The ROYAL COLLEGE of OPHTHALMOLOGISTS

focus

An occasional update commissioned by the College.
The views expressed are those of the authors.

Update on Retinal Toxicity

Quresh Mohamed, Rachel Healey
Gloucestershire Hospitals NHS Foundation trust

The use of prescription medicines has surged, reportedly nearly 40% of adults 65 years and older use 5 or more medications. Treatment algorithms in particular for oncology, rheumatology and neurology have improved patient outcomes but also exposed patients and more importantly for ophthalmologists their eyes to potential harmful adverse effects.

This article covers some of the medications that can potentially harm the retina and are topical, interesting or are likely to impact our practice.

Hydroxychloroquine (HCQ) was originally used as malaria prophylaxis but is now increasingly used for its anti-inflammatory effects in various autoimmune conditions including systemic lupus erythematous and rheumatoid arthritis. It has a better side effect profile compared with alternative DMARDs and does not need on-going serological monitoring making it an attractive option for rheumatologists and physicians.

Despite the low systemic side effect profile, HCQ can cause ocular toxicity affecting the cornea, ciliary body and retina. HCQ binds strongly to melanin and accumulates in RPE cells with local toxicity ultimately leading to bilateral perifoveal rod and cone photoreceptors loss (with foveal cone sparing) leading in advanced cases to the classical "bulls eye" maculopathy and irreversible vision loss.

Symptomatic patients typically present with bilateral disease, paracentral scotomas, photopsia and subtle loss of colour vision. More extensive toxicity can cause narrowed arterioles, disc pallor and fine granularity of the retina and choroid

The Royal College Ophthalmologist guidelines from 2009 did not recommend systemic screening at that time "because clinically significant maculopathy is very rare and there is currently no reliable test for detecting it at a reversible stage."

Although there is no effective treatment, and the long half-life of the drug and tight binding to melanin in RPE can lead to progressive retinopathy for up to 7 years even after cessation of treatment, more sophisticated imaging and examination techniques now allow earlier detection of toxicity and prevention of progression to irreversible visual loss.

Longitudinal mfERG and microperimetry studies show progressive sub-clinical decline in retinal function in patients on HCQ preceding fundus autofluorescence and visual field changes suggesting the actual incidence of retinopathy may be significantly higher. Potential newer tests may include microperimetry and adaptive optics imaging (show parafoveal cone density loss correlating with increasing doses of HCQ)

The potential to detect toxicity before vision is affected has lead to evolving screening recommendations. The AAO revised its guideline in 2011 and removed Amsler grid as an acceptable screening tool and recommended screening on patients on HCQ for more than 5 years. The more recent revision to the AAO guidelines in 2016 recommended baseline fundus exam within 1st year and assessment of visual fields (10-2 and/or 24-2/30-2) and SD-OCT if macular changes present. Followed by annual screening after 5 years use and sooner in patients with major risk factors (Daily dosage HCQ >5mg/kg real weight, Duration of use > 5 years, renal Disease/subnormal glomerular filtration rate; concomitant drugs e.g. tamoxifen; co-existing macular disease). See Table 1.

The College is due to update the guidelines from 2009 and if they mirror the recent AAO guidelines this will have major implications for the workload in ophthalmology departments. We have recently identified a number of asymptomatic patients recently with mfERG and VF abnormalities who have been screened due to cumulative doses of HCQ>1000mg over >5 years.

Tamoxifen is a selective oestrogen receptor modulator that is widely used in treatment of breast cancer. Ocular adverse effects include corneal changes, cataract and optic neuropathy. Retinopathy is characterised by bilateral fine retractile perifoveal crystalline deposits and subsequent "cystoid type" macular changes, which are best detected on SDOCT. Historically very high doses of 150mg+/day were used with reported visual side effects and retinal toxicity reported in up to 11%. The current standard lower doses of 20-40mg/day are thought to have much lower incidence of retinal adverse effects below 1%. Typically treatment is continued for 5 consecutive years but recent studies have shown additional benefits in terms of prevention of recurrence if treatment is continued for 10 consecutive years. Whether this has implications on long-term toxicity and incidence of retinopathy is unclear. It has been suggested that treatment may be continued in eyes with crystalline deposits in the absence of vision symptoms or structural OCT changes. However with the advent of alternative treatments including the aromatase inhibitors discussion with the patient and oncologist is advised. Treatment should be stopped in consultation with oncologist for patients with cystoid macular changes as continued treatment can lead to irreversible vision loss.

Fingolimod an oral sphingosine-1-phosphate receptor modulator was recommended by NICE for the treatment of relapsing-remitting forms of multiple sclerosis (MS) in 2012. One of the main adverse events reported in clinical trials was macular oedema. The macular oedema was dose dependent and typically occurred within 4 months of treatment initiation and was reported in 0.4% of patients on the standard 0.5mg/day dose (the studies used TDOCT and the incidence of changes on SD OCT may be higher). Fingolimod-associated macular oedema is postulated to be due to loss of sphingosine 1-phosphate receptor signaling in endothelial cells, leading to down-regulation of adhesion complexes with enhanced vascular permeability and breakdown of the blood-retinal barrier. The macular oedema appears to resolve in most cases within 6 months of stopping Fingolimod and there are recent reports that the oedema may respond to topical NSAIDs.

NICE recommended ocular screening of patients after treatment. Patients need baseline vision and assessment (ideally with SD-OCT) with repeat examination at 3 to 4 months. Patients should be warned to look for blurred vision or metamorphopsia. Patients with a history of diabetes or uveitis are at a higher risk and should be informed of this at initiation of treatment (not an absolute contraindication to treatment). Fingolimod initiation should be also ideally be avoided within 3 months of intraocular surgery

due to the increased risk of post operative oedema and difficulty differentiating this from drug toxicity.

Although the numbers of patients on Fingolimod in many centers is low there are implications to local services. A study looking at adherence to NICE screening guidelines in the neuro-ophthalmology clinics at the National Hospital for Neurology and Neurosurgery reported that these patients accounted for 9% of all new referrals over the study period.

Topiramate was originally used as an anticonvulsant to treat epilepsy, but is now more frequently used to prevent migraine headaches. It is also increasingly used in idiopathic intracranial hypertension and some other headache syndromes and has been used off-label for weight loss. Systemically it is relatively well tolerated.

A number of ocular adverse effects have been reported most notably ciliochoroidal effusion, which can lead to displacement of the lens-iris anteriorly with induced myopic shift and angle closure with elevated eye pressures. The changes resolve after stopping treatment and can be facilitated with cycloplegic drops (peripheral laser iridotomy is not effective). Fundal changes including maculopathy, choroidal folds and pigmentary changes with visual field loss have also been reported and may be linked to use.

MEK inhibitors are a new promising class of drug, which inhibit the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), also known as the MEK enzyme. This pathway is overactive in some cancers in particular metastatic melanoma with BRAF gene mutations. Treatment has revolutionized treatment and prolonged survival in many of these cases but a significant number of ocular and in particular retinal adverse effects have been reported including uveitis, atypical central serous type retinopathy and multiple retinal pigment epithelial detachments. The changes resolve on cessation of treatment.

Retigabine is a novel anticonvulsant used as an adjunctive treatment for partial epilepsy. Treatment can cause blue skin discolouration and pigmentary retinopathy and more recently maculopathy with features of acquired vitelliform type maculopathy. The manufacturer GlaxoSmithKline have recommended macular OCT and routine eye monitoring at baseline and at least every 6 months for patients taking retigabine.

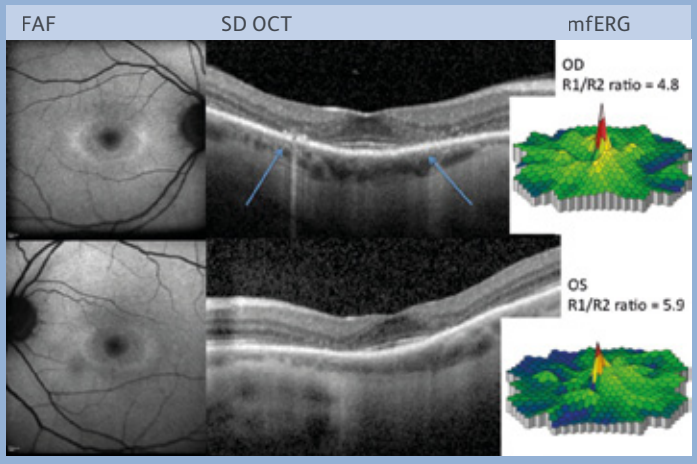

Figure 1: Typical hydroxychloroquine retinopathy changes on autofluorescence, SD OCT and multifocal ERG (Asymptomatic patient on HCQ > 5 years)

Miscellaneous

A number of drugs including the phenothiazines (most commonly Thioridazine which is now less commonly used), Clofazamine, Deforoxamine, Chemotherapeutic agents (e.g. cisplastin and carmustine, Denieleukin diftitox), and Didanosine (reverse transcriptase inhibitor used to treat HIV usually as part of highly active anti retroviral treatment) can also disrupt the RPE leading to pigmentary type retinal changes which can mimic inherited retinopathies and can be associated with vision field loss and electrodiagnostic abnormalities.

Patients typically do not volunteer which medications they are on and rarely link medications to visual problems. Many of the toxic retinal changes are irreversible, initially asymptomatic, and timely diagnosis and cessation of treatment can prevent vision loss.

Conclusions

Retinal toxicity of certain medications can lead to irreversible vision loss and hence early diagnosis is crucial. It is important to get a detailed history and list of medications and check against reported adverse events if they may be predisposing, causing or contributing to observed retinal changes.

Modern retinal imaging (SD OCT, Autofluorescence) and functional measures (mfERG, microperimetry) can help identify early retinal toxicity. Ophthalmology departments would need to establish access to recommended screening modalities for retinal toxicities in early stages.

Table 1:

Screening modality	Findings
Humphrey 10-2 visual fields (24-2 recommended in Asians as have more peripheral loss)	Paracentral scotoma between 2-6 degrees of fixation
Spectral Domain Optical Coherence Tomography (SD-OCT)	Loss of the parafoveal photoreceptor inner segment/ outer segment with central foveal sparing. Posterior displacement of the overlying inner retinal layers described as 'the flying saucer sign'
Fundus auto-fluorescence (FAF)	Fine peri-central ring of increased autofluorescence, progressing to mottling and generalised loss of pigment epithelium
Multi-focal Electroretinogram (mfERG)	Increased R1/R2 ring ratio (may be more sensitive than FAF and can precede VF changes)
Fundus examination Amsler grid Colour testing Time domain OCT Fluorescein angiography Full field ERG or electroculogram (EOG)	Tests NOT recommended/ sensitive for screening as typically normal in early potentially preventable retinopathy

Visit **www.rcophth.ac.uk/standards-publications-research/focus-articles/** for references relating to this Focus feature