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Original article

Didanosine-induced retinopathy: new insights with long-term follow-up

Authors:
Céline Faure1,2, MD; Maxime Chassery1, MD; Raphaëlle Ores1, MD; Isabelle Audo1,3-4, MD, PhD.

Affiliations:
3. CHNO des Quinze-Vingts, DHU Sight Restore, INSERM-DHOS CIC1423, Paris, France.
4. Sorbonne Université, INSERM, CNRS, Institut de la Vision, 17 rue Moreau, F-75012 Paris, France.

Corresponding author:
Dr Céline Faure
Hôpital Privé Saint Martin, 18 rue des Roquemonts, 14000 Caen. France.
celinefaureoph@gmail.com
Tel +33 231433011
Fax +33 231433013

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Abstract:

Introduction: Didanosine is an adenosine analog, part of the nucleoside reverse-transcriptase inhibitor family. Since the description of didanosine-induced retinopathy in the early 1990s, little is known about the progression of this toxic retinopathy and the putative underlying mitochondrial defect.

Objectives: We report long-term follow-up for cases of didanosine-induced retinopathy and discuss a new hypothesis for pathophysiology based on the alteration of endogenous adenosine on the photoreceptor outer segment turnover and phagocytosis by the retinal pigment epithelium.

Methods: Ophthalmic data from six cases (12 eyes) of didanosine-induced retinopathy from a single institution were retrospectively analyzed.

Results: All patients displayed bilateral retinal alterations in the mid-periphery. Despite didanosine discontinuation, patients with advanced areas of patchy chorioretinal atrophy appeared to have a faster progression than those with limited lesions. Full-field electroretinogram revealed generalized rod-cone dysfunction in most cases that remained stable over time.

Conclusion: We propose new guidelines including early screening and long-term observations.
Keywords:

Adenosine
Didanosine
Electroretinography
Human immunodeficiency virus
Nucleoside analog reverse-transcriptase inhibitors
Purine analog
Retinal pigment epithelium
Rod-cone dysfunction
Tenofovir
Toxic retinopathy
Introduction:

Didanosine, also called ddI, with the trade name of Videx®, was the second FDA-approved antiretroviral drug against the human immunodeficiency virus (HIV). Didanosine is an analog of adenosine, part of the nucleoside analog reverse-transcriptase inhibitors (or NRTIs). NRTIs compete with the natural deoxynucleotides for incorporation into the replicating viral DNA chain. However, 3’-hydroxyl group are lacking in NRTIs and therefore they are acting as chain terminators and classified as competitive substrate inhibitors.

Whitcup et al. first described retinal toxicity cases in 1992 in children [1]. Most of them were on high-dose of ddI. The children did not report visual loss but some had progressive constriction of their visual field. Toxic retinopathy was also associated with mild cerebral atrophy, lethargy and failure to thrive. Fundus examination revealed mottling and retinal pigment epithelium (RPE) atrophy with well circumscribed atrophic areas surrounded by hyperpigmented borders in the mid periphery [2]. Didanosine-induced retinopathy was later described in adults [3-6].

To date, very few information is available about the progression of this toxic retinopathy and the appropriate follow-up.

The aim of this article is to describe long-term follow-up of didanosine-induced retinopathy after drug cessation, to identify risk factors, to discuss a new physiopathologic hypothesis about and to give some guidelines for patient surveillance.

Methods:

This study conformed to the tenets of the Declaration of Helsinki. We report an observational retrospective case series of 6 HIV seropositive patients with a history of ddI exposure referred
to the electrophysiology unit of the Quinze-Vingts National Eye Hospital (Paris, France) for difficulties in the peripheral vision under scotopic conditions. The following data were collected and analyzed: age, gender, medical history, concomitant antiretroviral medication, best-corrected visual acuity (BCVA), retinal findings with short wavelength fundus autofluorescence SWAF imaging and spectral-domain optical coherence tomography (HRA2 and Spectralis, Heidelberg Engineering Inc, Heidelberg, Germany), color fundus photography and Goldmann kinetic perimetry if available. Full-field electroretinogram (FF-ERG) was performed for all patients following the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) [7].

Results:

Six HIV seropositive patients (2 men and 4 females) were identified with fundoscopic and electroretinographic findings consistent with retinal toxicity secondary to didanosine exposure. The mean age at presentation was 50.7 ± 4 years (range 46-56 years). All patients reported difficulties in the peripheral vision under scotopic conditions. Demographic data are summarized in table 1.

The average duration of didanosine exposure was available for 4/6 patients, and was of 6.5 ± 1.7 years (range, 5-8 years). Didanosine was stopped for all patients after examination. Follow-up was available for 5/6 patients, and for these patients mean follow-up was 4 ± 2.4 years (range, 1-8 years).

BCVA was well preserved in all patients. Fundus examination revealed bilateral and symmetric fundus alterations in all patient that correspond with that a salt-and-pepper appearance of the SWAF in the mid-periphery. In more advanced toxic cases, patchy chorioretinal atrophic
areas with loss of SWAF were also present. Posterior pole was normal except in one patient displaying macular serous drusen deposits.

FF-ERG testing was within normal limits in one case (1/6) or showed a generalized rod-cone dysfunction for the other patients (5/6) that were severe in 3/5 with no detectable responses under scotopic conditions. Multifocal electoretinography (mf-ERG) was performed in 2/6 patients and all showed preserved responses for the central hexagons. One patient (patient 4) also had an electro-oculogram (EOG) performed showing a reduction in the EOG light rise. We observed a progression of the peripheral chorioretinal atrophy within the areas of diffuse RPE alterations in 3/5 patients, despite the discontinuation of didanosine (patient n°4, 5 and 6). Interestingly, these 3 patients were also taking the fixed combination emtricitabine / tenofovir with the trade name of Truvada®. The more the patients had extensive lesions at presentation, the more a progression of chorioretinal lesions was observed. For the 3 patients with the worse toxic retinopathy, FF-ERG remained surprisingly stable over time, probably because the extension of the atrophic lesions only concerned the already altered mid-periphery with no extension to the posterior and anterior retina.

Case report patient 1:
A 48-year-old man, HIV positive, who had been taking didanosine for 5 years (400mg/day) in combination with tenofovir, atanazavir and ritanovir, was referred for a progressive visual field constriction. Visual acuity was 20/20 in both eyes. FF-ERG showed generalized retinal dysfunction predominant on scotopic responses in keeping with generalized rod-cone dysfunction. Multifocal-ERGs revealed normal responses to the central hexagons. His fundus examination showed RPE changes with areas of chorio-retinal atrophy in the mid-periphery.
SWAF revealed a speckled appearance of the mid periphery. No major change could be observed over the one-year follow-up (figure 1).

Case report patient 2:
A 50-year-old woman, HIV positive, had a history of didanosine intake of unknown duration. She was also taking atazanavir and the fixed combination of emtricitabine/tenofovir. Right eye (RE) BCVA was 20/20 and Left (LE) BCVA was 20/25. FF-ERG showed a generalized rod-cone dysfunction. Multifocal-ERG responses were normal for all the tested hexagons. Fundus examination showed small macular drusen at the posterior pole and RPE changes in the midperiphery. A hyper and hypoautofluorescent granular pattern was also seen on SWAF in the mid-periphery (figure 2). Unfortunately, no follow-up examination was available for this patient.

Case report patient 3:
A 55-year-old woman, HIV positive, with a history of didanosine intake was referred for visual function testing. BCVA was 20/20 on both eyes. 24-2 Humphrey visual field showed decreased peripheral sensitivity for both eyes. FF-ERG was within normal limit under both scotopic and photopic conditions. SWAF imaging showed bilateral, symmetrical hyper and hypoautofluorescent speckled alterations in the mid-periphery. Didanosine-induced retinopathy was suspected and didanosine was stopped. Two years later, fundus autofluorescence alterations appeared to be stable on both eye (figure 3).

Case report patient 4:
A 46-year-old woman, HIV positive, complained of night vision disturbances. She had been taking didanosine for 5 years (250 mg/day) in association with ritonavir, darunavir,
emtricitabine and tenofovir. RE BCVA was 20/15 and 20/20 in the LE. Goldmann kinetic perimetry was within normal limits. FF-ERG showed generalized rod-cone dysfunction which remained stable over time. Multifocal ERG was normal in both eyes. Fundus examination revealed bilateral peripheral RPE changes with patchy areas of atrophy. SWAF imaging showed well-circumscribed areas of loss of autofluorescence surrounded by speckled hyperautofluorescent lesions. Didanosine was discontinued; and the patient was examined every 2 years for 8 years. Retinal lesions displayed slow confluence of patchy atrophic areas in the mid-periphery sparing the posterior pole (figure 4).

Case report patient 5:
A 56-year-old man, who had been taking didanosine for 8 years in addition to efavirenz, emtricitabine and tenofovir, was referred for visual field constriction. FF-ERG showed no response under scotopic conditions and reduced responses under photopic conditions. Five years after didanosine cessation, FF-ERG remained stable whereas SWAF imaging showed extension of the atrophic areas in the mid-periphery crossing the temporal inferior vascular arcade (figure 5A-D).

Case report patient 6:
A 49-year-old woman, from Ivory Coast, complained of visual field constriction and dyschromatopsia. On her past medical history, she had taken chloroquine for malaria and didanosine, emtricitabine, tenofovir and ritonavir for HIV. Duration of didanosine medication is not known. Her RE BCVA was 20/40 and LE BCVA 20/40. Goldmann kinetic perimetry showed normal V4 and V1 periphery isopter and reduced III1 and II1 central sensibility with exclusion of the blind spot on both eyes. FF-ERG showed no response under scotopic conditions for both eyes. Delayed and reduced responses were present on photopic conditions.
Multifocal ERG showed preserved responses to the central hexagons. Four years after didanosine cessation, and despite relatively unchanged FF-ERG, autofluorescence pictures showed enlargement of the atrophic areas around the vascular arcades with persistent macular sparing (figure 5E-H).

Concerning SD-OCT findings, macular structure was normal in patient 1 but irregularity of the RPE was seen in the area of speckled autofluorescence (figure 6A). In patient 4, SD-OCT revealed small cysts at the level of the inner nuclear layer (figure 6B). SD-OCT scan through the patchy atrophic areas confirmed the total loss of RPE with gradual disappearance of the ellipsoid zone in patient 5 (figure 6C).

Discussion:

Didanosine-induced retinopathy present various chorioretinal atrophic lesions predominant in the mid-periphery. Even after drug cessation, we observed an extension of the atrophy in 3 out of 5 patients. Interestingly, progression rates of atrophy seemed to depend on baseline lesion size, multifocality and autofluorescence pattern: when didanosine was stopped early with only speckled alteration of the autofluorescence the progression rate was slow; whereas progression speed was faster when atrophic lesions were large at baseline. We recommend a follow-up period, after didanosine discontinuation, to document disease progression even for early stage of toxic retinopathy. We would like to underline that our study has limitations including its small sample size, its retrospective design, some missing data and the lack of complete neuro-ophthalmologic investigations for all patients.
In previously published case series of patients with didanosine retinopathy, the length of didanosine treatment in adults ranged between 5 and 11 years [3-6] and was shorter in children [2]. Our data also suggest that toxic retinopathy become more evident after 5 years of didanosine intake.

Co-administration of tenofovir appears to be a risk factor of didanosine-induced retinopathy. In our case series, 5 out of 6 patients were taken tenofovir in addition to didanosine. Tenofovir is known to increase plasma availability of didanosine and can be responsible for specific tubulopathy [8-9]. In this context, special attention must be paid to medications that impair renal function. Hawkins and al previously reported 3 cases of ddI-induced retinopathy in children taking tenofovir and didanosine together [10]. Tenofovir also interacts with atazanavir, a HIV-1 protease inhibitor, by decreasing atazanavir concentrations while increasing tenofovir concentrations [9].

The reason for progression of didanosine-induced retinopathy despite drug cessation remain unclear. One explanation could be that retinal cells have been induced into an irreversible cell death pathway prior to stopping the drug and therefore continue their degeneration process despite cessation. An additional toxicity to the drugs given as a therapeutic switch cannot be excluded. This has indeed been reported with other nucleoside analog reverse-transcriptase inhibitors (zidovudine, entecavir [11-12] and lamuvidine [13]), and protease inhibitor (ritonavir [14-16]). In line with this, a closer retinal monitoring of patients taking new generation NRTIs may be necessary to answer this issue.

FF-ERG showed a generalized rod-cone dysfunction in 5 out 6 patients and mf-ERG performed on 2 patients (patient 1 and 4) showed a good preservation of central macular function. EOG was performed on one patient (patient 4) and showed a reduction of the light rise which could be related to photoreceptor dysfunction or an additional alteration of RPE function. Our
electrophysiological findings are similar to those of Fernando et al. [3]. However, we were not able to see improvement on FF-ERG after drug cessation. Rod-cone dysfunction seems to be surprisingly stable overtime despite the progression of atrophic lesions on fundus autofluorescence imaging. This finding may be due to the global information on retinal function that FF-ERG provides which is less sensitive to detect subtle retinal changes. In this respect, multimodal retinal imaging may be better suited to closely monitor retinal toxicity while FF-ERG may detect changes after a longer follow up period.

Concerning the pathophysiology, some authors hypothesized that didanosine may potentiate mitochondrial DNA damage and lead to continued chorioretinal degeneration [5,17]. In this respect, the retinal lesions with patchy atrophic areas and speckled fundus autofluorescence characterizing didanosine retinopathy resemble retinal lesions seen in inherited mitochondrial disorders (such as chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome (MIM #530000), maternally inherited diabetes and deafness (MIM #520000) and mitochondrial encephalopathy with lactic acidosis and stroke-like episode (MIM #540000)) are mainly localized inside the vascular arcade with macular involvement. The topography of the chorioretinal lesions in didanosine toxicity is quite the opposite and better match with the map of rod photoreceptor maximum density [18]. The highest rod densities are located along an elliptical ring at the eccentricity of the optic disc and extended into the nasal retina. Rod densities declines slowly from the rod ring to the far periphery and is higher in the nasal and superior retina with some individual variability.

Whitcup and al published a clinicopathologic report of ddI-induced retinopathy showing multiple areas of RPE loss, surrounded by hypo or hypertrophy of the RPE [19]. The choriocapillaris and the neurosensory retina were partly absent in the areas of diseased RPE
while they were normal at the macula. In addition, the most anterior portion of the peripheral retina was spared. In the histopathological study, Whitcup et al. observed normal mitochondriae, however inclusion bodies were seen in defective RPE cells resembling those found in lysosomal storage diseases. This finding suggested that RPE cell metabolism would be primarily affected by didanosine toxicity.

The main role of RPE cells is to phagocytose the photoreceptor outer segments (POS) and mainly rod POS which are more numerous than those of cones [20]. POS phagocytosis activity is thus very intense at the ring of increased rod density.

Biochemical studies had shown that the RPE possess receptor for purines. Sanderson et al. reported that the balance between extracellular ATP and adenosine may alter the lysosomal activity of RPE cells and thus its autophagic function [21-23]. Didanosine, acting as a competitive adenosine analog may compromise this process leading to decrease POS phagocytosis, lipofuscin accumulation and progressive RPE degeneration.

Interestingly, small cysts were also present on SD-OCT at the level of the inner nuclear layer (INL) in 2/6 patients (figure 6C). These cysts may be structural alterations secondary to outer retinal changes or a manifestation of Müller cell dysfunction maybe through a direct toxicity of purine analog. Cysts of INL related to Muller cell loss have already been reported in several pathologies, but for first time in DDI-induced retinopathy. Cohen et al reported pseudocysts changes in INL in atrophic age macular degeneration and suggested involvement of Muller cells as an intermediate stage during the process of retinal atrophy [24]. Similarly, the relation between INL microcystic changes and Muller cell degeneration has been suggested in tamoxifen retinopathy [25] and macular telangiectasia type 2 [26]. Several authors also reported
retinal inner nuclear layer microcytic changes in optic nerve atrophy of various etiologies [27, 28]. Wolff et al suggested the cysts could constitute "the translation of degeneration of Muller cells in severe optic nerve fiber loss » [29]. Recently, purinergic signaling was also shown to play a key role in Müller cells volume regulation, via P2Y<sub>1</sub>-receptor, enabling correct transcellular ion and fluxes in the retina to maintain good retinal homeostasis [30].

Conclusion:

Didanosine-induced retinopathy is a progressive disorder despite drug session. Patients taking didanosine should be informed about the risk of toxic retinopathy, which becomes significant after five years of treatment and referred yearly for ophthalmic screening including multimodal imaging based on short wavelength fundus autofluorescence and SF-OCT. FF-ERG is important for the diagnosis of retinal dysfunction but is not sensitive enough to closely monitor disease progression. It could be performed every other year. In case of toxic retinopathy, advise should be given on didanosine and other potential retinotoxic drugs that should be discontinued as soon as possible with patients needing to be referred to their infectious disease specialists for a treatment switch. Since HIV seropositive patients are often taking HAART (High Active Antiretroviral Therapy) with various antiretroviral drugs and since retinal toxicity has also been described with other nucleoside analogs a special attention must be paid to these patients.

References:


[21] Sanderson J, Dartt DA, Trinkaus-Randall V, et al. Purines in the eye: recent evidence for the physiological and pathological role of purines in the RPE, retinal neurons, astrocytes,


Legends:

Table 1: Summary of our six cases of didanosine retinal toxicity

Figure 1: Retinal imaging from patient 1: Right eye (RE) (1A) and left eye (LE) color fundus (1B); RE (1C) and LE short wavelength fundus autofluorescence (1D) showing RPE changes in the mid-periphery with mottled hyperautofluorescence.

Figure 2: Retinal imaging for patient 2: RE (2A) and LE color fundus (2B) displaying macular drusen at the posterior pole. RE (2C) autofluorescence showing no significant alteration at the posterior pole and LE (2D) composite autofluorescence picture with granular alteration in the mid-periphery.

Figure 3: Short wavelength fundus autofluorescence imaging of patient 3 showing mid-peripheral mottled-lacy hyperautofluorescence of right (3A) and left eye (3B). Two years later, the autofluorescence pictures remained unchanged on both eyes (3C-3D).

Figure 4: Short wavelength fundus autofluorescence pictures of patients 4 taken at presentation, 2 years, 4 years and 6 years later showing a slow progression of the small atrophic patches in the midperiphery of both eyes.

Figure 5: Short wavelength fundus autofluorescence imaging of patient 5 at presentation (5AB) and 5 years later (5CD) and patient 6 at presentation (5EF) and 4 years later (5GH) revealing progression and increasing confluency of atrophy.

Fig. 6: SD-OCT findings in patients with didanosine-induced retinopathy: OCT scan targeted on speckled alteration in autofluorescence of patient 1 nasal to the optic nerve disc showing irregularity of the RPE (red arrow) (6A); horizontal scan through the macula with minimal retinal thickening related to micro-cysts (yellow arrow) in the inner nuclear layer of patient 4 (6B); vertical scan of patient 5 with total atrophy of the RPE (6C, dark blue arrow)
corresponding to the patchy atrophic areas and gradual disappearance of the ellipsoid zone (blue arrow).