Uveitis associated with cancer immunotherapy: long-term outcomes

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Title page

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Abbreviated title: Cancer immunotherapy-associated uveitis

Key words
Uveitis, macular edema, hypopion, cancer immunotherapy, rituximab, nivolumab, ipilimumab, anti-BRAF, anti-MEK, ibritunib

Abstract

Background *:* to report the long-term outcome of uveitis associated with cancer immunotherapy (CIT)

Methods: retrospective review of serial patients with CIT-associated uveitis treated using various regimen.

Results: Eight included patients treated with rituximab (anti-CD20), nivolumab (anti-PD-1), ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (anti-BRAF), trametinib (anti-MEK), and ibritunib, showed uveitis with hypopion (1 patient), macular edema (5 patients) and choroiditis (2 patients). Various regimen of corticosteroid therapy showed a favorable ophthalmological outcome, whether the CIT was continuing or suspended.

Discussion-Conclusion*:* Local corticosteroids injections in combination with CIT could be suggested as a first-line treatment. This could help to preserve the quality of life without threatening the vital prognosis.

LayAbstract:

*Purpose:*To report the long-term outcome of intra-ocular inflammation (uveitis) associated with cancer immunotherapy (CIT)

Methods: Serial patients complaining of blurred vision and painful eyes, showed intra-ocular inflammation that was related to CIT, after infectious, inflammatory, and tumoral causes of uveitis have been ruled out. The length of follow-up was more than 12 months for most patients.

Results: Eight serial patients treated with rituximab (anti-CD20), nivolumab (anti-PD-1), ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (anti-BRAF), trametinib (anti-MEK), and ibritunib, showed intra-ocular inflammation with hypopion (1 patient), macular edema (5 patients) and choroiditis (2 patients). Various regimen of corticosteroid therapy showed a favorable ophthalmological outcome, whether the CIT was continuing or suspended.

Conclusions: Local corticosteroids injections in combination with CIT could be suggested as a first-line treatment. This could help to preserve the quality of life without threatening the vital prognosis.

Key words
Uveitis, macular edema, hypopion, cancer immunotherapy, rituximab, nivolumab, ipilimumab, anti-BRAF, anti-MEK, ibritunib

Summary points :

1. This study reported 8 cases of CIT-associated uveitis, among which 7 experienced a visual loss and 5 had a macular edema, 2 had nodular choroiditis, 1 had hypopion.
2. Changes in macular edema, choroiditis, and hypopion were analysed for a long-term follow-up superior to 12 months.
3. The underlying metastatic cancer were heterogenous, and immunotherapy drugs were numerous. However the clinical ophthalmological uveitis related to CIT showed a similar good response to the corticosteroid treatment, regardless of further CIT.
4. At 3 months, the short-term visual outcomes were favorable after treatment with systemic or local injections of cortosteroids, whether the CIT was continuing or suspended.
5. At 12 months, CIT continuation was associated with uveitis activity, that showed sustained good response to sub-Tenon's triamcinolone injections.
6. So the role of the ophthalmologist may be useful in (1) making quickly the diagnosis relating uveitis to CIT, ruling out infectious, auto-immune and tumoral causes (2) explaining the often favorable uveitis outcome using corticosteroid local injections (3) reassuring patients and oncologists, worried about visual fonction (4) performing quickly ophthalmological treatment to keep a good quality of life (5) following the patients to assess positive and negative treatment effects (6) repeating the corticosteroid local injections if needed (7) rediscussing the treatment in case of ophthalmological failure.

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Abstract

Background: We report the long-term outcome of uveitis associated with cancer immunotherapy (CIT). **Methods:** This retrospective review included serial patients with CIT-associated uveitis treated using various regimen. **Results:** Eight patients treated with rituximab (anti-CD20), nivolumab (anti-PD-1), ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (anti-BRAF), trametinib (anti-MEK) and ibritunib showed uveitis with hypopion (one patient), macular edema (five patients) and choroiditis (two patients). Various regimens of corticosteroid therapy showed a favorable ophthalmological outcome, whether the CIT was continuing or suspended. **Conclusion:** Local corticosteroid injections in combination with CIT could be suggested as a first-line treatment. This could help to preserve the quality of life without threatening the vital prognosis.

Keywords: anti-BRAF; anti-MEK; cancer immunotherapy; hypopion; ibritunib; ipilimumab; macular edema; nivolumab; rituximab; uveitis.

Plain Language Summary

Lay abstract This study aims to report the long-term outcome of intra-ocular inflammation (uveitis) associated with cancer immunotherapy (CIT). Serial patients complaining of blurred vision and painful eyes showed intra-ocular inflammation that was related to CIT, after infectious, inflammatory and tumoral causes of uveitis have been ruled out. The length of follow-up was more than 12 months for most patients. Eight serial patients treated with rituximab (anti-CD20), nivolumab (anti-PD-1), ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (anti-BRAF), trametinib (anti-MEK) and ibritunib showed intra-ocular inflammation with hypopion (one patient), macular edema (five patients) and choroiditis (two patients). Various regimens of corticosteroid therapy showed a favorable ophthalmological outcome, whether the CIT was continuing or suspended. Local corticosteroid injections in combination with CIT could be suggested as a first-line treatment. This could help to preserve the quality of life without threatening the vital prognosi

Introduction

Uveitis can affect all layers of the eye and may be due to various etiologies: autoimmune, infectious, iatrogenic or tumor such as mascarade syndrome. Macular edema is the leading cause of visual loss in uveitis [1,2]. Recently, a new iatrogenic uveitis entity has been associated with cancer immunotherapy (CIT). CIT inhibits T-cell inactivation driven by tumor cells [3,4]. The promising results of CIT have led to an increasing number of indications involving larger cohorts of patients [5]. For 10 years, about 50 novel agents have been approved for the treatment of metastatic cancers, including (1) monoclonal antibodies directed against tumor cell surface receptors (such as rituximab, an anti-CD20); (2) immune checkpoint inhibitors (ICIs) such as anti-PD-1 (pembrolizumab, nivolumab), anti-PD-L1 (atezolimab, avelumimab) and anti-CTLA-4 (ipilimumab) monoclonal antibodies that block the interaction between inhibitory T-cell receptors and their ligands; and (3) small-molecule kinase inhibitors, in particular BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib) that inhibit the mitogen-activated protein kinase signaling pathway involved in cell regulation.

Immune-related adverse events (irAEs) have been associated with ICIs, BRAF inhibitors and MEK inhibitors in about 25% of patients, including skin (vitiligo, rash, pruritis) and liver (auto-immune hepatitis) AEs as well as colitis and thyroiditis [6,7]. However, the severity of the reported ocular AEs varies from mild (dry eyes and conjunctivitis) to serious (intraocular and orbital inflammation).

Intraocular inflammation was mainly reported in the anterior chamber while a posterior segment involvement may lead to Vogt-Koyanagi-Harada (VKH) disease, retinal vascular occlusion, macular edema and papillitis [8-19].

The aim of this study was to report the long-term outcomes of patients with CIT-associated uveitis, and discuss the various therapeutic options based on a literature review.

Patients and methods

Serial patients with CIT-associated intraocular inflammation seen between January 1, 2018 and December 31, 2019 were retrospectively included. Patients treated with CIT and reporting eye problems were promptly referred to an ophthalmologist and then to a reference tertiary uveitis center. A collegial therapeutic discussion about the therapeutic interventions involving oncologists, and ophthalmologists was held in a multidisciplinary meeting.

This was a retrospective interventional case series on the approved indications of CIT in France. Informed consent was obtained for all patients before performing retinal angiography, aqueous humor sampling, and before treatment change. Ethic institutional committee approval was obtained.

For each patient, the following data were collected: cancer history and disease progression, previous and current treatments, and detailed ophthalmologic examinations performed at baseline and during the follow-up.

All subjects underwent a comprehensive eye examination including the best-corrected visual acuity (BCVA) on a decimal scale converted into LogMAR, a slit-lamp examination, and a dilated fundus examination. Intraocular inflammation in the aqueous humor and vitreous was scored using the SUN grading system[20]. Color fundus photographs, autofluorescence photographs, fluorescein (FA) and indocyanine green (ICGA) angiography were performed using CR2 plus (Canon, Tokyo, Japan) devices, the HRA2 (Heidelberg Engineering, Heidelberg, Germany), and Optos (Optos Inc. Marlborough, MA 01752 USA) respectively. Spectral-Domain Optical Coherence Tomography (SD-OCT) was performed using the Spectralis (Heidelberg Engineering, Heidelberg, Germany). Flare measurements were performed using the FC-2000® flare meter (KOWA, Tokyo, Japan), to objectively quantify the inflammatory reaction in the aqueous humor [21]. Goldmann visual field examinations

were performed by orthoptists. A thorough work-up was performed to exclude infectious and common ocular and systemic auto-immune causes of uveitis. Particular attention was paid to the systemic causes such as sarcoidosis that can be induced by CIT [22]. So the work-up included for all patients serogy for Human Immunodeficiency virus, syphilis, Lyme disease, B and C hepatitis, and Quantiferon® test, along with blood count, ionogram, protein electrophoresis, sedimentation rate, angiotensine convertase enzyme, lyzozyme, antinuclear and anti DNA. In case of clinical doubt aqueous humor sampling was performed for IL10/IL6 rate to rule out intraocular lymphoma diagnosis. HLA A29 was tested to rule out Birdshot retinochoroiditis which is an auto-immune posterior uveitis characterized by fundus showing deep cream-coloured spots predominantly located in nasal inferior to the optic nerve head. Chest scan and brain magnetic resonance imaging results were known thanks to the patient's oncologic department. If induced-sarcoidosis was suspected, pulmonary function tests and salivary glandular biopsy were performed. Alternative causes of autoimmune-associated or infectious uveitis were excluded from the analysis.

AE severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [23].
The tumor response to CIT was classified according to the revised RECIST guideline [24].
AEs were reported to the National and world Global pharmacovigilance after checking accuretely each case.
Clinical uveitis features along with OCT, FA, ICGA, and flare meter results were described at baseline and during the follow-up.
Therapeutic interventions were collegially discussed and decided by consensus with the oncologists. They included ICI discontinuation or continuation, ICI resumption or not if ICI had been previously discontinued and/or the use of systemic or local corticosteroids. Local corticosteroids were given as drops or subconjunctival dexamethasone injections. Delayed local corticosteroids were given as sub-Tenon's triamcilonone injections. Systemic corticosteroids were given as methylprednisone pulses for 3 days followed by oral prednisone at 1mg/kg for 10 days and then tapered until a daily dose of 10 mg/kg.
Patients were followed one month after the first examination and at least quarterly thereafter to assess the efficacy of the therapeutic intervention and the occurrence of AEs. The study was conducted in compliance with the Good Clinical Practice and the tenets of the Declaration of Helsinki. We focussed on chronic intraocular inflammation that is a rare irAEs. However, this study gave us the opportunity to discuss the risk/benefit ratio in a context of life-threatening disease.

Statistical analysis.
Descriptive statistical analysis was performed using STATA/SE 11.0 software (College Station, Texas, US). Variables were compared using a U Mann-Whitney non-parametric test for continuous variables and a p-value <0.05 was considered significant.

Results

Eight patients (4 women and 4 men) with intraocular inflammation associated with CIT given for metastatic cancer were included (table 1). Patients median age was 68.5 years (IQ1 60.5, IQ3 75.7; range: 58-83). The presence of neoplasia and its grading are described in table 1.
Treatments included rituximab (case 1), ibrutinib (case 2), nivolumab (cases 4, 5, 6, 8), ipilimumab (case 8), dabrafenib + trametinib (case 3), and verumafenib (case 7). One patient (case 3) received a combination of nivolumab, dabrafenib and trametinib for 6 months and only dabrafenib and trametinib thereafter (table 1).

Three patients experienced additional extra-ocular irAEs, including interstitial pneumonitis (cases 3, 6), cryoglobulinemia (case 3), and peripheral neuropathy (case 7) leading to CIT discontinuation (table 1).

Uveitis occured after a median treatment duration of 4.5 months (IQ1 3.7, IQ4 14.2; range: 1-24 months). Upon admission, uveitis was predominant in the anterior segment in 3 patients (cases 5, 7, 8), including in association with hypopyon in 1 case (figure 5), in the intermediate segment in 2 patients (cases 1, 3) and 3 patients (cases 2, 4, 6) had panuveitis. The baseline features and grading of uveitis are shown in table 2. None of the patients had a previous history of uveitis.

The median baseline VA was 0.2 LogMAR (range: 0-2) in both eyes. One patient (case 1) with a history of corneal scars was monophtalm. The median flare was 26.2 photons/ms (range: 7.9-315.3) in both eyes. The median intraocular pressure was 15 mmHg (range: 9-18). Posterior synechias were present in 6 eyes of 4 patients (table 2).

Macular edema was present in 9 eyes of 5 patients, and 3 of these patients showed macular cysts that were mainly located in the inner nuclear layer (cases 2, 3, 4, figure 3). The median central foveal thickness was 260 microns (range: 248-500) in both eyes. Choroidal nodular lesions were seen in 4 eyes of 2 patients (cases 2, 4); on ICGA, they appeared hypofluorescent 10 minutes after dye injection and disappeared after 30 minutes, suggesting a stronger inflammatory choroidal involvement than suggested on the fundus examination (Figure 4).

No case of diplopia and ocular paralysis was found. No systemic auto-immune disease induced by CIT was found; in particular the sarcoidosis work-up was negative.

The first-line therapeutic intervention was based on corticosteroids. Systemic corticosteroids were given in 2 patients with a good ophthalmological response at 3 months in both cases (case 2 and case 6, respectively). Corticosteroids were injected locally in 4 patients with a good ophthalmological response at 3 months. CIT was discontinued in 4 patients: 2 due to ocular AEs (cases 1, 5) and 2 due to extra-ocular AEs (cases 6, 7) (Table 1).

At 3 months, the median BCVA was 0.05 LogMAR (range: 0-2) in both eyes and was significantly different compared to the mean baseline VA ($p = 0.02$). The median flare (n=5) was 8.0 photons/ms (IQ1 3.1, IQ4 19.6; range: 2.1-54.3) in both eyes and was significantly different compared to the baseline value ($p = 0.001$). The median central foveal thickness was 273 microns (IQ1 264, IQ4 366; range: 231-376) in both eyes and was significantly different compared to the baseline value ($p < 0.001$).

The second-line therapeutic intervention consisted in CIT resumption at various timepoints: (1) at 1 month, with a switch from vemurafenib to nivolumab in 1 patient (case 7), and from ipilimumab to nivolumab in 1 patient (case 8); (2) at 6 months in 1 patient (case 5), associated with an increase in tumor mass leading to a rapid death; and (3) at 3 years in 1 patient (case 1) without uveitis recurrence in the short term.

Meanwhile, CIT was continued in 3 patients (cases 2, 3, 4) and did not seem to prevent a good ophthalmological response at 3 months in these three cases. However, bilateral uveitis remained active in 2 out of these 3 patients (cases 3, 4). Case 3 presented a good response to sub-Tenon's triamcilonone injections with a sustained efficiency on the macular edema. Case 4 experienced a recurrence of bilateral uveitic macular edema, but unfortunatly the patient died before receiving a new ophthalmological intervention.

Discussion

This study reported 8 cases of CIT-associated uveitis, among which 7 experienced a visual loss. Five had a macular edema, 2 had nodular choroiditis, and 1 had hypopion. The follow-up was at least 12 months, except for the last included patient case 8. So changes in ME, choroiditis, and hypopion had been analysed for a long-term period of time. First, at 3

months, the short-term visual outcomes were favorable after corticosteroids treatment using either systemic or local injections way. CIT was continued in 3 patients, with no negative effects on the ophthalmological response. At 12 months, CIT continuation was associated with sustained uveitis activity in 2 patients: one died a few weeks later and the other one received sub-Tenon's triamcinolone injections every 10 months.
The occurrence of CIT uveitis has been currently described in metastatic melanomas (4/8 patients) as in other advanced cancers, suggesting that the uveitis is associated with the CIT rather than related to the immune response to the original cancer. Moreover the visual fields of the current patients were preserved contrary to what is usually found in cancer associated retinopathy and melanoma associated retinopathy which are subtypes of paraneoplastic syndrome. Two current patients were investigated for antigenic retinal proteins known to be remated to cancer-associated retinopathy, in particular arrestin and recoverin search was negative.

The reported incidence of severe ocular irAEs is less than 1% [16,25]. A prevalence and an incidence of irAEs of respectively 0.4% and 0.7 per 1,000 patients-months have been reported in patients treated with anti-PD-L1 [10]. Another recent systematic review on the ocular manifestations associated with ICIs has reported an estimated prevalence ranging between 0.3% and 0.6% [13].
Combining nivolumab and ipilimumab has been associated with a stronger antitumor effect, but also with more irAEs, such as uveitis, with a frequency of 6% [26-28]. In a systematic review of 234 patients, ipilimumab has also been strongly associated with irAEs, including autoimmune complications in 10.3% of cases, 4.3% being classified as uveitis [29].
In a review on ocular toxicities induced by targeted anticancer agents, Fu et al. have found that small-molecule drugs are associated with a higher incidence of ocular toxicites than monoclonal antibodies (37.5% *versus* 28.6%) [30].

A mean age of 54 ± 10 years has been reported at the time of the diagnosis of uveitis in patients treated with anti-CTLA-4 and anti-PD-1 antibodies (ipilimumab/pembrolizumab, nivolumab/acetoluzumab, avelumab, durvalumab) [31]. In the current study the patients were younger and this could be due to the various types of neoplasia included.

Uveitis occured after a median treatment duration of 4.5 months, close to previously described treatment durations. Indeed, in a review of 15 cases of uveitis associated with anti-CTLA-4 and anti-PD-1 antibodies, most cases occurred in the first 6 months following ICI initiation [31]. However, shorter treatment durations have also been associated with the occurrence of uveitis. In patients treated with nivolumab and pembrolizumab, 15 cases of uveitis have been reported by Wei Wang et al. after a median treatment duration of 9 weeks [32]. After an infusion of anti-PD-1 and anti-PD-L1 antibodies, the median period of time to ocular irAE occurrence was 29 ± 41 days [10]. In our study, uveitis also occurred after treatment discontinuation in one patient as previously described [10].

The CIT-associated uveitis is usually bilateral; no strictly unilateral cases have been reported. They corresponded either to enucleated patients or corneal scars preventing the intraocular evaluation, as for one patient of the current study [8,33].

The spectrum of CIT-associated uveitis ranged from anterior uveitis to panuveitis. Most of the reported cases had anterior uveitis, as in the case series of 22 CIT-associated uveitis reported by Whilst et al. in which half of the patients had anterior uveitis [8,16,34-40]. Posterior segment inflammation showed various aspects, and most of them are summarized in table 3

[41-59]. Serous retinal detachment suggesting VKH-like disease has been reported with the use of anti-CTLA-4 treatment [41,42] and nivolumab combined with antiBRAF [11,46]. Moreover, bilateral cystoid macular edema shown in 4 of the current cases has been previously reported to be associated with nivolumab [14,15,45], BRAF [12,52] and MEK inhibitors [8,53]. The cysts were mainly located in the inner nuclear layer in 3 out of the 4 current cases experiencing cystoid macular edema (cases 1, 3, 4), as previously shown in a large case series [8]. The inner and outer layers were more rarely involved (case 1) [45]. ME has been previously reported in patients treated with rituximab [57-59].
An association between ibrutinib, Bruton tyrosine kinase inhibitor, and macular edema has been previously reported [56]. In the global pharmacovigilance database (Vigilyze), 46 cases of uveitis associated with ibrutinib (3 in France) have been reported, and ibrutinib was the only suspected drug in 44 cases. The disproportionality analysis (based on the IC025) was significant, suggesting an over-representation of AEs compared to other drugs.

Optic disc edema, papillitis, and leakage of the optic nerve head have been reported, in particular in patients treated with pembrolizumab [34], in patients with severe hypotony treated with pembrolizumab [50], and in patients treated with nivolumab [15]. Choroidal involvements seen as hypofluorescent spots on ICGA were found in 2 current patients and previously reported in patients treated with ipilimumab, nivolumab and pembrolizumab [16,43,44,47].

In a recent study of 22 cases of CIT-associated uveitis, the combination of trametinib and dabrafenib has been most often associated with the occurrence of inflammatory macular edema [8]. Among the ICIs, nivolumab has been associated with posterior pole inflammation leading to macular edema or disc leakage, and peripheral leakage on FA [15,31,43,45]. Pembrolizumab has also been associated with macular edema and disc and peripheral leakage [33,48].
In patients treated with anti-CTLA-4 antibodies, including ipilimumab and tramelimumab, secondary uveitis has been frequently reported. Anti-CTLA-4 antibodies act on the lymph nodes while anti-PD-1 antibodies act in the peripheral tissues [60]. This could explain why CTLA-4-associated irAEs are more common than anti-PD-1/anti-PD-L1-associated irAEs [61].

Uveitis was scored using the CTCAE version 5.0 that defines successive grades [23]. Grade 1 corresponds to anterior uveitis with trace cells, grade 2 to anterior uveitis with 1 to 2+ cells, grade 3 to anterior uveitis with 3+ or more cells or intermediate/posterior/panuveitis and grade 4 to a vision at 20/200 or worse in the affected eye. Thresholds at which treatment should be discontinued have been defined based on irAE severity. In particular, ICI discontinuation in the presence of any grade 3 or 4 irAE has been suggested, associated or not with the use of systemic corticosteroids [61]. However, the application of the CTCAE grading scale may be limited to ocular toxicity management. In our series, even grade 3 and 4 irAEs responded well to dexamethasone subconjunctival injections, long-term dexamethasone drops, and sub-Tenon's triamcinolone injections, avoiding the initiation of systemic corticosteroids. Previous studies have described a good response to local corticosteroid injections. For example, grade 4 panuveitis with bilateral serous retinal detachment in patients treated with nivolumab has been successfully treated with late dexamethasone implant injections (Ozurdex®) [32]. Recent studies have shown a similar successful control of inflammation using local corticosteroid injections and drops in patients treated with CICs, associated with targeted therapy [10,19].

Overall, a high sensitivity to corticosteroids has been observed in cases of anterior uveitis and most cases of posterior uveitis and panuveitis reported associated with CIT [8,10,19].

The AEs of local corticosteroid injections are well known and include induced cataract and glaucoma. For example, cataract occurrence has been reported at 6 months in 20% of uveitis eyes treated by corticosteroid periocular injections [62]. However, cataract surgery is a well codified procedure, especially in elderly patients. Moreover, the endophthalmitis rate has been reduced using systematic intracamerular cefuroxime injections at the end of the surgical procedure [63]. That is why cataract may appear as an acceptable AE in elderly patients undergoing surgery with a rapid visual improvement.
Regarding raised intraocular pressure, it reached ≥24 mmHg in one third of eyes 6 months after periocular corticosteroid injections in patients treated for uveitis [62]. Thus, the intraocular pression should be monitored in the second month following local corticosteroid injections.

Systemic corticosteroids: The efficacy of systemic corticosteroids has been reported in uveitis secondary to CIT in various case reports, as in 2 of the current patients [11,41, 44,46,48,49]. Indeed, the classical management of macular edema associated with bilateral uveitis may include systemic corticosteroids as a first-line therapy, associated with immunosuppressive and immunomodulatory agents thereafter to spare the daily corticosteroid dose needed to control uveitis, and a treatment algorithm has been previously suggested [64,65]. However, it has been suggested that systemic corticosteroids could decrease the overall response in patients treated with anti-PD-(L)1 antibodies for lung cancer and taking more than 10 mg/kg of prednisone daily [66]. On the other hand, systemic corticosteroids have been shown not to influence the antitumor response to anti-CTL-4 [67].

CIT discontinuation: In a recent study, ICIs were continued in 2 patients despite the occurrence of ocular complications and their ocular irAEs were resolved at 1 and 6 months, respectively [10]. In our series, CIT discontinuation for 6 months was associated with tumor progression and a rapid death despite a late resumption in one patient.
Thus, CIT continuation while promptly managing uveitis with corticosteroids injections could be discussed as a first-line therapy.

Recurrence of uveitis: A tendency to relapse was observed in 2 of our patients after CIT restart, as previously reported in studies assessing various ICIs, in particular nivolumab, pembrolizumab, and ipilimumab [8,19,32]. In case of posterior pole involvement, corticosteroid injections could be repeated if well tolerated. Moreover, the long-term use of dexamethasone drops has been suggested to effectively maintain a low level of inflammation in the anterior chamber [19].

All previous recommendations suggest to have an immediate assessment performed by an ophthalmologist in case of ophthalmological problem [61,68].
In the context of a first-line management, it could be justified to use first topical and peri-ocular injections of corticosteroids while continuing CIT. Most of the current cases were good responders to local corticosteroids, even patients with a severe vision loss, and patients with inflammation of the macular area.
The use of corticosteroids as a first line is supported by: (1) the good response to corticosteroids of the inflammation in the aqueous humor and the posterior pole, (2) the long period of time to recurrence, (3) the advanced age of patients making acceptable the occurrence of cataract as an AE, and (4) the possibility to avoid the use of systemic

corticosteroids that could negatively affect the expected response. Moreover, CIT continuation did not seem to prevent a good visual prognosis. CIT discontinuation should be discussed on a case-by-case basis, in case of poor response to the ophthalmological treatment. Although the underlying metastatic cancer are heterogenous, and immunotherapy drugs are numerous, the clinical ophthalmological uveitis related to CIT had shown a similar response to the corticosteroid treatment, regardless of further CIT. So the role of the ophthalmologist may be useful in (1) making quickly the diagnosis relating uveitis to CIT, ruling out infectious, auto-immune and tumoral causes (2) explaining the often favorable uveitis outcome using corticosteroid local injections (3) reassuring patients and oncologists, worried about visual fonction (4) performing quickly ophthalmological treatment to keep a good quality of life (5) following the patients to assess positive and negative treatment effects (6) repeating the corticosteroid local injections if needed (7) rediscussing the treatment in case of ophthalmological failure.

This study has some limitations, including the lack of power due to a small sample size. Moreover, this was a real-life study in which various types of first-line ophthalmological treatments were assessed.
The study strenght could be the ophthalmological follow-up that allowed assessing the long-term results of the therapeutic options.

In summary, local corticosteriod injections for uveitis seem to be associated with favorable visual outcomes while continuing CIT. They could be suggested as a first-line therapy for the management of CIT-associated uveitis.
Ophthalmologists should explain the often favorable visual outcome of CIT-associated uveitis when treated early with local corticosteroids, reassure patients and the care team, explain the expected rapid visual improvement and the possible occurrence of AEs, including cataract and glaucoma, and regularly check corticosteroid efficacy and AEs. In case of failure, they should early adapt treatment after collegial discussion on a case-by-case basis.

Conclusion

The long-term ophthalmological and systemic assessements of patients with CIT-associated uveitis described in this series together with literature data suggest to use local corticosteroid injections as a first line while CIT is continued. The ophthalmological interventions should be given early not to alter patients' quality of life. Indeed, preserving the quality of life could be a new important challenge for the numerous patients treated with CIT, and represent a huge progress in terms of survival outcomes. Uveitis treatment could maintain the quality of life while not impairing the expected outcome of CIT on tumor mass increase. An adapted uveitis management could improve the visual prognosis, without impairing the vital prognosis.

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Figure captions

Figure 1: Patient 1. 81-year old woman treated with rituximab for 4 months for chronic lymphoid leucemia and referred for visual loss of her only fonctional eye (RE) due to macular edema complicating intermediate uveitis. The left eye showed former corneal scars. 1A OCT of the RE: cysts mainly located in the inner nuclear layer. 1B OCT of the RE: 1 month after sub-Tenon's triamcinolone injection, the macular edema disappeared, the visual acuity improved from 0.2 to 0 LogMAR.

Figure 2: Patient 2. An 88-year old man previously treated for Waldestrom disease, experienced 3 years later a metastatic dermic-hypodermic sarcoma treated with ibrutinib and

cyclophosphamide. Eighteen months later, a bilateral visual loss was reported due to panuveitis associated with bilateral macular edema and multifocal peripheral nodular choroidal lesions. Both eyes showed similar lesions. RE : 2A wide field retinography showing peripheral nodular lesions 2B FA 10 min after dye injection, showed a leakage in the central macular area and papillitis 2C: ICGA 4 min after dye injection, showed numerous hypofluorescent nodular lesions 2D they disappeared at 30 min, suggesting an inflammatory activity although an effect of masking by the normal staining of the retinal pigmentary epithelium at 10 minutes may interfere. 2E OCT showing macular cysts mainly located in the inner nuclear layer. 2F the macular edema resolved after treatment with systemic corticosteroids for 6 months in both eyes.

Figure 3: Patient 3. 61-year old man treated with nivolumab, dabrafenib, and trametinib for a BRAF V600E mutation-positive melanoma. Intermediate uveitis complicated by macular edema occured 18 months after treatment discontinuation due to cryoglobulinemia and pneumopathy. The peripheral isopters of the visual field remained normal and the etiological work-up was negative. In particular, the aqueous humor testing showed a cytokine profile consisent with an inflammatory or infectious process (IL-10 at 3 pg/mL and IL-6 at 105 pg/mL). The Herpes virus PCR was negative. Diagnostic vitrectomy showed the presence of pigmented histiocytes, a few lymphocytes and the absence of malignant cells. The anti-recoverin antibody assay was negative. Both eyes showed similar lesions. RE : 3A: wide-field retinography. 3B: autofluorescence showing a shadowing of the inflammatory vitreous. 3C: OCT showed macular edema cysts located mainly in the inner nuclear layer. 3D: A sub-Tenon's triamcinolone injection was effective, the macular cysts disapeared and the visual acuity improved from 0.2 to 0.1 LogMAR.

Figure 4: Patient 4. A 63-year old woman with KRAS-mutant bronchial adenocarcinoma (T3, N3, M1b) was treated with nivolumab and bevacizumab for more than one year. She experienced a bilateral visual loss due to bilateral panuveitis associated with macular edema and focal choroidal nodular lesions. Both eyes showed similar lesions. RE 4A retinography showing papillitis and peripheral nodular lesions. 4B: OCT horizontal scan showing cysts in the inner nuclear layer. 4C: autofluorescence showing nodular hyperautofluorescent lesions.4D: FA showing a papillary and macular leakage and cyst filling. 4E: ICGA showing numerous focal hypofluorescent nodular lesions, well visible at 10 minutes. 4F: they disappeared during the late phase (30 min).

Figure 5: Patient 5. A 75-year old woman was treated with nivolumab for metastatic pleural mesothelioma for 4 months when a bilateral visual loss occurred, due to acute anterior uveitis with hypopyon, successfully treated with dexamethasone subconjonctival injections. In the RE, hypopyon complicating acute anterior uveitis.

Figure 1

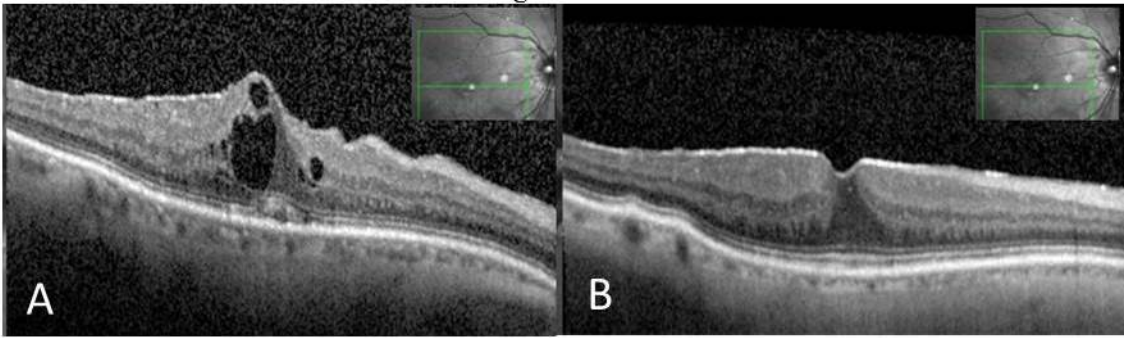


Figure 2

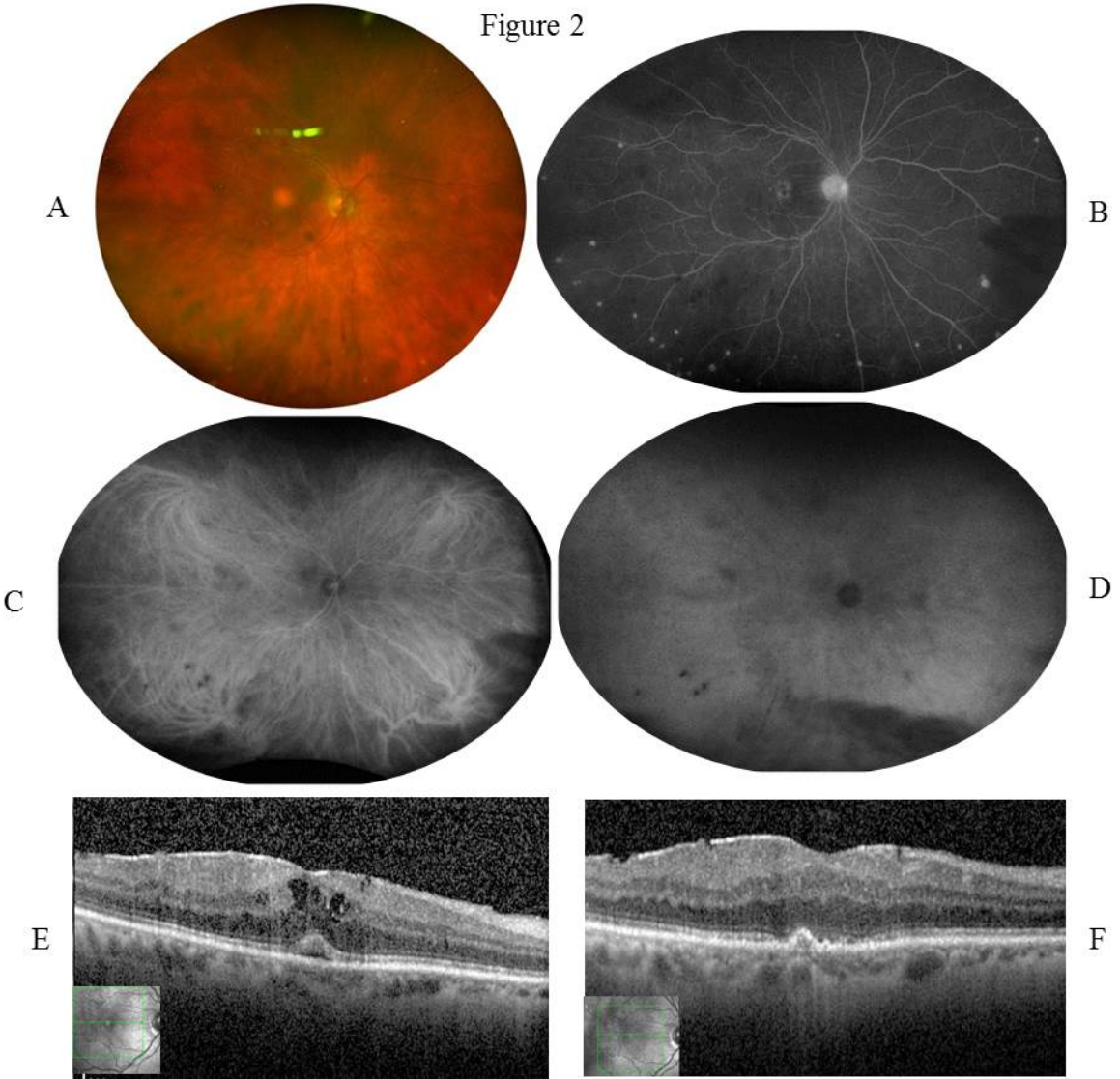


Figure 3

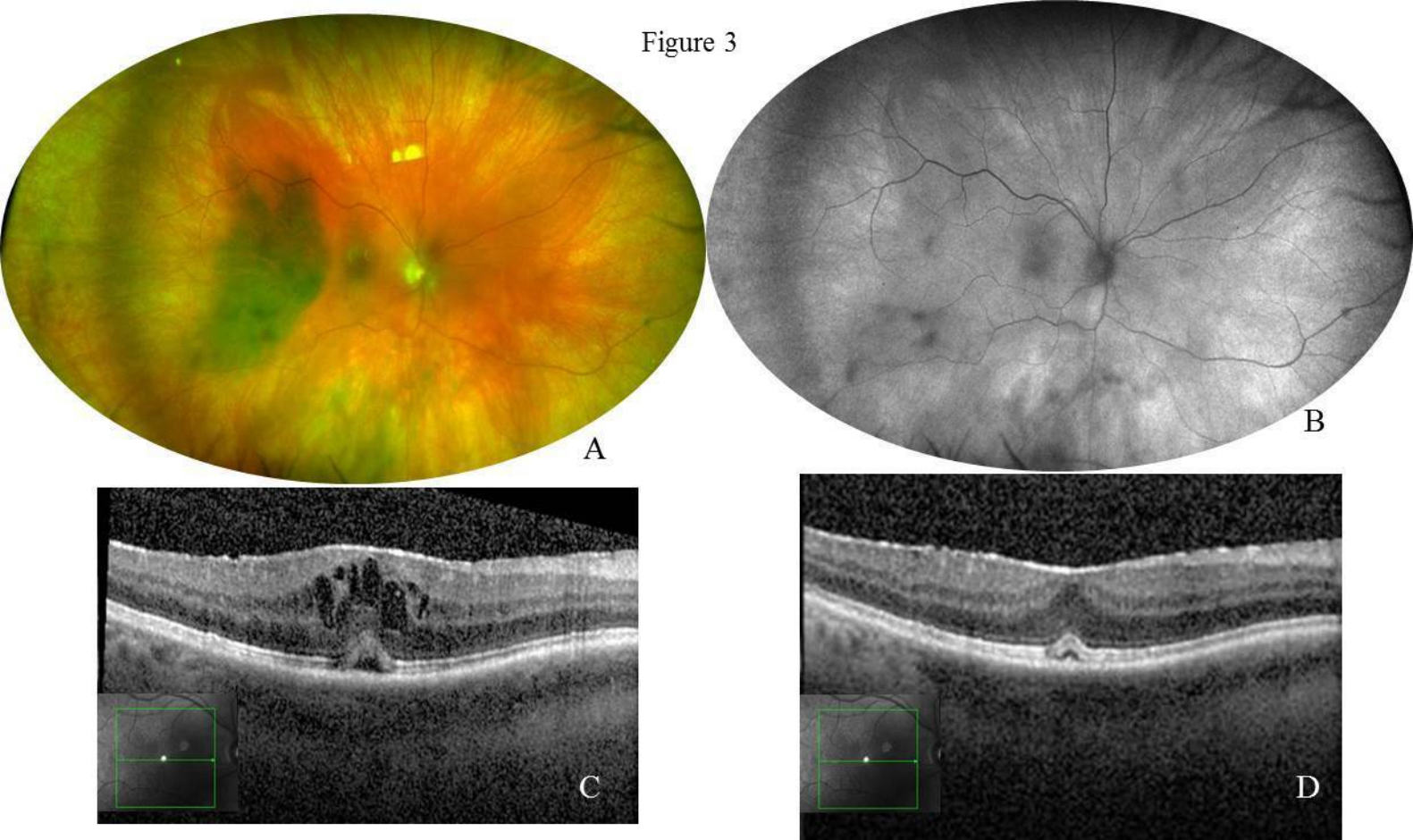
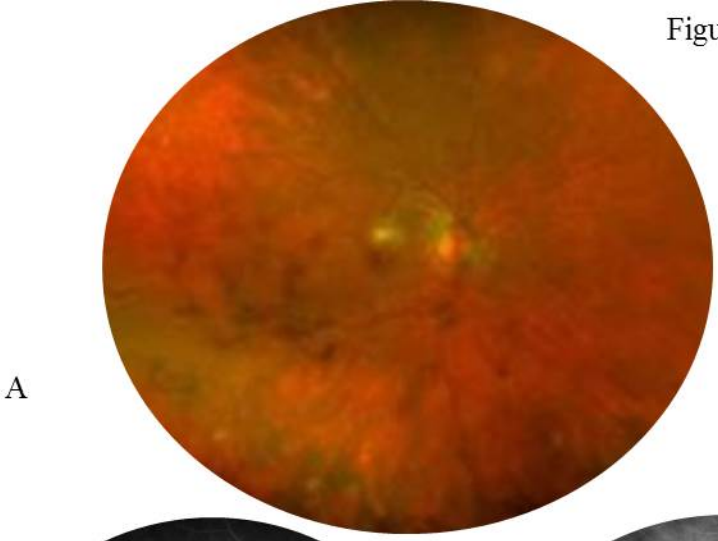


Figure 4



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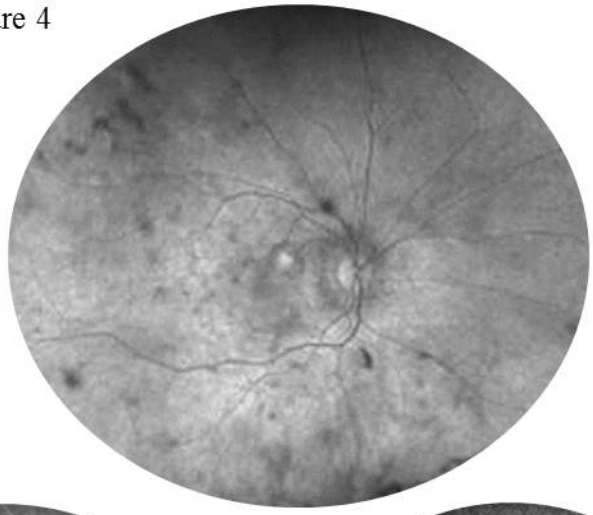

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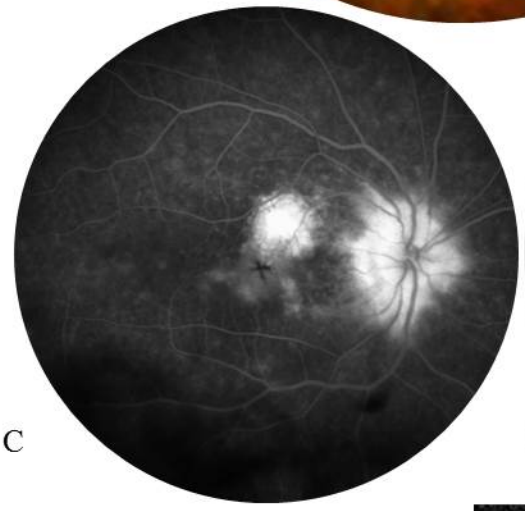

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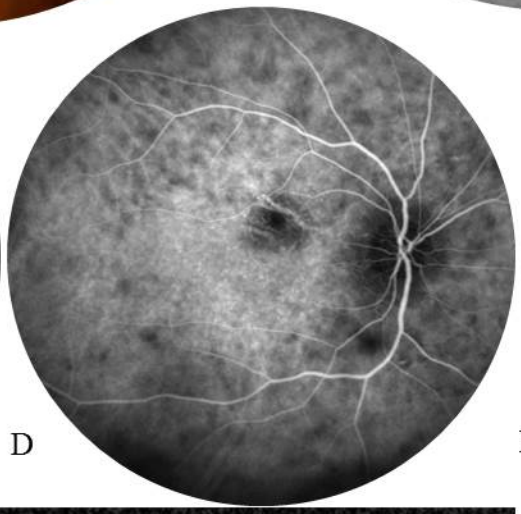

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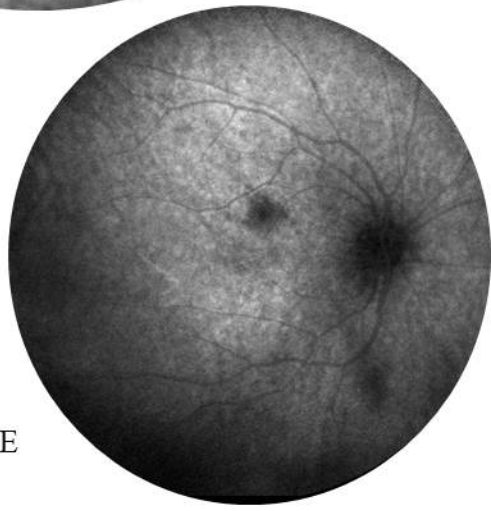

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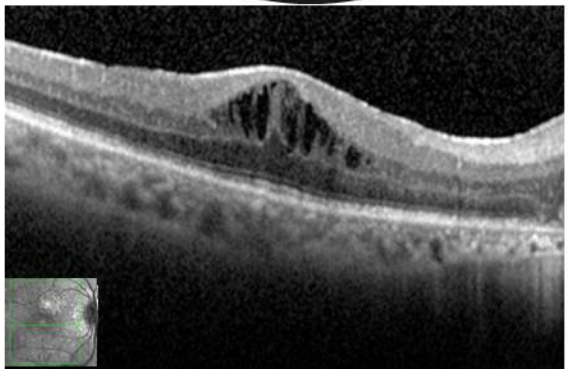

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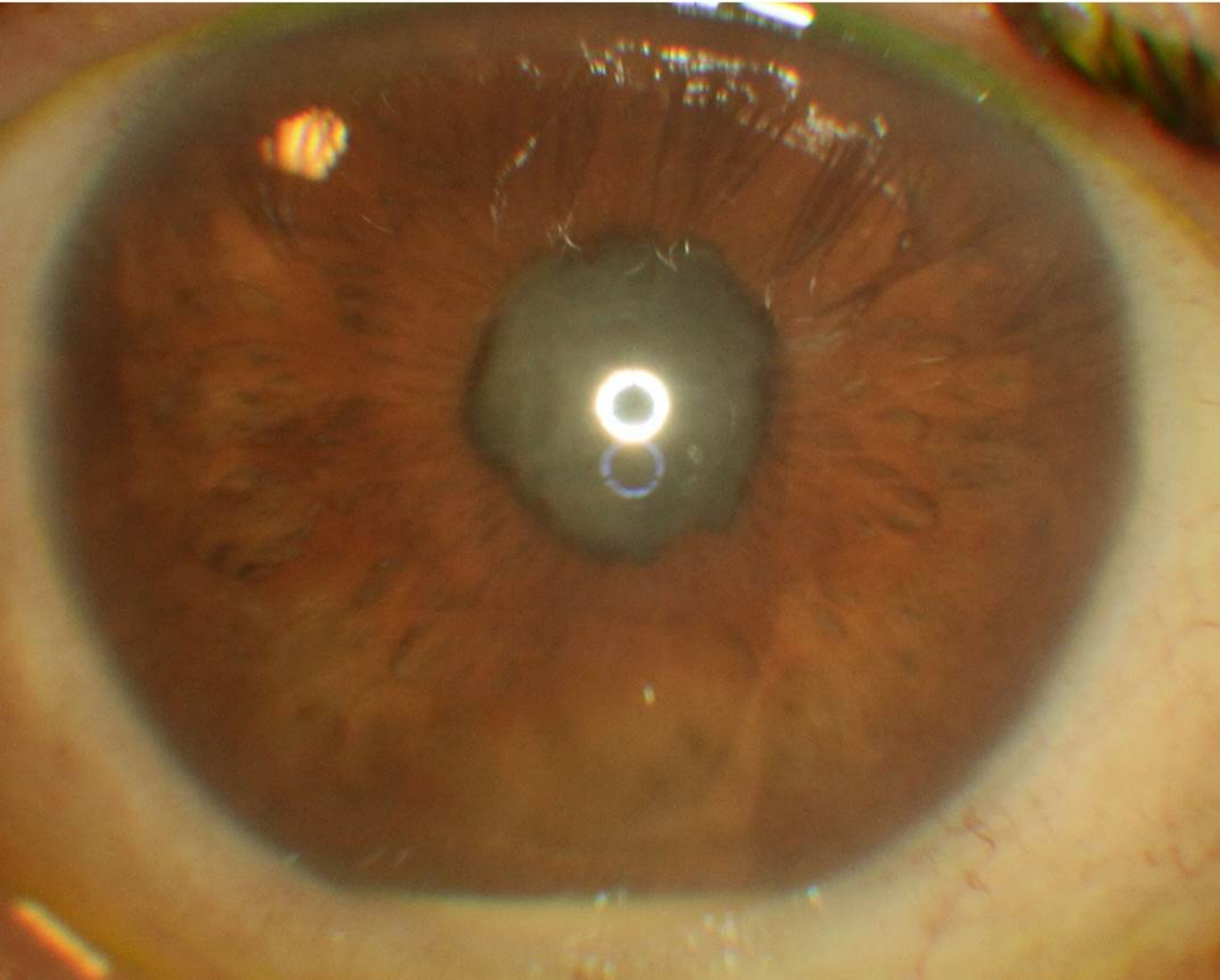
Figure 5



							1st therapeutic intervention		2nd intervention				
Patient number, gender and age at uveitis onset	Neoplasia grading	CIT type	Time between ICI initiation and uveitis onset (months)	Oncological response	Baseline visual acuity in the RE/LE in decimals and LogMAR	Active uveitis features	CIT discontinuation	Ophthalmological treatments	Visual acuity at 3 months RE/LE LogMAR	Favorable ophthalmological outcome at 3 months	CIT resumption	Uveitis activity at 12 months	Final outcome at 12 months
1 F. 81	Chronic lymphoid leukemia	Rituximab (Anti-CD20)	4	CR	0.6/0.01 0.2/2	Bilateral intermediate Uveitis and ME	yes	Local corticosteroids Sub-Tenon's triamcinolone injection	0/2	Yes	Resumption after 3 years for leukemia recurrence	No	Alive CR
2 M. 72	Less differentiated sarcoma in Waldenstrom disease	Ibrutinib (Bruton tyrosine Kinase inhibitor)	18	PR	0.5/0.5 0.3 /0.3	Bilateral panuveitis choroiditis and ME	no	Systemic corticosteroids	0.2/0.1	Yes	ongoing	No	Alive PR
3 M. 61	Stage 4 BRAF V600E mutation-positive melanoma	Nivolumab (Anti-PD-1) + Dabrafenib (Anti-BRAF) + Trametinib (Anti-MEK)	24	PR	0.8/0.8 0.1/0.1	Bilateral intermediate uveitis and ME	no	Sub-Tenon's triamcinolone injection	0.2/0.2	yes	ongoing	Yes Good VA with triamcinolone injections	Alive PR
4 F. 65	T3 lung adenocarcinoma	Nivolumab (Anti-PD-1)	13	PR	0.5 /0.7 0.3/0.2	Bilateral panuveitis choroiditis and ME	no	Dexamethasone subconjunctival injections	0.1/0.1	yes	ongoing	Yes Bilateral ME	Death
5 **F. 74**	Pleural mesothelioma	Nivolumab (Anti-PD-1)	4	CR	0.01/0.01 2/2	Bilateral anterior uveitis Bilateral hypopion	yes	Local antibiotics and dexamethasone drops Dexamethasone subconjunctival injections	0/0	Yes	Resumption after 6 months for tumor mass increase	No	Death
6 **F. 83**	Melanoma	Nivolumab (Anti-PD-1)	5	CR	0.8/0.1 0.1/1	Bilateral posterior uveitis Papillary edema Contiguous ME	Yes for interstitial pneumonitis	Systemic corticosteroids	0/0.3	no	no	no	Alive PR
7 **M. 58**	BRAF V600E mutation-positive superficial spreading melanoma	Vemurafenib (Anti-BRAF)	5	CR	0.6/0.8 0.2/0.1	Bilateral anterior uveitis	Yes for peripheral neuropathy	Local corticosteroids Dexamethasone drops	0/0	yes	Yes with nivolumab	no	Alive CR
8 **M.59**	Stage 4 BRAF V600E mutation-positive melanoma	Nivolumab + Ipilimumab (Anti-CTLA-4)	1	PR	1.0/1.0 0/0	Bilateral anterior uveitis	Yes ipilimumab discontinuation	Local corticosteroids Dexamethasone drops	0/0	yes	Yes with nivolumab	No at 3 months	Alive PR at 3 months

CIT: Cancer ImmunoTherapy; PR: Partial response; CR: complete response; ME: macular edema; OPH:

Patient	Baseline uveitis features	Corneal precipitates	Post synechiae	Hypopyon	IOP >21 mmHg	Vitreous cells grading RE/LE	Flare Photon/ms RE/LE	Macular edema	Central foveal thickness Microns RE/LE	FA and ICGA findings	Uveitis grading CTCAE
1	Bilateral intermediate uveitis	fine	NO	NO	NO	++/+	8.4/ND	YES	462/ND	Retinal peripheral venous leakage Papillitis	3
2	Bilateral panuveitis	Small granulomatous	NO	NO	NO	+/+	26.2/16.6	YES	441/483	Retinal edematous capillaritis Choroidal nodular lesions	3
3	Bilateral intermediate uveitis	fine	YES	NO	NO	++/+++	108.1/315.3	YES	500/399	Macular leakage	3
4	Bilateral panuveitis	Small granulomatous	YES	NO	NO	++/+++	44.9/50.4	YES	455/410	posterior pole leakage Choroidal nodular lesions	3
5	Bilateral anterior uveitis	fine	YES	YES	NO	+/+	152.3/64.7	NO	282/259	ND	4
6	Bilateral posterior uveitis	fine	NO	NO	NO	+/+	3.1/3.9	YES	295/360	Papillitis	4
7	Bilateral anterior uveitis	fine	YES	NO	NO	½+/½+	23.5/25.4	NO	275/269	ND	2
8	Bilateral anterior uveitis	fine	NO	NO	NO	½+/½+	nd	NO	248/250	Papillary edema	1

CTCAE: Common terminology criteria for adverse events; ND: not determined; IOP: intraocular pressure

Posterior segment involvement	Posterior segment involvement features	CIT drug(s)	Number of cases	Corticosteroid type (local/systemic/topical) (local=IVT , subTenonien injections)	CIT drug stop	Uveitis resolution after therapeutic intervention
Wong et al. 2012	VKH-like	ipilimumab	1	Systemic	Yes	Yes
Crosson et al. 2015	VKH-like	ipilimumab	1	None	No	ND
Fierz et al. 2016	Papillary edema Choroidal nodular lesions	ipilimumab	1	Systemic	Yes	No
Robinson et al. 2004	ME and papillitis	ipilimumab	1	Local	Yes	Yes
Tsui et al. 2019	ME and retinal vasculitis	ipilimumab	1	Local and systemic	Yes	Yes
Sun et al. 2019	CME Panuveitis	ipilimumab ipilimumab + nivolumab	2 2	Periocular triam/topical Local	ND ND	Yes / no Yes / no
Conrady et al. 2018	Subretinal fluid Multifocal choroiditis	ipilimumab + nivolumab	2	Systemic/local	Yes	Yes
Conrady et al. 2018	Central retinal artery occlusion Multifocal choroiditis	ipilimumab + nivolumab	1	Systemic	ND	No
Venkat et al. 2019	Papillitis and peripheral leakage on FA	ipilimumab + nivolumab	1	Local	Yes Ipilimumab discontinued	Yes
Obata et al. 2019	VKH-like Granulomatous corneal precipitates Choroidal granulomas	nivolumab	1	Local IVT	Yes	Yes
Arai et al. 2017	VKH-like	nivolumab	1	Local	Yes	
Theillac et al. 2017	ME, papillary edema Granulomatous corneal precipitates	nivolumab	1	Systemic	Yes	Yes
Wei et al. 2019	Serous retinal detachment	nivolumab	1	Local and systemic IVT DXM implant	Yes	Yes
De Velasco et al. 2016	CME	nivolumab	1	Intraocular steroids	No	Yes
Richardson et al. 2017	ME and papillitis	nivolumab	1	Local IVT	Yes	Yes
Conrady et al. 2018	Subretinal fluid Multifocal choroiditis	nivolumab	1	Local	ND	Yes
Sun et al. 2019	Panuveitis	nivolumab	1	Local	ND	Yes
Fujimura et al. 2018	VKH-like	Nivolumab + dabrafenib/trametinib	2	Systemic	Yes	Yes
Matsuo et al 2017	VKH-like	Nivolumab + vemurafenib	1	Systemic	Yes	Yes
Bitton et al.2019	Subretinal fluid	pembrolizumab	1	Systemic	Yes	Initial improvement and then relapse
Sun et al. 2019	Panuveitis	pembrolizumab	2	Local	ND	Yes / no
Conrady et al. 2018	ME	pembrolizumab	1	Local IVT	ND	Yes
Aaberg et al. 2017	Posterior uveitis, retinal vasculitis	pembrolizumab	1	Local IVT	No	Yes
Hanna et al. 2016	Panuveitis Multifocal choroiditis	pembrolizumab	1	Local and systemic	Yes	Yes
Diem et al. 2016	panuveitis	pembrolizumab	1	Systemic	Yes	Yes
Manusow et al. 2014	Retinal vasculitis	pembrolizumab	1	Local and systemic	No	Yes
Abu et al. 2016	Papillitis	pembrolizumab	1	Local	ND	Yes
Bricout et al 2017	VKH-like	pembrolizumab	1	Systemic	ND	Yes
Reid et al. 2019	Optic disc edema hypotony	pembrolizumab	1	Systemic	Yes	No
Whist et al. 2019	hypotony	pembrolizumab	1	Systemic	Yes	No
Venkat et al. 2019	ME and peripheral leakage on FA	atezolizumab	1	Local IVT	Yes	Yes
Conrady et al. 2018	Retinal vasculitis	atezolizumab		Systemic		Yes
Guedj et al. 2014	ME	vemurafenib	1	Systemic	Yes	No
Fierz et al. 2016	Retinal vasculitis	vemurafenib	1	Local	Yes	Yes
Whist et al.2019	ME	vemurafenib	1	Local	No	Yes
Fonollosa et al 2015	ME	vemurafenib	1	ND	ND	Yes
Gavric et al 2018	ME Subretinal fluid	Vemurafenib + cobimetinib	1 5	Topical	ND	ND
Whist et al.2019	ME	Dabrafenib + trametinib	4	Systemic	ND	Yes
Draganova et al. 2015	Multiple subretinal detachment	Dabrafenib + trametinib	1		Yes	Yes
Sarny et al. 2017	ME and focal lesions	Dabrafenib + trametinib	1	ND	Yes	Yes
Joshi et al 2013	Panuveitis	Dabrafenib + trametinib	1	ND	Yes	Yes
Flaherty et al. 2012	RPE detachment	trametinib	1		Yes	Yes
Mirgh et al. 2020	ME	ibrutinib	1	Local	ND	Yes
Bussone et al. 2010	ME	rituximab	2	Systemic	ND	ND
Gilca et al. 2019	ME	rituximab	1	Systemic followed by local	Yes	Yes
Juric et al. 2021	ME	Rituximab	1	Local	ND	yes

IVT: intravitreal therapy; Triam: triamcinolone; CME: cystoid macular edema; ME: macular edema; ND: not determined; RPE: retinal pigmentary epithelium; FA: fluorescein angiography; VKH: Vogt–Koyanagi–Harada disease; DXM dexamethasone