <5mm in both eyes	3	topical DXM (4 drops/day) / systemic CS (prednisone 15mg ongoing) + scleral lens	7	controlled	no	ocular manifestation	yes
7	2	1	yes	bilateral orbital myositis, with bilateral ptosis and complete left ophthalmoplegia, right limitation of adduction.	3	systemic CS (1mg/kg) + IVIG (2g/kg) + methotrexate (15mg/week)	6	resolution	no	ocular and cardiac manifestations	yes
8	2	1	yes	bilateral severe dry eye disease with Oxford grade 3 SPK, Schirmer test <5mm, in both eyes	2	topical CS (3 drops/day) / punctal plugs	6	controlled	yes	NA	NA

**Table 2:** Anti-PD-(L)1 associated ocular complications. CTCAE = Common Terminology Criteria for Adverse Events, irAE = immune related adverse effect, NA = non applicable, CS = corticosteroid, IVIG = intravenous immunoglobulins, DXM = dexamethasone, ICI = immune checkpoint inhibitor. Rows highlighted in grey correspond to the cases from the prospective cohort.