



Update on Retinal Drug Toxicities

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Abstract

Purpose of Review This review aims to provide an update on the clinical presentations and diagnostic findings of drug-induced retinal toxicities.

Recent Findings Several newly FDA-approved medications have been associated with acute retinal toxicities, including brolocizumab, MEK inhibitors, ulixertinib, and FGFR inhibitors. Additionally, as previously believed-to-be well-tolerated medications, such as pentosan sulfate sodium, anti-retroviral therapies, and certain intraoperative ocular medications, are used more frequently or for longer periods of time, associated toxic retinopathies and inflammatory reactions have been reported. Finally, advances in ocular imaging have revealed novel findings in hydroxychloroquine and tamoxifen maculopathies.

Summary Discovery of new medications, increased frequency of use, and longer-term use have led to increased reports of retinal toxicities. Advances in retinal imaging have allowed for earlier detection of subclinical changes associated with these medications, which may help prevent progression of disease. However, more research is needed to determine the point at which vision loss becomes irreversible. Risks and benefits must be assessed prior to discontinuation of the offending, but potentially lifesaving, therapy.

Keywords Retinal toxicity · Drug-induced retinopathy · Toxic retinopathy · Drug-induced maculopathy · Hemorrhagic occlusive retinal vasculitis, Brolocizumab, Pentosan sulfate

Introduction

The year 2020 kicked off with conjectures about cures for coronavirus 2019 (COVID-19) and multiple experts sounding reminders to the public and ophthalmic community that medications, such as hydroxychloroquine, can result in devastating vision loss [1, 2]. Another medication that was newly FDA approved for neovascular age-related macular

degeneration, brolocizumab, was found to cause potential retinal toxicities in patients. Potential therapies for advanced malignancies may also have side effects on the retina. Furthermore, the increase in popularity of dropleless cataract surgery and, with it, intraoperative medications such as intracameral aminoglycosides, triamcinolone, and vancomycin have also led to a surge of associated side effects such as hemorrhagic occlusive vasculitis and other retinal toxicities. Simultaneously, long-term use of previously believed to be well-tolerated medications such as pentosan polysulfate sodium and some anti-retroviral therapies have also been associated with retinal toxicity. Furthermore, new findings are also reported as imaging methods advance to allow for more detailed characterization of previously known retinopathies.

Hydroxychloroquine

As described above, recent events over the past year put hydroxychloroquine, a medication prescribed to treat malaria and autoimmune diseases such as systemic lupus

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erythematosus and rheumatoid arthritis, in the spotlight as a potential treatment or prophylaxis for COVID-19. However, hydroxychloroquine has multiple significant systemic side effects, including retinal toxicity, that may cause irreversible loss of vision [3]. As a result, there have been multiple recent warnings from experts urging prescribers and the public to be aware of the potential life- and sight-threatening adverse effects associated with hydroxychloroquine, especially when used concurrently with certain medications that may increase the toxicity [4, 5].

In the past year, new findings have been reported regarding retinal changes associated with hydroxychloroquine. Classically, hydroxychloroquine retinopathy has been described as a toxic retinopathy affecting the outer retina, primarily the

photoreceptor layer and the retinal pigment epithelium (RPE), usually in the parafoveal and perifoveal regions, as shown in Fig. 1 (1A–B) [3]. In a recent longitudinal study of patients taking hydroxychloroquine without retinal toxicity, the inner retina, specifically the ganglion cell layer in the foveolar and paracentral areas, was found to thin progressively over time despite any observed changes in the outer retina [6]. Another longitudinal study focused on the long-term outcome of patients who presented with pericentral retinopathy, a pattern more prevalent in Asian patients rather than the often-taught parafoveal/perifoveal pattern of bull's eye maculopathy [7, 8]. This study found that 80% of eyes with moderate or severe pericentral retinopathy led to progression centrally towards the fovea even after discontinuing hydroxychloroquine [8]; this

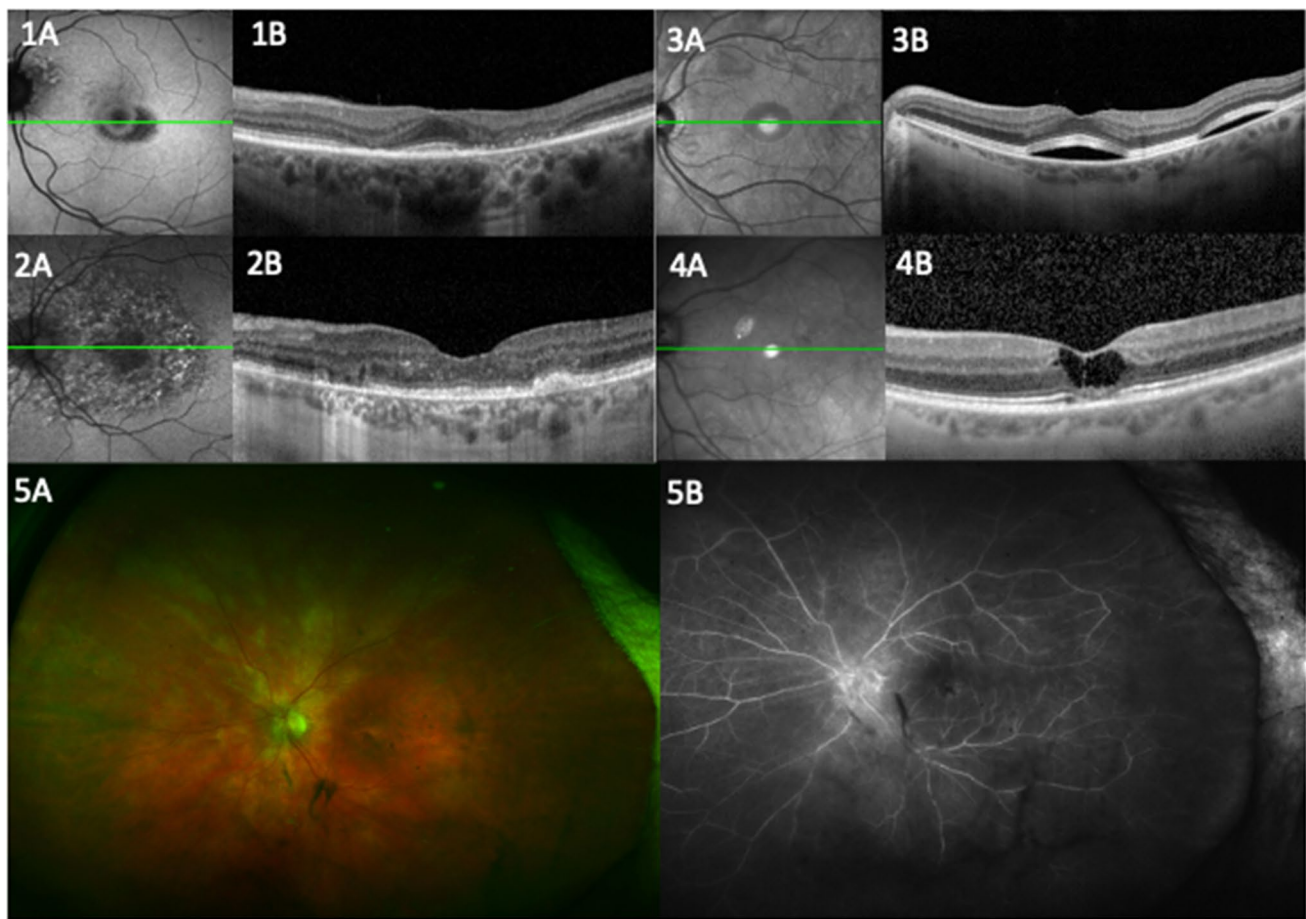


Fig. 1 (1A) Autofluorescence (AF) image in a patient with retinal hydroxychloroquine toxicity demonstrates a bull's eye pattern of hypoautofluorescence in the perifoveal area, consistent with EZ loss seen in corresponding optical coherence tomography (OCT) image (1B); note the subfoveal sparing and a rim of hyperautofluorescence on AF. (2A) AF image in a patient with pentosan polysulfate sodium retinal toxicity shows a highly irregular pattern involving a well-defined region in the posterior pole characterized by a network of hyperautofluorescent spots with corresponding OCT (2B) showing patchy retinal pigment epithelium (RPE) loss (images courtesy of Dr.

Dilraj Grewal). (3A, 3B) Infrared reflectance (IR) image and corresponding OCT image in a patient with retinal MEK inhibitor toxicity showing subretinal fluid. (4A, 4B) IR and corresponding OCT image in a patient with retinal tamoxifen toxicity demonstrating hyporeflective foveal cavitation and photoreceptor disruption. (5A) Brolucizumab retinal occlusive vasculitis captured on widefield fundus photos, illustrating superior retinal artery sheathing as well as a vitreous opacity; (5B) late-phase FA image demonstrates sclerotic retinal arteries, peripheral nonperfusion, and hyperfluorescence of the optic nerve and perifoveal region (images courtesy of Dr. Glenn Jaffe)

may be due to existing RPE cell damage that leads to further loss of the photoreceptors. Additionally, even though hydroxychloroquine is primarily stored in melanotic tissue, the liver, and the kidneys, low concentrations are also present in other parts of the body including fat. It is possible that this residual amount of the medication is redistributed into the plasma so that there is a continued effect after drug cessation [9–12].

Several recent studies have attempted to identify earlier biomarkers for hydroxychloroquine retinopathy. An experimental method using quantitative fundus autofluorescence, which allows quantification and comparison of the intensity of fundus autofluorescence in an eye over time and between eyes, found that patients taking hydroxychloroquine or chloroquine had higher values of autofluorescence intensity compared to age-matched controls [13]. However, the authors discuss that the cause of the increased intensity is not clear and may simply be due to presence of the drug, stored metabolic by-products, or increased metabolic activity, and is not necessarily a sign of hydroxychloroquine/chloroquine maculopathy. Another study utilized optical coherence tomography angiography to compare the quantitative retinal vascular measurements (foveal avascular zone area, superficial foveal/parafoveal/perifoveal vascular density, and deep foveal/parafoveal/perifoveal vascular density) between patients taking hydroxychloroquine and controls, and did not find any differences in those parameters [14]. There was also an attempt to identify genetic factors making patients susceptible to hydroxychloroquine, which was undertaken in a case–control study of 26 Caucasian patients with confirmed hydroxychloroquine retinal toxicity, but no susceptibility or protective factors were identified [15].

As ophthalmic imaging and ancillary testing become more advanced, we will identify earlier markers of toxicity. Ideally, we will find a marker that precedes irreversible anatomic and vision changes allowing physicians to discontinue therapy prior to permanent damage. In a 2020 review paper by Browning et al., he notes that the guidelines regarding hydroxychloroquine use and discontinuation are published without inclusion of the prescribing physicians. As the newly detected retinal findings from hydroxychloroquine may not be clinically significant enough to cause retinopathy and vision loss, and discontinuation of the drug in treatment of autoimmune disease includes its own risks, Browning makes the point that updates to hydroxychloroquine dosing and screening guidelines should be updated with input from both ophthalmologists and prescribing physicians, typically rheumatologists [10].

Pentosan Polysulfate Sodium

Pentosan polysulfate sodium (PPS) (Elmiron, Janssen Pharmaceuticals, Inc., Beerse, Belgium) was initially approved by the FDA in 1998 and is the only oral FDA-approved

medication specifically for the symptomatic treatment of interstitial cystitis [16]. PPS has recently been associated with a toxic maculopathy, as shown in Fig. 1 (2A–B). This associated was first reported in 2018 by Pearce et al. and is described as a paracentral hyperpigmentation in the RPE layer with surrounding vitelliform deposits, yellow subretinal deposits, and patchy parafoveal RPE atrophy [17–19]. Since then, several lawsuits have been filed regarding vision loss due to Elmiron [20].

However, the association between PPS and maculopathy is still somewhat controversial. Ludwig et al. reviewed a cohort of 227,325 patients with interstitial cystitis and treated with PPS and did not find an exposure or a dose-dependent relationship with less than 1 year of PPS use; there was, however, a possible dose-dependent relationship with greater than 4 years of use and an increased risk of diagnosed with a hereditary dystrophy [21]. A retrospective matched cohort study by Jain et al. looked for an association in a large national cohort, and found that PPS exposure was associated with a diagnosis of atypical maculopathy and age-related macular degeneration (AMD) at the 7-year follow-up [22]. A recent case report describes a patient that was initially diagnosed with Stargardt disease, but then attributed the maculopathy to PPS after genetic testing was negative [23].

Barnes et al. utilized masked review of multimodal fundus images to evaluate whether PPS maculopathy had features that allowed differentiation from other hereditary maculopathies. Results showed 100% sensitivity and 99.6% specificity in identifying PPS maculopathy by masked review of the fundus imaging, thus suggesting that PPS maculopathy does indeed have characteristics that distinguish it from hereditary maculopathies [24]. Another study reported that OCTA showed choriocapillaris flow voids. The authors hypothesize that the drug toxicity primarily damages the choriocapillaris, which then leads to observed RPE changes and atrophy [25].

Another recent retrospective case study of 11 patients who were diagnosed with PPS maculopathy reported that despite cessation of PPS, progression of RPE atrophy continued and patients endorsed worsening visual symptoms [26]. Given the possible association of PPS with toxic maculopathy, Mogica and De recommended weighing the risks and benefits of use of PPS, as well as performing regular screening ophthalmic exams [16].

Brolucizumab

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) medications are commonly administered for treatment of retinal vascular diseases such as neovascular AMD. Post-injection intraocular inflammation has been

previously reported after all anti-VEGF agents, ranging from 0.05 to 2.9% [27]. Brolocizumab (Beovu, Novartis AG, East Hanover, NJ), another anti-VEGF agent, was recently approved by the FDA for treatment of neovascular AMD in 2019 [28, 29]. After its approval, several case reports and case series described a severe post-injection intraocular inflammation and occlusive vasculitis, shown in Fig. 1 (5A–B) [30–35].

A summary of the patient characteristics for these is reported in Table 1. Interestingly, most of the patients in which brolocizumab retinal vasculitis was reported were female. Witkin et al. analyzed a case series of 26 eyes of 25 patients who developed retinal vasculitis after treatment with brolocizumab for neovascular AMD. Eighty-eight percent of the patients were female, and they presented at a mean of 25 days after the most recent injection. At the final follow-up visit, 46% of the eyes were 20/200 or worse, from the mean of 20/52 prior to the development of retinal vasculitis [32]. Another case series of 15 eyes of 12 patients (all of which were women) had similar results, with a mean presentation of 30 days after the last brolocizumab injection, and mean visual acuity of 20/136 at around 25 days, from a mean of 20/53 at prior to injection. An important distinction in the retinal vasculitis caused by brolocizumab as compared to the hemorrhagic occlusive retinal vasculitis from vancomycin is the lack of retinal hemorrhages associated with brolocizumab [31].

A post-approval post hoc analysis by an independent safety review committee assessed the risk of inflammation, retinal vasculitis, and retinal occlusion and found the risk of intraocular inflammation to be 4.6%. The risk of intraocular inflammation and vasculitis was 3.3% and the risk of intraocular inflammation and occlusive vasculitis was 2.1%. Brolocizumab-associated intraocular inflammation was associated with at least moderate vision loss (≥ 15 EDTRS letters) in 0.74% of cases [36].

Mitogen-Activated Extracellular Signal-Regulated Kinase (MEK) Inhibitors

MEK inhibitors such as trametinib, cobimetinib, and binimetinib are of great interest in the oncology community as they can target specific oncogenic pathways in the treatment of various cancers, such as metastatic melanoma. In 2020, the FDA also approved selumetinib for use in treatment of neurofibromatosis type I [37]. MEK inhibitors have been known to cause retinopathy (MEK inhibitor-associated retinopathy or MEKAR), commonly presenting as multifocal serous retinal detachments involving the central and peripheral retina, as shown in Fig. 1 (3A–B) [38, 39]. These findings are thought to be transient and self-limited, although structural signs without functional impairment can

still be identified on imaging after long-term treatment [40]. A recent study by Booth et al. examined 247 patients with advanced melanoma who were treated with cobimetinib and vemurafenib to identify risk factors associated with developing MEKAR. They found that risk factors for developing retinopathy included age, glomerular filtration rate, and history of ocular disease [41].

Ulixertinib

Ulixertinib is a novel anticancer drug currently undergoing multiple clinical trials for a variety of malignancies, including advanced solid tumors, lymphomas, gastrointestinal tumors, and uveal melanoma [42]. It acts by inhibiting extracellular signal-regulated kinase (ERK) 1 and 2, a component that is part of an often-upregulated pathway in tumor cells [43]. Sioufi et al. reported the first known case of ERK inhibitor-associated retinopathy (ERKAR) associated with ulixertinib. The patient was on 600 mg of ulixertinib twice a day and presented with bilateral blurred vision, a diffuse dermatitis, and fundus findings notable for cystoid macular edema, subretinal fluid, and subretinal deposits between the RPE and interdigitation zone. Four weeks after cessation of the drug, the patient's vision returned to baseline and the subretinal fluid resolved. The authors note that in comparison to MEKAR, this case of ERKAR demonstrated cystoid macular edema and accumulation of subretinal deposits, features not commonly seen in MEKAR [44]. As the various clinical trials progress and long-term outcomes are studied, perhaps more cases will be identified and characterized.

Fibroblast Growth Factor Receptor (FGFR) Inhibitors

Erdafitinib is a fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor newly FDA approved in 2019 for use in treatment of urothelial carcinoma [45]. A recent case described foveal serous retinal detachment associated with use of erdafitinib; however, the patient was asymptomatic. Parikh et al. note that the findings in the case were similar to the bilateral serous detachments seen in MEKAR [46]. Another study monitored the long-term outcomes in patients with metastatic urothelial cancer treated with erdafitinib, and noted that central serous retinopathy occurred in 27 of 101 patients [47].

Another FGFR inhibitor, AZD4547, recently underwent a phase II study for the treatment of malignant pleural mesothelioma as a second-line treatment for patients who relapse after first-line chemotherapy. In the study, 12 of 24 patients developed subretinal fluid in one or both eyes. The onset

Table 1 Summary of all reported vasculitis adverse events after intravitreal injection of brodalumab

Report	# of cases described	Age (years)	Sex	# of previous anti-VEGF injections	Total # of brodalumab injections	Presenting symptoms	Days from last injection to presentation with vasculitis	Features of retinal pathology
Baumal et al	12	$M = 77.6$ (65–85)	100% F	$M = 27.5$ (2–80)	1 (58.3%) 2 (33.3%) 3 (8.3%)	Floater ($n = 8$), reduced or blurred vision ($n = 7$), scotoma ($n = 3$), and ocular discomfort ($n = 2$)	$M = 30.3$	Narrowing and/or occlusion of retinal arteries, retinal vessel sheathing, Kyrieleis plaques, dilation/narrowing of retinal veins, phlebitis, and late perivenular hemorrhages. Retinal whitening from arterial occlusion, cotton-wool spots, paracentral acute middle maculopathy, and intraretinal hemorrhages
Witkin et al	26	$M = 79.1$ (58–92)	88% F 12% M	$M = 39.1$ (2–78)	1 (42%) 2 (42%) 3 (16%)	Blurry vision in 62%, floaters in 46%, pain in 31%, redness in 19%, scotomas in 12%, and asymptomatic vasculitis found only on routine exam in 8%	$M = 25$ (3–63)	Vasculopathy that involved retinal arteries in 91%, retinal veins in 79%, and choroidal vessels in 48%. Occlusive disease seen on FA in 83%
Kondapalli et al	1	77	F	Yes, number not described	2	Initial blurry vision then asymptomatic prior to vasculitis diagnosis	21	Boxcarring of the retinal arteries; vascular pruning and arterial/venous filling defects on early FA and retinal ischemia with nonperfusion and late disc leakage on late phase FA
Haug et al	1	88	F	21	1	Painless reduction in VA and light sensitivity	28	Retinal arterial occlusion, vasculitis, and optic nerve inflammation seen on FA. Retinal intra-arterial grayish materials also detected
Hikichi et al	3	$M = 82.66$ (72–94)	33% F 67% M	$M = 28.33$ (20–33)	1	Redness, pain, decreasing VA, floaters	$M = 10.66$ (3–17)	Sheathing of retinal vessels, new intraretinal hemorrhage, recurrence of intraretinal and subretinal fluid, vitreous haze
Iyer et al	1	76	F	Multiple, number not described	3	Pain, floater, and decreased VA	51	Peripheral vascular sheathing; then worsening uveitis, vitritis, and increased vascular sheathing

M, mean; *FA*, fluorescein angiogram; *VA*, visual acuity

was noted between 3 and 19 weeks after the initial dose of AZD4547. All 12 patients were asymptomatic [48].

Pemigatinib (Pemazyre, Incyte Corporation, Wilmington, DE), also a novel FGFR inhibitor, received accelerated FDA approval in April 2020 for locally advanced or metastatic cholangiocarcinoma, and is currently undergoing trials for treatment of other malignancies [49]. Alekseev et al. report a case of a 67-year-old-male with metastatic colon adenocarcinoma on pemigatinib who developed bilateral multifocal serous retinopathy. The patient was 42 days into treatment when he noticed a slight blurring of his vision; visual acuity was 20/20–2 in the right eye and 20/20–1 in the left eye. Five days after discontinuation of the drug, the subretinal fluid almost fully resolved. The authors note the similarities to cases of MEK retinopathy with multifocal subretinal fluid [50].

Intraoperative Ocular Medications

Aminoglycosides

Intravitreal injections of gentamicin have been previously reported to cause retinal toxicity, which presented as macular whitening, intraretinal hemorrhages, cotton wool spots, arteriolar narrowing, and venous beading [51]. Recently, two cases were reported of multiple retinal vascular occlusions that developed after subconjunctival injection of gentamicin following vitrectomy. Both cases presented with macular whitening and retinal hemorrhages within the immediate post-op period [52]. A case of subconjunctival aminoglycoside injection causing retinal toxicity was imaged with fluorescein angiography (FA) and optical coherence tomography angiography (OCTA), revealing corresponding areas of vascular nonperfusion [53].

Moxifloxacin

Droplec cataract surgery commonly uses a compounded mixture of moxifloxacin and triamcinolone delivered into the eye during surgery in place of the multiple eye drops prescribed for post-operative use. However, these intraoperative medications can have side effects. Patel et al. examined a case series of 7 patients who presented with toxic posterior segment syndrome attributed to the intracameral triamcinolone-moxifloxacin administered during droplec cataract surgery. Findings included decreased visual acuity, loss of the subfoveal ellipsoid zone on OCT, reduction of full-field retinal responses, and negative ERG on electrophysiologic testing [54]. More recently, Ferreira et al. performed a prospective randomized trial to determine whether intracameral moxifloxacin was associated with any changes in the retina and choroid. They did not find any significant differences

between the moxifloxacin and control group in the thickness of the retina and choroid [55].

Vancomycin

Use of intracameral vancomycin as part of droplec cataract surgery has been reported to cause a hemorrhagic occlusive retinal vasculitis (HORV). Characteristic findings include vascular sheathing, diffuse retinal hemorrhages, and inner retinal ischemia and edema [56–58]. Recent case reports of HORV include that noted in both eyes of a 9-month-old who received intraoperative vancomycin as a routine part of sequential bilateral lensectomies, the first reported case of HORV in a pediatric patient [59]. Another report of HORV occurred in an elderly patient who underwent cataract surgery with intracameral injection of vancomycin; however, she did have previous exposure to systemic vancomycin for a 6-week course about 21 years ago for a breast implant infection and another one-time dose 1 year prior for a toe infection, and thus the authors wonder whether the prior exposure may have led to sensitization to vancomycin [60].

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, is a medication that has been used to treat breast cancer. Multiple case reports have long described the retinopathy that tamoxifen can cause crystalline deposits and pseudocystic foveal cavitations, shown in Fig. 1 (4A–B) [61–63]. The findings have been previously compared to macular telangiectasia type 2, suggesting a similar pathogenesis involving Muller cell dysfunction. Of note, the pseudocystic foveal cavitations noted in tamoxifen retinopathy can be differentiated from cystic macular edema by absence of leakage noted on fluorescein angiogram and normal-to-reduced retinal thickness [64]. A recent cross-sectional case–control study by Crisostomo et al. looked at previously unreported OCT findings in patients taking tamoxifen as compared to controls. They found that those taking tamoxifen had thinner choroid and total retinal thickness, suggesting that there were structural changes in patients without symptoms that could be early signs of RPE and photoreceptor damage [65].

Hwang and Chung recently published a study examining how sulfasalazine, a disease-modifying anti-rheumatic drug used to treat diseases such as rheumatoid arthritis, may help reduce the toxic effects of tamoxifen on the retina. They noted multiple mechanisms, including reduction of RPE cell death caused by tamoxifen-mediated reactive oxygen species and caspase-1-mediated pyroptosis, reduction in mRNA levels of the genes for tamoxifen-induced pyroptosis, and downregulation of tamoxifen-induced AMD-related genes [66]. The potential for medications to help prevent or treat

toxic retinopathy is an intriguing concept warranting further study.

Antiretroviral Therapies

Antiretroviral therapies (ART) such as ritonavir, efavirenz, and didanosine are used in the treatment of human immunodeficiency virus (HIV). Although these medications can help prevent the development of HIV or other infection-associated retinal disease, it is important to also be aware of the rare potential for causing retinal toxicity [67, 68]. There have been a few case reports published recently that present additional cases of ritonavir-induced retinal toxicity. One case of a patient with HIV who had been on ritonavir for 7 years described findings of bilateral maculopathy, parafoveal RPE mottling, and midperipheral retinal pigmentary changes [69]. Another case reported extensive macular atrophy in both eyes of a patient with HIV and hepatitis C who had been on ritonavir for 18 years and didanosine for 4 years. Multi-modal imaging and electrophysiology were performed and characterized the retinopathy as loss of outer retinal and choriocapillaris layers, as well as cone-rod dysfunction [70]. Similar findings were reported in a patient who had been on ritonavir for over 10 years [71]. There has also been a recent case of macular toxicity reported in a HIV-positive patient who was on efavirenz for 9 months, presenting with bilateral central and paracentral visual field

defects, RPE mottling, loss of the outer retinal layers, and reduced macular responses on multifocal electroretinogram [72]. These reports of ART-associated retinopathy are quite uncommon, and one would think that the benefits of continuing the ART regimen would outweigh these potential side effects. However, these findings do raise the question of whether ophthalmologic screening might be beneficial in patients who remain on these medications long term.

Alkyl Nitrites

Non-prescription drugs can also cause retinal toxicity. An example recreational use of alkyl nitrites or “poppers,” a vasodilatory chemical inhaled to induce an instantaneous euphoric sensation. Poppers maculopathy has been reported more frequently as use of the drug increases and more sensitive methods for imaging are used. Law et al. report a case of a 35-year-old healthy man who presented with bilateral blurry vision 12 h after a one-time use of alkyl nitrites. Fundus exam showed a yellow spot at the fovea, and OCT showed disruption of the foveal photoreceptors [73]. Similar findings were reported in another report of a 36-year-old man with poppers maculopathy who underwent multimodal imaging; of note, no vascular changes were noted on OCTA [74]. The findings in these reports are consistent with a previous case series of 39 patients by Van Bol in 2017. Interestingly, of the 39 patients, only 2 were women [75]. Further

Table 2 Summary of retinal drug toxicities and pertinent features discussed in this review

Drug	Features of retinal drug toxicity
Hydroxychloroquine	Changes in the photoreceptor layer and the RPE, usually in the parafoveal and perifoveal regions; OCT shows progressive thinning of the inner retina in patients without diagnosed retinal toxicity; changes usually noted after years of using the drug
Pentosan polysulfate sodium	Paracentral hyperpigmentation in the RPE layer with surrounding vitelliform deposits; OCTA shows choriocapillaris flow voids; changes usually noted after years of using the drug
Intravitreal brolocizumab	Intraocular inflammation and occlusive retinal vasculitis presenting around 25–30 days post-injection
MEK inhibitors (i.e., cobimetinib)	Transient and self-limiting multifocal serous retinal detachments involving the central and peripheral retina
Ulixertinib	CME, SRF, and subretinal deposits between the RPE and interdigitation zone
FGFR inhibitors (i.e., erdafitinib)	Central serous retinal detachment, usually asymptomatic or very mild symptoms
Subconjunctival gentamicin	Macular whitening and retinal hemorrhages within the immediate post-op period
Intraocular moxifloxacin	Toxic posterior segment syndrome; decreased visual acuity, loss of the subfoveal ellipsoid zone on OCT, reduction of full-field retinal responses and negative ERG
Intracameral vancomycin	Hemorrhagic occlusive retinal vasculitis (vascular sheathing, diffuse retinal hemorrhages, inner retinal ischemia, and edema)
Tamoxifen	Crystalline deposits, pseudocystic foveal cavitations, thinner choroid, and total retinal thickness
Ritonavir	Bilateral parafoveal RPE mottling, loss of outer retinal and choriocapillaris layers, cone-rod dysfunction
Efavirenz	Bilateral central and paracentral visual field defects, RPE mottling, loss of the outer retinal layers, reduced macular responses on multifocal ERG
Alkyl nitrites	A yellow spot at the fovea; OCT shows disruption of the foveal photoreceptors

FGFR, fibroblast growth factor receptor; *RPE*, retinal pigment epithelium; *CME*, cystoid macular edema; *SRF*, subretinal fluid; *ERG*, electroretinogram

studies are needed to understand the mechanism, risk factors, and long-term effects of poppers maculopathy.

Conclusion

As new therapies are released, and as old therapies are used for longer durations and administered in novel ways, retinal drug toxicity should remain at the forefront of the ophthalmologist's mind. We reviewed some of the current literature and most recent updates on some of these retinal drug toxicities above; these are summarized in Table 2. Brolucizumab, an exciting new medication to add to the potential therapies to treat neovascular AMD, has been reported to cause a severe occlusive retinal vasculitis, while potentially life-saving anti-cancer therapies such as MEK inhibitors, ulixertinib, and FGFR inhibitors have also been reported to cause retinopathies characterized by serous retinopathy detachments that appear to have limited visual significance. New findings regarding retinal changes have also been discovered in medications that have been for years, such as hydroxychloroquine and tamoxifen. Retinopathy may also take years to present, such as those associated with long-term use of some anti-retroviral therapy. Furthermore, as the face of ophthalmic surgery evolves and new methods such as dropless cataract surgery become more widespread, the side effects associated with the medications used may present more frequently.

Finally, with the advancement of imaging methods, more retinal changes are identified in otherwise asymptomatic patients. Whether these changes are clinically significant, and the turning point at which cessation of the drug becomes necessary to prevent irreversible vision-threatening symptoms, requires further study. As these critical points are elucidated, the question then becomes a discussion between the ophthalmologists, prescribers, and patients regarding risks and benefits of these medications, and what alternative treatments exist to treat their potentially life-threatening disease.

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Declarations

Conflict of Interest None of the authors has disclosures related to the submitted work. Dr. Deaner has the following disclosures outside of the submitted work: Alimera Sciences, Inc.: honoraria. Dr. Vajzovic has the following disclosures outside of the submitted work: Applied Genetic Technologies Corporation (AGTC): investigator; Alcon: investigator, consultant; Aldeyra: investigator; Alimera Sciences: consultant; Allergan — consultant; Aerie: consultant; Baush & Lomb: consultant; Beaver-Visitec International (BVI): consultant; Dutch

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