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Pimasertib-associated ophthalmological adverse events

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Abstract

Purpose: To analyse ophthalmological adverse events associated with mitogen-activated protein kinase kinase (MEK) inhibition with pimasertib treatment for metastatic cutaneous melanoma (CM).

Methods: In this prospective observational, cohort-based, cross-sectional study, 8 patients treated with the MEK inhibitor pimasertib received a complete ophthalmic examination. This included Early Treatment of Diabetic Retinopathy Study best-corrected visual acuity, visual field testing, color vision testing, slit-lamp examination, applanation tonometry, indirect ophthalmoscopy, digital color fundus photography, and optical coherence tomography (OCT). In selected cases fluorescein angiography was performed.

Results: Serous subretinal fluid (SRF) developed in all patients, within a time frame of 92 ~~-20~~7 days after the start of treatment. The fovea was involved in 6/8 patients (75%). None of the patients with foveal SRF (excluding a patient who developed a bilateral retinal vein occlusion (RVO)) experienced visual symptoms. SRF decreased or resolved in all patients, despite continuation of study medication in 6/8 patients (75%). Complaints in the CM patient (13%) consisted of experiencing a dark fleck in the inferior part of the visual field of the right eye ~~unilateral vision loss~~ 1 week after the start of treatment, due to an RVO. Subsequent intravitreal bevacizumab treatment resulted in functional and anatomical improvement.

Conclusions: Patients with metastatic CM who are treated with the MEK inhibitor pimasertib are at high risk of development of ocular adverse events including serous retinopathy and possibly RVO, stressing the need of adequate ophthalmological follow-up including OCT during ~~the~~ administration of pimasertib, despite the fact that SRF generally does not lead to ophthalmological complaints.

Key words

MEK inhibitor; ophthalmological adverse events; pimasertib; retinal vein occlusion; serous retinopathy

Introduction

Spectral-domain optical coherence tomography (OCT) is a sensitive means to detect serous retinopathy, which is defined as retinal lesions on ophthalmoscopy corresponding to a localized separation of the neuroretina and retinal pigment epithelium (RPE).(van Dijk et al. 2015) ~~Serous retinopathy may be classified according to the underlying cause, which is either rhegmatogenous, tractional, or exudative.(Ghazi & Green 2002)~~ It may occur as an independent entity, but may also be associated with a broad spectrum of other diseases or may follow the use of certain drugs.(Ghazi & Green 2002) We and others recently described that serous retinopathy is seen in patients with metastatic melanoma during the treatment with mitogen-activated protein kinase kinase (MEK) inhibitors such as binimetinib,(van Dijk et al. 2015; Weber et al. 2016) cobimetinib,(McCannel et al. 2014) trametinib,(Infante et al. 2012) and RO5126766.(Martinez-Garcia et al. 2012) ~~For many drugs, it is unknown how often this complication occurs.~~ Luckily, in many cases vision is not affected by the treatment, but serious problems including retinal vein occlusion (RVO) may occur.(LoRusso et al. 2010; Leijen et al. 2012)

As treatment options for metastatic malignant cutaneous melanoma (CM) are scarce, much effort is being put into the development of possible new treatments for this patient group. One of the target pathways for treatment is the mitogen-activated protein kinase (MAPK) signalling (Ras - Raf - MEK - extracellular signal-regulated kinase) pathway. A broad spectrum of cellular processes is coordinated by this pathway~~, which can be activated by various stimuli, such as hormones, growth factors, stress, and by ischemic and inflammatory injuries~~. Activation of the MAPK pathway influences processes such as cell differentiation and metabolism, cell migration, and cell death.(Krishna & Narang 2008) Although visual symptoms may be absent or relatively mild in patients to whom MEK inhibition is prescribed, OCT imaging has shown that some of the MEK inhibitors induce retinal changes in a high percentage of patients.(Flaherty et al. 2012; Ascierto et al. 2013; McCannel et al. 2014; Urner-Bloch et al. 2014; van Dijk et al. 2015)

~~Preliminary results of p~~Preclinical studies have shown that the new MEK inhibitor pimasertib displays activity against ~~N~~*RAS* and *BRAF* mutated cell lines.(Kim et al. 2010; Yoon et al. 2011)

Moreover, induction of apoptosis in *BRAF* mutated human malignant melanoma cell lines has been described after the administration of a combination of pimasertib and the BRAF inhibitor PLX4032, whereas either drug alone did not.(Park et al. 2013) In the first human trial IMP28062, activity against *NRAS* mutated tumors could be detected after prescription of pimasertib. In a recently published report of a patient with metastatic ovarian cancer bilateral multifocal retinal detachments were described 2 days after the start of pimasertib.(AlAli et al. 2016) This patient developed complaints of blurred vision, and treatment was discontinued. Three days after stopping pimasertib treatment, ocular complaints and lesions had disappeared.(AlAli et al. 2016) The occurrence of serous retinal detachments in patients, to whom pimasertib was prescribed, was not further specified in ~~an~~other stud~~y~~ies.(Houede et al. 2011; Macarulla et al. 2015) In 1 of these studies, the occurrence of an RVO in a patient was also not discussed in detail.(Houede et al. 2011) No other ocular adverse events during the prescription of pimasertib have been reported so far.

~~As we are very interested in the mechanism behind the development of serous retinopathy during MEK inhibition, w~~We hypothesized that this drug may also lead to subretinal fluid (SRF) and wondered whether SRF would occur in only in a sensitive subset of patients, or that it might be a general phenomenon. As patients are in quite a good general condition when using this treatment, we were able to perform a prospective study of patients using the new MEK inhibitor pimasertib, and included high resolution OCT imaging to examine the macular area in detail.

Materials and methods

Patient characteristics

Eight patients from an academic medical center (Erasmus University Medical Center, Rotterdam, the Netherlands) were included in this study. All patients were diagnosed with a measurable, histologically or cytologically confirmed, locally advanced or metastatic *NRAS* mutated malignant CM. Patients with a medical history of retinal degenerative disease, uveitis, or RVO were excluded. Local ethics committee approved the study. Each patient gave written informed consent ~~after explanation of the nature and possible consequences of the study~~, and the study was performed in accordance with the Declaration of Helsinki. The clinical trial was registered in the Clinical Trial

Register with number NCT01693068. Patients were included in this trial from September 2013 to June 2014.

Treatment

All patients received ~~the MEK inhibitor~~ pimasertib in a randomized phase II trial, in which the comparator arm was chemotherapy with dacarbazine (intravenous administration at dose of 1000 mg per square meter of body surface area, every 3 weeks). Patients received 60 mg of pimasertib orally twice a day, continuously for 21 days (defined as a 1 treatment cycle, for scheduling purposes). Within this trial 7 patients were primarily randomized to pimasertib, whereas 1 patient made a cross-over to treatment with pimasertib after having developed progressive disease upon chemotherapy with dacarbazine. ~~In all patients study treatment was continued until either disease progression or unacceptable toxicity occurred.~~

Ophthalmic examinations

All patients received complete ophthalmic examination, including Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) testing, visual field testing, color vision testing using the Desaturated Panel D-15 test, slit-lamp examination, intraocular pressure measurement, indirect ophthalmoscopy, digital color fundus photography (Topcon Corporation, Tokyo, Japan), and OCT using the spectral-domain OCT (Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany)), before ~~the~~ start of the study. Part of these examinations was performed after dilation of pupils by topical administration of 1% tropicamide and 5% phenylephrine drops. Moreover, study protocol instructed the BCVA measurement ~~OCT scanning was~~ at every evaluation visit: ~~performed~~ at the beginning of treatment cycle 2~~,~~ and at the beginning of every subsequent odd treatment cycle. At these evaluation visits, ~~Pupils were dilated by topical administration of 1% tropicamide and 5% phenylephrine drops~~slit-lamp examination and assessment of the posterior pole using indirect ophthalmoscopy were also prescribed to be executed, together with OCT scanning. When ETDRS BCVA testing was not available, Snellen BCVA was determined and a previously-established conversion method was used to achieve ETDRS values.(Gregori et al. 2010)

In patients with visual disturbances or abnormal retinal findings on ophthalmological assessments, fluorescein angiography was performed with the spectral-domain OCT. Treatment had to be interrupted when a serous retinal detachment with a decrease in ETDRS BCVA of ≥15 letters occurred. A serous retinal detachment was defined as a localized separation of the neuroretina and RPE on OCT, with an accumulation of SRF between these layers. Restart of treatment could only be scheduled after full resolution of the detachment and full recovery of vision within 2 weeks, after weekly follow-up visits. In case of the occurrence of an RVO the study medication had to be stopped, unless the event resolved within 2 weeks.

Safety and efficacy monitoring

~~During every visit to the outpatient clinic of the Department of Oncology, a report was completed.~~ After clinical assessment at the evaluation visits at the Department of Oncology, the dose of study medication was reduced or medication was discontinued, when either unacceptable signs of toxicity or disease progression had developed. Subjects with documented tumor progression on the dacarbazine arm could choose to switch to receiving pimasertib. ~~Every 2 treatment cycles, a CT scan was made for evaluation of disease.~~

Statistical analysis

Both ETDRS BCVA at the time point of most pronounced SRF on OCT and at final follow-up were compared to ETDRS BCVA at initial screening, using an independent t-test in IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, United States).

Results

The 8 CM patients (4 male, 4 female) had a mean age of 62.9 years (median: 64 years; range, 56-67 years). The clinical patient characteristics ~~of the CM patients~~ are summarized in Table 1.

During this study, 1 patient (13%) developed visual complaints, consisting of experiencing a dark fleck in the inferior part of the visual field of the right eye. These complaints started 1 week after the restart of pimasertib treatment, after a previous discontinuation because of a reversible decrease in

left ventricular ejection fraction. In the right eye, ETDRS BCVA had dropped from 95 to 67 letters, while ETDRS BCVA of the left eye had not changed at the time of visual complaints ~~in the right eye~~. Indirect ophthalmoscopy and fluorescein angiography led to the diagnosis of a hemi-RVO of the superior temporal vein of the right eye and an asymptomatic mild hemi-RVO of the inferior temporal retinal vein of the left eye (Fig. 1A-L). Because of cystoid macular edema, a single intravitreal injection of bevacizumab in the right eye was given to this patient, after which ETDRS BCVA recovered to 89 letters at follow-up visit 8 days later (Fig. 1M-P). Because of the need for palliative care, which this patient preferred to receive in another hospital, and because of the good functional and anatomical result of this single injection, no additional follow-up was scheduled.

OCT indicated that SRF developed in 16/16 eyes (100%). None of the patients (excluding the patient with RVO) experienced visual symptoms ~~during the onset or presence of SRF~~. Moreover, no measurable significant influence on visual acuity could be detected, as (converted) median BCVA ETDRS was 88 letters (range, 77-93 letters) at screening, 87 letters (range, 66-98 letters) at the moment of most prominent SRF on OCT, and 89 letters (range, 75-98 letters) at the final follow-up visit. Differences in ETDRS BCVA were not statistically significant (p=0.58 (screening versus most prominent SRF), p=0.31 (most prominent SRF versus final follow-up visit), and p=0.51 (screening versus final follow-up visit)).

Ophthalmoscopy revealed transparent to yellowish vitelliform lesions at the time that SRF was observed on OCT (Fig. 1D, 1K-L, 2A), whereas either no abnormalities or mild RPE changes were observed after disappearance of SRF. The SRF~~, detected on OCT in all CM patients,~~ was bilateral and fairly symmetrical (Fig. 2K-T). These lesions were seen in all patients at the time of their first OCT after the start of the study medication, which was performed after 92 ~~-2~~07 days (median: ~~11~~ 20 days). Foveal SRF accumulation was present in 6/8 patients (75%)~~, and this occurred bilaterally in all patients~~. The center of these lesions was hyperreflective on infrared reflectance ~~(IRR)~~ imaging, and the lesions were surrounded by a hyporeflective zone. On OCT, SRF was detected extrafoveally in all 8 patients (Fig. 1K-L, 2D, 2I-J). ~~In 2 of these patients (25%), only extrafoveal SRF could be detected (Fig. 2I-J).~~ The median total number of extrafoveal lesions in the posterior pole, based on a 30˚ infrared reflectance photograph, was 6 (mean: 5, range, 3-13 lesions) in the 16 eyes.

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At last ophthalmological follow-up at 14-126 days (median: 81 days) after the first appearance of SRF, the SRF had disappeared in both eyes in 5/8 patients (63%). In the patient who received intravitreal bevacizumab ~~for cystoid macular edema associated with hemi-RVO~~, resolution of both cystoid macular edema and SRF had occurred. Administration of pimasertib had been discontinued in this patient. In the other 4 patients, SRF disappeared spontaneously while pimasertib was either still administered according to the original dose ~~to~~ (2 ~~of these~~ patients~~) who showed spontaneous resolution, 1 patient had received pimasertib~~ or dose of pimasertib was reduced (1 patient)~~tion~~, ~~and~~ or ~~in 1 patient~~ pimasertib was discontinued because of a decrease in left ventricular ejection fraction (1 patient). Three patients had persistent SRF, during treatment with 60, 60, and 30 mg of pimasertib twice a day, respectively. ~~These patients were seen for follow up after 56, 41, and 34 days after the (re)start of pimasertib, respectively.~~ However, during follow-up the amount of SRF had decreased in all 3 patients. Color vision testing and visual field testing revealed no significant changes, despite macular SRF accumulation during pimasertib treatment. For all patients, information on the occurrence and evolution of SRF, and the possible relationship with orally administered dose of pimasertib has been depicted in Fig. 3.

During the period of the administration of ~~the~~ study medication~~,~~ in 1 patient who had previously been diagnosed with bilateral diabetic macular edema, (Fig. 4~~3~~A-D) edema had increased unilaterally at ophthalmological follow-up, 9 days after the start of study medication (Fig. 3~~4~~E-F). This patient also developed bilateral foveal SRF~~, but did not report visual complaints~~. No signs of other ophthalmological diseases were detected during follow-up. Eleven days later, SRF and edema had decreased spontaneously (Fig. 3~~4~~G-H). At final follow-up 106 days later, only minimal unilateral foveal SRF remained (Fig. 3~~4~~I-J). Ophthalmic characteristics of all patients are summarized in Table 1.

Discussion

Spectral-domain OCT is a sensitive means to detect a typical serous retinopathy in patients treated with MEK inhibitors such as pimasertib. Despite these striking MEK inhibitor-associated retinal abnormalities in all 8 metastatic CM patients, all but 1 patient remained asymptomatic. This patient

experienced central vision loss due to bilateral RVO, which responded to intravitreal bevacizumab treatment. Lesions occurred both foveally and extrafoveally in most of the 8 patients, indicating a more extensive dysfunction of the retina and/or RPE that extended beyond the fovea. Serous retinopathy had either disappeared or decreased at the last ophthalmological follow-up in all patients.

The exact pathogenesis of both serous retinopathy and RVO associated with MEK inhibitor treatment is as yet unclear. A time-dependent and reversible serous retinopathy, resembling the clinical picture we present in the current study, was previously described in association with several other MEK inhibitors such as cobimetinib,(McCannel et al. 2014) trametinib,(Infante et al. 2012) and RO5126766.(Martinez-Garcia et al. 2012) We described this specific phenotype by a mildly symptomatic, time-dependent, and reversible accumulation of both foveal and extrafoveal serous SRF, with abnormalities on electro-oculography but without any evidence of choroidal abnormalities.(van Dijk et al. 2015) This serous retinopathy is most probably related to a class effect of this type of drugs, and thereby an on-target side effect of treatment,(Duncan et al. 2015; Kurbel et al. 2015) although pharmacological differences between several MEK inhibitors exist.(Hatzivassiliou et al. 2010) We have previously described prolonged abnormalities on electro-oculography in patients with transient binimetinib-associated serous retinopathy, indicating panretinal RPE dysfunction and dysfunction of the RPE pump.(McCannel et al. 2014; van Dijk et al. 2015) In addition, anti-RPE and anti-retinal autoantibodies may play a role ~~in the pathogenesis of MEK inhibitor-associated serous retinopathy~~.(van Dijk et al. 2015) ~~Both direct RPE toxicity and the presence of autoantibodies could contribute to both these abnormalities and to the occurrence of SRF, which can occur within a few days after the start of MEK inhibition treatment.(McCannel et al. 2014; Urner-Bloch et al. 2014; van Dijk et al. 2015)~~ In a cell model of RPE and neuroretina, binimetinib administration resulted in inactivation of the MAPK pathway, and discontinuation of administration of the MEK inhibitor binimetinib led to reactivation, mimicking the mild and reversible retinopathy.(van Dijk et al. 2016) The occurrence of an RVO, during the prescription of MEK inhibition has also been described previously in up to 5% of patients.(LoRusso et al. 2010; Houede et al. 2011; Leijen et al. 2012) MEK inhibitors could influence the vasculature of the retina, leading to both this serous retinopathy and RVO.(van der Noll et al. 2013; van Dijk et al. 2015) The RVO that occurred in 1 of our patients could

have been associated with the previous reversible decrease in left ventricular ejection fraction in this case, which had been detected 3 weeks before the diagnosis of RVO had been established. Moreover, ~~A~~after oral administration of the MEK inhibitor PD0325901 to rats, retinal gene expression suggested an increase in inflammatory and oxidative stress response, endothelial and blood-retinal barrier damage, and effects on blood coagulation, possibly characteristic for RVO.(Huang et al. 2009) Effects of oxidative stress and endothelial cell inflammation could lead to vascular hyperpermeability and damage to the blood-retinal barrier.(Huang et al. 2009) Moreover, an imbalance between thrombosis and fibrinolysis has previously been described to play an active role in the development of RVO.(Lip et al. 1998; Rehak & Rehak 2008) ~~However, the administration of PD0325901 to rats did not result in the occurrence of clinical effects of RVO similar to the effects as observed in treated patients. This was in contrast with intravitreal injection of a MEK inhibitor in rabbits, which did lead to effects of RVO.(Huang et al. 2009)~~

MEK-associated serous retinopathy has to be discerned from several other retinal diseases. In contrast to central serous chorioretinopathy, in which lesions usually start unilaterally or bilateral asymmetrically, the MEK-associated serous retinopathy is not associated with RPE detachments on OCT, and there are no “hot spots” of trans-RPE subretinal leakage on fluorescein angiography.(McCannel et al. 2014; Urner-Bloch et al. 2014) In cancer-associated retinopathy, melanoma-associated retinopathy, or non-neoplastic autoimmune retinopathy, symptoms may include a relatively rapid-onset photopsia, night blindness, scotomas, and progressive visual field loss.(Heckenlively & Ferreyra 2008) Interestingly, this spectrum of autoimmune retinopathy is associated with anti-retinal and/or anti-RPE antibodies, which we have also described in association with MEK inhibitor-associated serous retinopathy.(van Dijk et al. 2015) Hereditary retinal dystrophies such as autosomal dominant inherited Best vitelliform macular dystrophy and autosomal recessive bestrophinopathy usually have an earlier onset in combination with typical fundus lesions and a markedly abnormal electro-oculogram.(Boon et al. 2009)

In conclusion, we show that serous retinopathy associated with MEK inhibition treatment such as pimasertib is very common. This ~~MEK inhibitor-associated~~ serous retinopathy generally does not lead to marked ophthalmological complaints,(van Dijk et al. 2015) and lesions may resolve

despite continuous treatment. Therefore, discontinuation of ~~MEK inhibition~~ treatment in most patients with metastatic cancer is not necessary. As ophthalmological complaints ~~due to serous retinopathy~~ may occur in a noteworthy number of patients,(van Dijk et al. 2015) and as survival may increase in these patients because of the use of this new type of treatment for metastatic melanoma, performing OCT scanning before, during, and after MEK inhibition treatment may be advisable for monitoring and follow-up of fundus lesions ~~in relation to possible visual complaints~~. Another ophthalmological side effect of MEK inhibition is RVO, which can cause visual complaints that requires therapeutic intervention. Especially OCT follow-up ~~was~~ is able to precisely monitor such abnormalities even in patients that remain asymptomatic. It is currently unclear if MEK inhibitor-associated serous retinopathy correlates with other clinical parameters of MEK inhibition treatment such as treatment response of metastases.(van Dijk et al. 2015) Further studies are needed to unravel the exact pathogenesis and clinical consequences of MEK inhibitor-associated ophthalmological adverse events.

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Figure legends

Figure 1. Bilateral retinal vein occlusion associated with pimasertib treatment

A-B, Optical coherence tomography (OCT) scan of the right (A) and left eye (B) of a 60-year-old male patient ~~with metastatic cutaneous melanoma~~ revealed a~~n entirely~~ normal macular structure at ~~the~~ baseline examination~~, before the first administration of pimasertib~~. C-D, Fundus photography of the right (C) and left eye (D), 41 days after the start of pimasertib treatment, revealed bilateral foveal and extrafoveal yellowish lesions. E-F, Foveal OCT scanning of both the right (E) and left eye (F) showed a serous neuroretinal detachment ~~at that time~~. ~~Pimasertib t~~Treatment was discontinued 22 days later~~, because of a decrease in left ventricular ejection fraction.~~ Nine days after discontinuation, treatment with 45 mg pimasertib twice daily could be restarted and patient attended a follow-up visit 12 days later. At that time, ~~the~~ patient experienced ~~had visual complaints of experiencing~~ a dark fleck in the inferior part of the visual field of the right eye~~.~~ ~~Visual acuity had dropped from 95 to 67 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters in that eye, whereas visual acuity in the left eye was stable~~. G-J, Fluorescein angiography and fundus photography revealed a hemi-retinal vein occlusion (RVO) ~~of the superior temporal vein~~ in the right ~~eye~~ (G, I), and ~~a hemi-RVO of the inferior temporal retinal vein in the~~ left eye (H, J). K, OCT of the right eye showed cystoid macular edema~~, and a single intravitreal injection of bevacizumab was given to this patient. On OCT~~, and both foveal and extrafoveal neuroretinal detachments were also present. L, OCT scanning of the left eye revealed both foveal and extrafoveal neuroretinal detachments~~, but no cystoid macular edema~~. At this time, administration of pimasertib was discontinued. M-N, At follow-up 8 days after a single intravitreal injection of bevacizumab~~later~~, fundus photography of the right (M) and ~~the~~ left eye (N) revealed persistent cotton-wool spots and haemorrhages associated with the RVO in the right eye, and an increase of haemorrhages and cotton-wool spots in the left eye. ~~At that time, in the right eye ETDRS BCVA had recovered to 89 letters, whereas visual acuity was still stable in the left eye.~~ O-P, On an OCT scan during this ~~follow-up~~ visit, both cystoid macular edema and SRF had resolved in the right eye (O), and resolution of the neuroretinal detachment had occurred in the left eye (P). ~~No additional follow-up was available because of a further palliative care strategy in this patient.~~

Figure 2. Spectrum of ophthalmological findings in pimasertib-associated serous retinopathy

A, Fundus photography of the right eye of a 67-year-old male patient ~~with metastatic cutaneous melanoma (CM)~~ who developed foveal and extrafoveal yellowish lesions, at 13 days after the start of ~~the mitogen-activated protein kinase kinase inhibitor~~ pimasertib treatment. B, Infrared reflectance (IRR) imaging showed ~~a~~ hyperreflective foveal and extrafoveal lesions, which were surrounded by a ~~a~~ hyporeflective zone~~, corresponding to the lesion on fundus photography. Lesions with similar reflectance characteri~~ stics could be detected throughout the posterior pole. C, Optical coherence tomography (OCT) had shown~~ed~~n a normal macular structure at ~~the~~ baseline ~~examination, before the administration of pimasertib~~. D, Thirteen days after the start of study treatment, both foveal and extrafoveal serous neuroretinal detachments on OCT had developed~~, but the patient experienced no visual complaints~~. E, At final follow-up, 63 days after the start of the prescription ~~of pimasertib~~, resolution of ~~both the foveal and extrafoveal~~ lesions had occurred. ~~At this final examination, pimasertib was still administered to the patient in a dosage of 30 mg twice daily.~~

F, Fundus photography of the right eye of a 63-year-old female ~~CM~~ patient showed subtle extrafoveal transparent to yellowish lesions, 27 days after the start of pimasertib treatment. G, IRR imaging showed corresponding ~~subtle~~ hyperreflective lesions. H, Before treatment~~the administration of pimasertib~~, OCT had shown~~ed~~n a normal macular structure. I, An extrafoveal neuroretinal detachment could be detected on OCT, 27 days after the beginning of pimasertib. ~~At that moment, the patient had no visual complaints.~~ J, This serous retinopathy was still present at final follow-up 14 days later~~, when the patient still received 60 mg pimasertib twice daily~~.

K-L, In a 66-year-old ~~CM~~ patient, showing ~~bilateral and fairly symmetrical~~ pimasertib-associated serous retinopathy, fundus photography revealed both foveal and extrafoveal yellowish lesions, 20 days after the start of pimasertib. ~~M-N~~P-Q, These lesions corresponded to hyperreflective ~~foveal and extrafoveal~~ lesions, surrounded by a hyporeflective zone on IRR imaging. ~~O-P~~M-N, At baseline examination, ~~before the start of pimasertib treatment~~ no abnormalities had been found ~~were seen~~ on

OCT. ~~O~~O and ~~-~~R, Twenty days after the start of ~~pimasertib~~ treatment, an OCT scan showed a bilateral foveal neuroretinal detachment~~, which was not accompanied by any visual complaints~~. S-T, ~~Bilateral r~~Resolution of this ~~serous neuroretinal~~ detachment was detected ~~on OCT~~, 62 days after discontinuation of ~~pimasertib~~ treatment.

Figure 3. Occurrence and evolution of subretinal fluid over time, and possible relationship with orally administered dose of pimasertib

For all 8 patients included in this study, the prescribed dose of pimasertib and the occurrence of subretinal fluid (SRF) on optical coherence tomography (OCT) over time have been depicted. Colors in the 'pimasertib dose' rows correspond to the following doses: black = 60 mg twice daily, dark grey = 45 mg twice daily, light grey = 30 mg twice daily, white = no treatment. 'STOP' corresponds to end of treatment. 'Y' in the 'SRF on OCT' rows corresponds to presence of SRF on OCT at evaluation, with the maximum amount of SRF over time in bold. 'N' corresponds to the absence of SRF on OCT.

Figure 4~~3~~. Worsening of diabetic macular edema and occurrence of serous retinopathy associated with pimasertib treatment

A-B, Fluorescein angiography in a 67-year-old male patient with metastatic cutaneous melanoma and diabetes mellitus type 2 ~~at baseline examination~~ before the start of pimasertib treatment, showed bilateral microaneurysms and mild fluorescein leakage. C-D, Optical coherence tomography (OCT) at baseline examination showed very mild diabetic macular edema (DME) without other abnormalities ~~an otherwise normal macular structure in the right eye~~ (C), and mild DME in the left eye (D). E, OCT scanning at 9 days after the start of pimasertib treatment showed a foveal serous neuroretinal detachment ~~and roughly stable DME~~ in the right eye. F, At this moment, the left eye showed both a foveal serous neuroretinal detachment and worsening of the DME ~~edema~~ on OCT. ~~The patient did not report any ocular complaints during follow-up.~~ G-H, Eleven days later the amount of serous subretinal

fluid had decreased spontaneously in the right (G) and the left eye (H). ~~H, The left eye also showed a spontaneous decrease in the amount of subretinal fluid, as well as in DME.~~ I-J, Despite the fact that this patient still used pimasertib in a dosage of 60 mg twice daily, the neuroretinal detachment had almost resolved in both eyes, together with the DME in the left eye, at final ophthalmological follow-up ~~at 126 days after the start of pimasertib treatment~~.

Tables

Table 1. Characteristics of the cutaneous melanoma patients.

Pimasertib-associated ophthalmological adverse events

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Abstract

Purpose: To analyse ophthalmological adverse events associated with mitogen-activated protein kinase kinase (MEK) inhibition with pimasertib treatment for metastatic cutaneous melanoma (CM).

Methods: In this prospective observational, cohort-based, cross-sectional study, 8 patients treated with the MEK inhibitor pimasertib received a complete ophthalmic examination. This included Early Treatment of Diabetic Retinopathy Study best-corrected visual acuity, visual field testing, color vision testing, slit-lamp examination, applanation tonometry, indirect ophthalmoscopy, digital color fundus photography, and optical coherence tomography (OCT). In selected cases fluorescein angiography was performed.

Results: Serous subretinal fluid (SRF) developed in all patients, within a time frame of 9-27 days after the start of treatment. The fovea was involved in 6/8 patients (75%). None of the patients with foveal SRF (excluding a patient who developed a bilateral retinal vein occlusion (RVO)) experienced visual symptoms. SRF decreased or resolved in all patients, despite continuation of study medication in 6/8 patients (75%). Complaints in the CM patient (13%) consisted of experiencing a dark fleck in the inferior part of the visual field of the right eye 1 week after the start of treatment, due to an RVO. Subsequent intravitreal bevacizumab treatment resulted in functional and anatomical improvement.

Conclusions: Patients with metastatic CM who are treated with the MEK inhibitor pimasertib are at high risk of development of ocular adverse events including serous retinopathy and possibly RVO, stressing the need of adequate ophthalmological follow-up including OCT during administration of pimasertib, despite the fact that SRF generally does not lead to ophthalmological complaints.

Key words

MEK inhibitor; ophthalmological adverse events; pimasertib; retinal vein occlusion; serous retinopathy

Introduction

Spectral-domain optical coherence tomography (OCT) is a sensitive means to detect serous retinopathy, which is defined as retinal lesions on ophthalmoscopy corresponding to a localized separation of the neuroretina and retinal pigment epithelium (RPE).(van Dijk et al. 2015) It may occur as an independent entity, but may also be associated with a broad spectrum of other diseases or may follow the use of certain drugs.(Ghazi & Green 2002) We and others recently described that serous retinopathy is seen in patients with metastatic melanoma during the treatment with mitogen-activated protein kinase kinase (MEK) inhibitors such as binimetinib,(van Dijk et al. 2015; Weber et al. 2016) cobimetinib,(McCannel et al. 2014) trametinib,(Infante et al. 2012) and RO5126766.(Martinez-Garcia et al. 2012) Luckily, in many cases vision is not affected by the treatment, but serious problems including retinal vein occlusion (RVO) may occur.(LoRusso et al. 2010; Leijen et al. 2012)

As treatment options for metastatic malignant cutaneous melanoma (CM) are scarce, much effort is being put into the development of possible new treatments for this patient group. One of the target pathways for treatment is the mitogen-activated protein kinase (MAPK) signalling (Ras - Raf - MEK - extracellular signal-regulated kinase) pathway. A broad spectrum of cellular processes is coordinated by this pathway. Activation of the MAPK pathway influences processes such as cell differentiation and metabolism, cell migration, and cell death.(Krishna & Narang 2008) Although visual symptoms may be absent or relatively mild in patients to whom MEK inhibition is prescribed, OCT imaging has shown that some of the MEK inhibitors induce retinal changes in a high percentage of patients.(Flaherty et al. 2012; Ascierto et al. 2013; McCannel et al. 2014; Urner-Bloch et al. 2014; van Dijk et al. 2015)

Preclinical studies have shown that the new MEK inhibitor pimasertib displays activity against *RAS* and *BRAF* mutated cell lines.(Kim et al. 2010; Yoon et al. 2011) Moreover, induction of apoptosis in *BRAF* mutated human malignant melanoma cell lines has been described after the administration of a combination of pimasertib and the BRAF inhibitor PLX4032, whereas either drug alone did not.(Park et al. 2013) In the first human trial IMP28062, activity against *NRAS* mutated tumors could be detected after prescription of pimasertib. In a recently published report of a patient

with metastatic ovarian cancer bilateral multifocal retinal detachments were described 2 days after the start of pimasertib.(AlAli et al. 2016) This patient developed complaints of blurred vision, and treatment was discontinued. Three days after stopping pimasertib treatment, ocular complaints and lesions had disappeared.(AlAli et al. 2016) The occurrence of serous retinal detachments in patients, to whom pimasertib was prescribed, was not further specified in other studies.(Houede et al. 2011; Macarulla et al. 2015) In 1 of these studies, the occurrence of an RVO in a patient was also not discussed in detail.(Houede et al. 2011) No other ocular adverse events during the prescription of pimasertib have been reported so far.

We hypothesized that this drug may also lead to subretinal fluid (SRF) and wondered whether SRF would occur in only in a sensitive subset of patients, or that it might be a general phenomenon. As patients are in quite a good general condition when using this treatment, we were able to perform a prospective study of patients using the new MEK inhibitor pimasertib, and included high resolution OCT imaging to examine the macular area in detail.

Materials and methods

Patient characteristics

Eight patients from an academic medical center (Erasmus University Medical Center, Rotterdam, the Netherlands) were included in this study. All patients were diagnosed with a measurable, histologically or cytologically confirmed, locally advanced or metastatic *NRAS* mutated malignant CM. Patients with a medical history of retinal degenerative disease, uveitis, or RVO were excluded. Local ethics committee approved the study. Each patient gave written informed consent, and the study was performed in accordance with the Declaration of Helsinki. The clinical trial was registered in the Clinical Trial Register with number NCT01693068. Patients were included in this trial from September 2013 to June 2014.

Treatment

All patients received pimasertib in a randomized phase II trial, in which the comparator arm was chemotherapy with dacarbazine (intravenous administration at dose of 1000 mg per square meter of

body surface area, every 3 weeks). Patients received 60 mg of pimasertib orally twice a day, continuously for 21 days (defined as a 1 treatment cycle, for scheduling purposes). Within this trial 7 patients were primarily randomized to pimasertib, whereas 1 patient made a cross-over to treatment with pimasertib after having developed progressive disease upon chemotherapy with dacarbazine.

Ophthalmic examinations

All patients received complete ophthalmic examination, including Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) testing, visual field testing, color vision testing using the Desaturated Panel D-15 test, slit-lamp examination, intraocular pressure measurement, indirect ophthalmoscopy, digital color fundus photography (Topcon Corporation, Tokyo, Japan), and OCT using the spectral-domain OCT (Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany)), before start of the study. Part of these examinations was performed after dilation of pupils by topical administration of 1% tropicamide and 5% phenylephrine drops. Moreover, study protocol instructed the BCVA measurement at every evaluation visit: at the beginning of treatment cycle 2 and at the beginning of every subsequent odd treatment cycle. At these evaluation visits, slit-lamp examination and assessment of the posterior pole using indirect ophthalmoscopy were also prescribed to be executed, together with OCT scanning. When ETDRS BCVA testing was not available, Snellen BCVA was determined and a previously-established conversion method was used to achieve ETDRS values.(Gregori et al. 2010)

In patients with visual disturbances or abnormal retinal findings on ophthalmological assessments, fluorescein angiography was performed with the spectral-domain OCT. Treatment had to be interrupted when a serous retinal detachment with a decrease in ETDRS BCVA of ≥15 letters occurred. A serous retinal detachment was defined as a localized separation of the neuroretina and RPE on OCT, with an accumulation of SRF between these layers. Restart of treatment could only be scheduled after full resolution of the detachment and full recovery of vision within 2 weeks, after weekly follow-up visits. In case of the occurrence of an RVO the study medication had to be stopped, unless the event resolved within 2 weeks.

Safety and efficacy monitoring

After clinical assessment at the evaluation visits at the Department of Oncology, the dose of study medication was reduced or medication was discontinued, when either unacceptable signs of toxicity or disease progression had developed. Subjects with documented tumor progression on the dacarbazine arm could choose to switch to receiving pimasertib.

Statistical analysis

Both ETDRS BCVA at the time point of most pronounced SRF on OCT and at final follow-up were compared to ETDRS BCVA at initial screening, using an independent t-test in IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, United States).

Results

The 8 CM patients (4 male, 4 female) had a mean age of 62.9 years (median: 64 years; range, 56-67 years). The clinical patient characteristics are summarized in Table 1.

During this study, 1 patient (13%) developed visual complaints, consisting of experiencing a dark fleck in the inferior part of the visual field of the right eye. These complaints started 1 week after the restart of pimasertib treatment, after a previous discontinuation because of a reversible decrease in left ventricular ejection fraction. In the right eye, ETDRS BCVA had dropped from 95 to 67 letters, while ETDRS BCVA of the left eye had not changed at the time of visual complaints. Indirect ophthalmoscopy and fluorescein angiography led to the diagnosis of a hemi-RVO of the superior temporal vein of the right eye and an asymptomatic mild hemi-RVO of the inferior temporal retinal vein of the left eye (Fig. 1A-L). Because of cystoid macular edema, a single intravitreal injection of bevacizumab in the right eye was given to this patient, after which ETDRS BCVA recovered to 89 letters at follow-up visit 8 days later (Fig. 1M-P). Because of the need for palliative care, which this patient preferred to receive in another hospital, and because of the good functional and anatomical result of this single injection, no additional follow-up was scheduled.

OCT indicated that SRF developed in 16/16 eyes (100%). None of the patients (excluding the patient with RVO) experienced visual symptoms. Moreover, no measurable significant influence on

visual acuity could be detected, as (converted) median BCVA ETDRS was 88 letters (range, 77-93 letters) at screening, 87 letters (range, 66-98 letters) at the moment of most prominent SRF on OCT, and 89 letters (range, 75-98 letters) at the final follow-up visit. Differences in ETDRS BCVA were not statistically significant (p=0.58 (screening versus most prominent SRF), p=0.31 (most prominent SRF versus final follow-up visit), and p=0.51 (screening versus final follow-up visit)).

Ophthalmoscopy revealed transparent to yellowish vitelliform lesions at the time that SRF was observed on OCT (Fig. 1D, 1K-L, 2A), whereas either no abnormalities or mild RPE changes were observed after disappearance of SRF. The SRF was bilateral and fairly symmetrical (Fig. 2K-T). These lesions were seen in all patients at the time of their first OCT after the start of the study medication, which was performed after 9-27 days (median: 20 days). Foveal SRF accumulation was present in 6/8 patients (75%). The center of these lesions was hyperreflective on infrared reflectance imaging, and the lesions were surrounded by a hyporeflective zone. On OCT, SRF was detected extrafoveally in all 8 patients (Fig. 1K-L, 2D, 2I-J). The median total number of extrafoveal lesions in the posterior pole, based on a 30˚ infrared reflectance photograph, was 6 (mean: 5, range, 3-13 lesions) in the 16 eyes.

At last ophthalmological follow-up at 14-126 days (median: 81 days) after the first appearance of SRF, the SRF had disappeared in both eyes in 5/8 patients (63%). In the patient who received intravitreal bevacizumab, resolution of both cystoid macular edema and SRF had occurred. Administration of pimasertib had been discontinued in this patient. In the other 4 patients, SRF disappeared spontaneously while pimasertib was either still administered according to the original dose (2 patients)or dose of pimasertib was reduced (1 patient), or pimasertib was discontinued because of a decrease in left ventricular ejection fraction (1 patient). Three patients had persistent SRF, during treatment with 60, 60, and 30 mg of pimasertib twice a day, respectively. However, during follow-up the amount of SRF had decreased in all 3 patients. Color vision testing and visual field testing revealed no significant changes, despite macular SRF accumulation during pimasertib treatment. For all patients, information on the occurrence and evolution of SRF, and the possible relationship with orally administered dose of pimasertib has been depicted in Fig. 3.

During the period of the administration of study medication in 1 patient who had previously been diagnosed with bilateral diabetic macular edema, (Fig. 4A-D) edema had increased unilaterally at ophthalmological follow-up, 9 days after the start of study medication (Fig. 4E-F). This patient also developed bilateral foveal SRF. No signs of other ophthalmological diseases were detected during follow-up. Eleven days later, SRF and edema had decreased spontaneously (Fig. 4G-H). At final follow-up 106 days later, only minimal unilateral foveal SRF remained (Fig. 4I-J). Ophthalmic characteristics of all patients are summarized in Table 1.

Discussion

Spectral-domain OCT is a sensitive means to detect a typical serous retinopathy in patients treated with MEK inhibitors such as pimasertib. Despite these striking MEK inhibitor-associated retinal abnormalities in all 8 metastatic CM patients, all but 1 patient remained asymptomatic. This patient experienced central vision loss due to bilateral RVO, which responded to intravitreal bevacizumab treatment. Lesions occurred both foveally and extrafoveally in most of the 8 patients, indicating a more extensive dysfunction of the retina and/or RPE that extended beyond the fovea. Serous retinopathy had either disappeared or decreased at the last ophthalmological follow-up in all patients.

The exact pathogenesis of both serous retinopathy and RVO associated with MEK inhibitor treatment is as yet unclear. A time-dependent and reversible serous retinopathy, resembling the clinical picture we present in the current study, was previously described in association with several other MEK inhibitors such as cobimetinib,(McCannel et al. 2014) trametinib,(Infante et al. 2012) and RO5126766.(Martinez-Garcia et al. 2012) We described this specific phenotype by a mildly symptomatic, time-dependent, and reversible accumulation of both foveal and extrafoveal serous SRF, with abnormalities on electro-oculography but without any evidence of choroidal abnormalities.(van Dijk et al. 2015) This serous retinopathy is most probably related to a class effect of this type of drugs, and thereby an on-target side effect of treatment,(Duncan et al. 2015; Kurbel et al. 2015) although pharmacological differences between several MEK inhibitors exist.(Hatzivassiliou et al. 2010) We have previously described prolonged abnormalities on electro-oculography in patients with transient binimetinib-associated serous retinopathy, indicating panretinal RPE dysfunction and

dysfunction of the RPE pump.(McCannel et al. 2014; van Dijk et al. 2015) In addition, anti-RPE and anti-retinal autoantibodies may play a role.(van Dijk et al. 2015) In a cell model of RPE and neuroretina, binimetinib administration resulted in inactivation of the MAPK pathway, and discontinuation of administration of the MEK inhibitor binimetinib led to reactivation, mimicking the mild and reversible retinopathy.(van Dijk et al. 2016) The occurrence of an RVO, during the prescription of MEK inhibition has also been described previously in up to 5% of patients.(LoRusso et al. 2010; Houede et al. 2011; Leijen et al. 2012) MEK inhibitors could influence the vasculature of the retina, leading to both this serous retinopathy and RVO.(van der Noll et al. 2013; van Dijk et al. 2015) The RVO that occurred in 1 of our patients could have been associated with the previous reversible decrease in left ventricular ejection fraction in this case, which had been detected 3 weeks before the diagnosis of RVO had been established. Moreover, after oral administration of the MEK inhibitor PD0325901 to rats, retinal gene expression suggested an increase in inflammatory and oxidative stress response, endothelial and blood-retinal barrier damage, and effects on blood coagulation, possibly characteristic for RVO.(Huang et al. 2009) Effects of oxidative stress and endothelial cell inflammation could lead to vascular hyperpermeability and damage to the blood-retinal barrier.(Huang et al. 2009) Moreover, an imbalance between thrombosis and fibrinolysis has previously been described to play an active role in the development of RVO.(Lip et al. 1998; Rehak & Rehak 2008)

MEK-associated serous retinopathy has to be discerned from several other retinal diseases. In contrast to central serous chorioretinopathy, in which lesions usually start unilaterally or bilateral asymmetrically, the MEK-associated serous retinopathy is not associated with RPE detachments on OCT, and there are no “hot spots” of trans-RPE subretinal leakage on fluorescein angiography.(McCannel et al. 2014; Urner-Bloch et al. 2014) In cancer-associated retinopathy, melanoma-associated retinopathy, or non-neoplastic autoimmune retinopathy, symptoms may include a relatively rapid-onset photopsia, night blindness, scotomas, and progressive visual field loss.(Heckenlively & Ferreyra 2008) Interestingly, this spectrum of autoimmune retinopathy is associated with anti-retinal and/or anti-RPE antibodies, which we have also described in association with MEK inhibitor-associated serous retinopathy.(van Dijk et al. 2015) Hereditary retinal dystrophies

such as autosomal dominant inherited Best vitelliform macular dystrophy and autosomal recessive bestrophinopathy usually have an earlier onset in combination with typical fundus lesions and a markedly abnormal electro-oculogram.(Boon et al. 2009)

In conclusion, we show that serous retinopathy associated with MEK inhibition treatment such as pimasertib is very common. This serous retinopathy generally does not lead to marked ophthalmological complaints,(van Dijk et al. 2015) and lesions may resolve despite continuous treatment. Therefore, discontinuation of treatment in most patients with metastatic cancer is not necessary. As ophthalmological complaints may occur in a noteworthy number of patients,(van Dijk et al. 2015) and as survival may increase in these patients because of the use of this new type of treatment for metastatic melanoma, performing OCT scanning before, during, and after MEK inhibition treatment may be advisable for monitoring and follow-up of fundus lesions. Another ophthalmological side effect of MEK inhibition is RVO, which can cause visual complaints that requires therapeutic intervention. Especially OCT follow-up is able to precisely monitor such abnormalities even in patients that remain asymptomatic. It is currently unclear if MEK inhibitor-associated serous retinopathy correlates with other clinical parameters of MEK inhibition treatment such as treatment response of metastases.(van Dijk et al. 2015) Further studies are needed to unravel the exact pathogenesis and clinical consequences of MEK inhibitor-associated ophthalmological adverse events.

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Figure legends

Figure 1. Bilateral retinal vein occlusion associated with pimasertib treatment

A-B, Optical coherence tomography (OCT) scan of the right (A) and left eye (B) of a 60-year-old male patient revealed a normal macular structure at baseline examination. C-D, Fundus photography of the right (C) and left eye (D), 41 days after the start of pimasertib treatment, revealed bilateral foveal and extrafoveal yellowish lesions. E-F, Foveal OCT scanning of both the right (E) and left eye (F) showed a serous neuroretinal detachment. Treatment was discontinued 22 days later. Nine days after discontinuation, treatment with 45 mg pimasertib twice daily could be restarted and patient attended a follow-up visit 12 days later. At that time, patient experienced a dark fleck in the inferior part of the visual field of the right eye. . G-J, Fluorescein angiography and fundus photography revealed a hemi-retinal vein occlusion (RVO) in the right (G, I), and left eye (H, J). K, OCT of the right eye showed cystoid macular edema and both foveal and extrafoveal neuroretinal detachments were also present. L, OCT scanning of the left eye revealed both foveal and extrafoveal neuroretinal detachments. At this time, administration of pimasertib was discontinued. M-N, At follow-up 8 days after a single intravitreal injection of bevacizumab, fundus photography of the right (M) and left eye (N) revealed persistent cotton-wool spots and haemorrhages associated with the RVO in the right eye, and an increase of haemorrhages and cotton-wool spots in the left eye. O-P, On an OCT scan during this visit, both cystoid macular edema and SRF had resolved in the right eye (O), and resolution of the neuroretinal detachment had occurred in the left eye (P).

Figure 2. Spectrum of ophthalmological findings in pimasertib-associated serous retinopathy

A, Fundus photography of the right eye of a 67-year-old male patient who developed foveal and extrafoveal yellowish lesions, at 13 days after the start of pimasertib treatment. B, Infrared reflectance (IRR) imaging showed hyperreflective foveal and extrafoveal lesions, which were surrounded by a hyporeflective zone. C, Optical coherence tomography (OCT) had shown a normal macular structure at baseline. D, Thirteen days after the start of study treatment, both foveal and extrafoveal serous

neuroretinal detachments on OCT had developed. E, At final follow-up, 63 days after the start of the prescription, resolution of lesions had occurred.

F, Fundus photography of the right eye of a 63-year-old female patient showed subtle extrafoveal transparent to yellowish lesions, 27 days after the start of pimasertib treatment. G, IRR imaging showed corresponding hyperreflective lesions. H, Before treatment, OCT had shown a normal macular structure. I, An extrafoveal neuroretinal detachment could be detected on OCT, 27 days after the beginning of pimasertib. J, This serous retinopathy was still present at final follow-up 14 days later.

K-L, In a 66-year-old patient, showing pimasertib-associated serous retinopathy, fundus photography revealed both foveal and extrafoveal yellowish lesions, 20 days after the start of pimasertib. P-Q, These lesions corresponded to hyperreflective lesions, surrounded by a hyporeflective zone on IRR imaging. M-N, At baseline examination, no abnormalities had been found on OCT. O and R, Twenty days after the start of treatment, an OCT scan showed a bilateral foveal neuroretinal detachment. S-T, Resolution of this detachment was detected, 62 days after discontinuation of treatment.

Figure 3. Occurrence and evolution of subretinal fluid over time, and possible relationship with orally administered dose of pimasertib

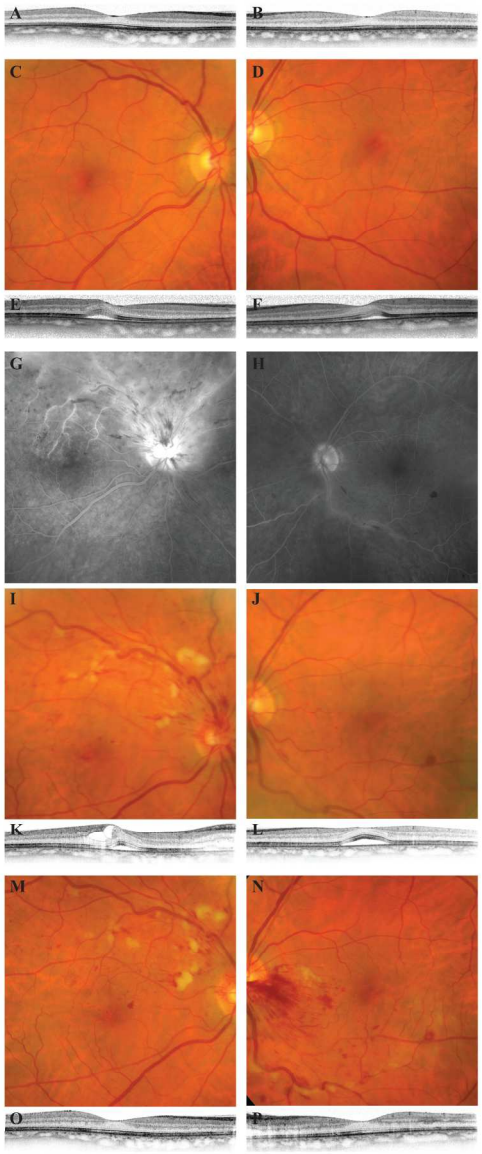
For all 8 patients included in this study, the prescribed dose of pimasertib and the occurrence of subretinal fluid (SRF) on optical coherence tomography (OCT) over time have been depicted. Colors in the 'pimasertib dose' rows correspond to the following doses: black = 60 mg twice daily, dark grey = 45 mg twice daily, light grey = 30 mg twice daily, white = no treatment. 'STOP' corresponds to end of treatment. 'Y' in the 'SRF on OCT' rows corresponds to presence of SRF on OCT at evaluation, with the maximum amount of SRF over time in bold. 'N' corresponds to the absence of SRF on OCT.

Figure 4. Worsening of diabetic macular edema and occurrence of serous retinopathy associated with pimasertib treatment

A-B, Fluorescein angiography in a 67-year-old male patient with metastatic cutaneous melanoma and diabetes mellitus type 2 before the start of pimasertib treatment, showed bilateral microaneurysms and mild fluorescein leakage. C-D, Optical coherence tomography (OCT) at baseline examination showed very mild diabetic macular edema (DME) without other abnormalities (C), and mild DME in the left eye (D). E, OCT scanning at 9 days after the start of pimasertib treatment showed a foveal serous neuroretinal detachment in the right eye. F, At this moment, the left eye showed both a foveal serous neuroretinal detachment and worsening of the DME on OCT. G-H, Eleven days later the amount of serous subretinal fluid had decreased spontaneously in the right (G) and the left eye (H). I-J, Despite the fact that this patient still used pimasertib in a dosage of 60 mg twice daily, the neuroretinal detachment had almost resolved in both eyes, together with the DME in the left eye, at final ophthalmological follow-up.

Tables

Table 1. Characteristics of the cutaneous melanoma patients.



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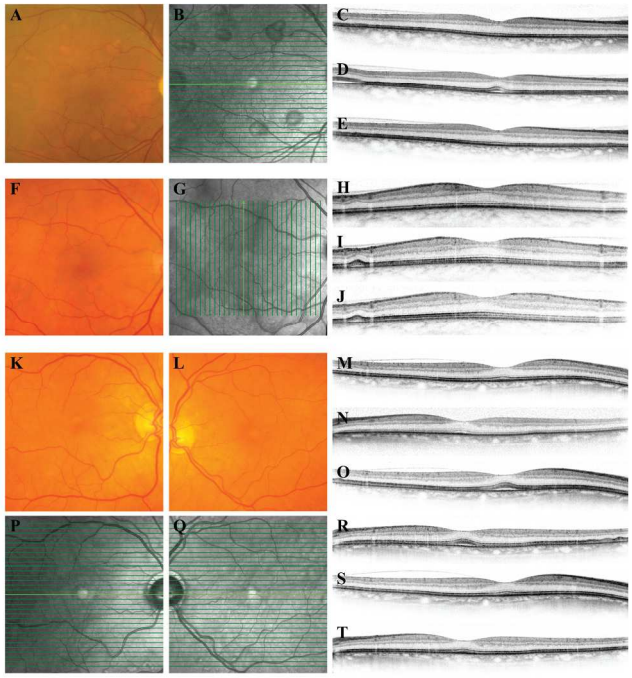

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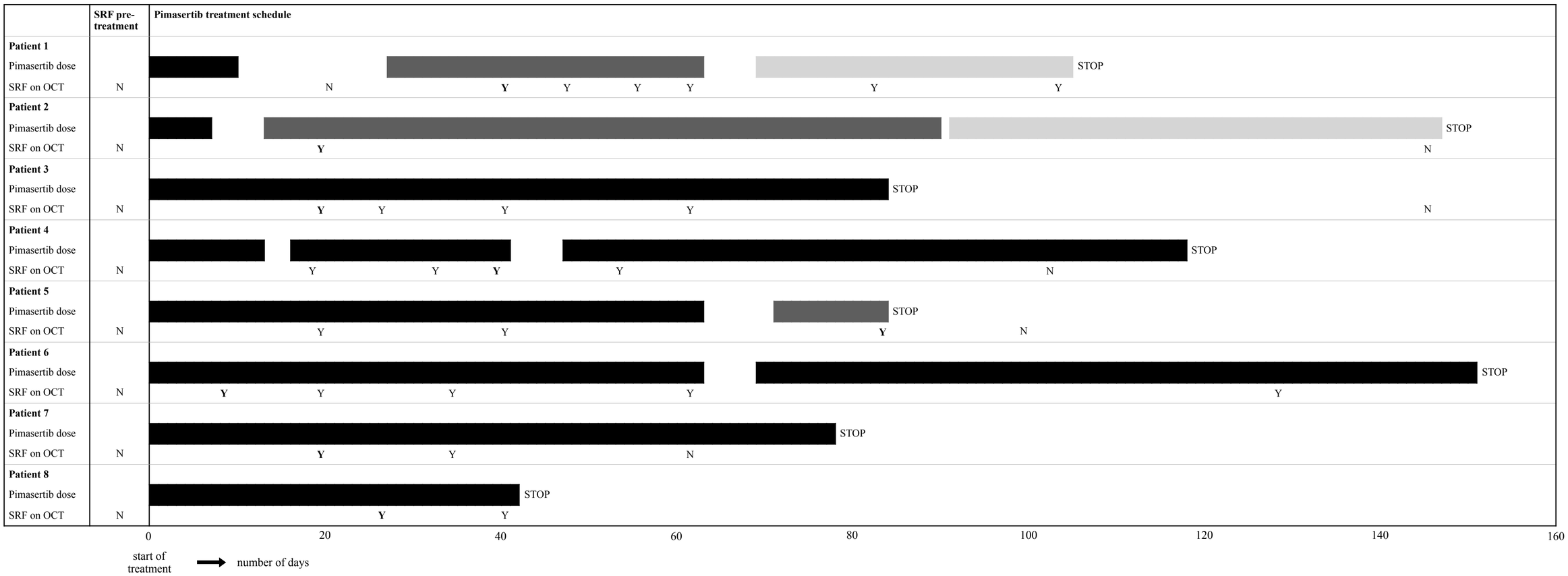
SRF pre-treatment
Pimasertib treatment schedule
Patient 1
Pimasertib dose
SRF on OCT
N
N
Y
Y
Y
Y
Y
Y
STOP
Patient 2
Pimasertib dose
SRF on OCT
N
Y
N
STOP
Patient 3
Pimasertib dose
SRF on OCT
N
Y
Y
Y
Y
N
STOP
Patient 4
Pimasertib dose
SRF on OCT
N
Y
Y
Y
Y
N
STOP
Patient 5
Pimasertib dose
SRF on OCT
N
Y
Y
Y
N
STOP
Patient 6
Pimasertib dose
SRF on OCT
N
Y
Y
Y
Y
Y
STOP
Patient 7
Pimasertib dose
SRF on OCT
N
Y
Y
N
STOP
Patient 8
Pimasertib dose
SRF on OCT
N
Y
Y
STOP
0
20
40
60
80
100
120
140
160
start of treatment
number of days

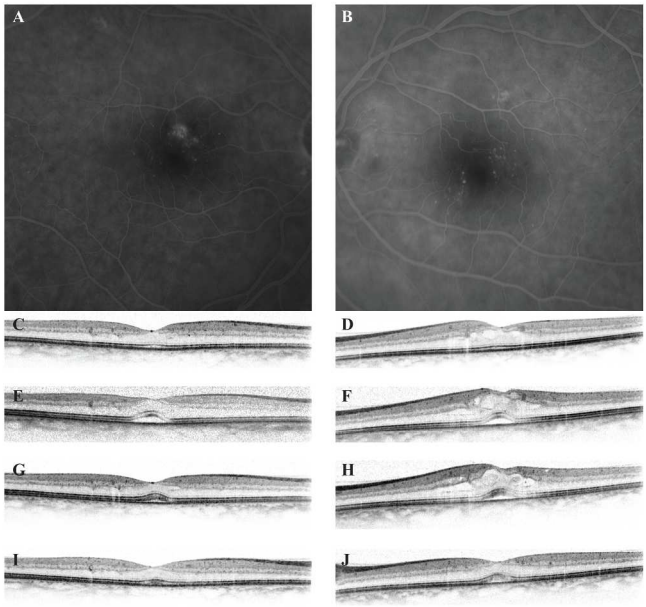

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Table 1. Characteristics of the cutaneous melanoma patients.

Clinical characteristics	
Number of patients	8
Number of males	4/8 (50%)
Number of females	4/8 (50%)
Mean age (years)	62.9
Median age (years)	64
Ophthalmic characteristics	
Number of patients developing visual complaints	1/8 (13%)
Ophthalmoscopy images available during ophthalmological follow-up (patients)	8
Transparent to yellowish fundus lesions (eyes)	16/16 (100%)
Single foveal lesion (eyes)	0
Multifocal lesions (eyes)	16/16 (100%)
OCT imaging available during ophthalmological follow-up (patients)	8
SRF on OCT (eyes)	16/16 (100%)
Foveal SRF (eyes)	12/16 (75%)
- Only foveal SRF	0/12
- Foveal and extrafoveal SRF	12/12
Extrafoveal SRF (eyes)	16/16 (100%)
- Only extrafoveal SRF	4/16
- Foveal and extrafoveal SRF	12/16
Infrared reflectance imaging available during ophthalmological follow-up (patients)	8
Extrafoveal lesions (eyes)	16/16 (100%)
Mean number of extrafoveal lesions	5
Median number of extrafoveal lesions	6

Abbreviations: OCT, optical coherence tomography; SRF, subretinal fluid