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Editorial

Modern management of antimalarial usage and retinopathy

Over the past few years, a number of studies have provided new information about the proper dosage, relative risk, fundus distribution, and screening guidelines for the use of hydroxychloroquine (HCQ) and chloroquine (CQ). These are excellent drugs for systemic lupus erythematosis (SLE) and rheumatoid diseases, but excessive and prolonged intake can cause irreversible retinopathy. However, the ocular safety profile is very good if the drugs are used wisely. Current standards of care are presented in the 2016 revision of the American Academy of Ophthalmology recommendations for screening, which illustrates findings and is available Open Access.[1] This editorial summarizes the key information.

Dose and duration of use

The most important new study was an analysis of almost 2500 patients using HCQ long-term.[2] The results showed that risk is a balance of daily dose and duration of use, and risk rises markedly with over-dosage (>5 mg/kg real weight) or durations beyond 10 years. For daily dose below 5 mg/kg real weight, prevalence of toxicity was <1% after 5 years, <2% after 10 years, but rose to 20% after 20 years. However, once a patient has been screened and is known to be normal, the incremental risk of developing toxicity in the ensuing year is much lower (only 4% after 20 years). There are two other major risk factors that accelerate toxicity: renal disease (since the drugs are largely cleared by the kidneys) and use of the breast cancer drug tamoxifen.

Dose measurement and adjustment

Dose should now be measured in real rather than ideal weight. The evidence for ideal weight (used in past years) was actually rather weak, and human demographics show that real weight gives more accurate assessment of risk over all body types. Bottom line: stay below 5 mg/kg real weight for HCQ, and an estimated 2.3 mg/kg for CQ. These drugs do not come in small tablets, and even a single CQ tablet is too big for most women. However, blood levels stabilize slowly, and one can vary the dose on different days to achieve the desired intake for a week.

Fundus distribution

Another important new finding was that people of Asian descent (including Filipinos) often show a different pattern of early fundus damage from those of Caucasian descent (including the Middle East and India).[3] Instead of a parafoveal bull's eye, Asians may show damage out near the vascular arcades.

Screening schedule

Toxicity cannot be prevented, but it can be detected before most patients will notice scotomas and before any loss of central vision. In the first year of use, patients should have a good fundus exam to rule significant macular degeneration, retinal dystrophy, or field loss (such as glaucoma) that might interfere with diagnosis. If that exam is unremarkable (e.g. a few hard drusen are not a contraindication), and there are no major risk factors (see above), then the risk of toxicity is so low in the first 5 years that annual screening can be deferred until that time.

Screening—visual fields

Probably the most sensitive screening tests are central automated fields, and I suggest using the SITA protocol that provides statistical pattern deviation plots. A 10-2 field is critical for Caucasians, as 24-2 patterns do not have sufficient parafoveal test points. A 24-2 field can be added for Asians, and with the SITA Fast protocol one can do both a 10-2 and 24-2 field in the time for one standard 10-2. Learn to recognize the pattern of early losses 2–5 deg from center, usually superotemporal or superonasal.

Screening—SD-OCT

Not all patients are good field takers, and the most specific screening test is the SD-OCT. Ideally, annual screening should do *both* fields and SD-OCT (or at least add the SD-OCT at

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occasional intervals). The goal of SD-OCT exams is to recognize in the parafovea (or arcade region in many Asian eyes) early thinning of the outer nuclear layer, and early break up of the ellipsoid zone (EZ) line. ETDRS thickness plots often show abnormal thinning in the parafovea, and the OCT cross-sections may have a "sombrero" or "flying saucer" appearance with normal appearance in the fovea, and again beyond the ring of damage.

Toxicity and progression

These changes are all recognizable before damage to the retinal pigment epithelium (RPE). Fundus examination is *not* sensitive enough for screening HCQ and should never be relied upon. If pathology is detected at an early stage, before RPE damage, there is little progression after stopping the drug.[4] However, once RPE changes are visible, retinal damage may progress and expand for many years after the drug is stopped, and eventually destroy the fovea. Early detection is critical.

Stoppage of drugs

HCQ or CQ should be stopped once toxicity is *clearly* identified. But keep in mind that these drugs are very useful medically, and should not be stopped for questionable or borderline findings. Retinopathy does not develop that fast, and there is always time to bring the patient back in a few months for re-testing to see whether ambiguous findings are consistent, or for the addition of confirmatory studies such as multifocal electroretinography (mfERG) or fundus autofluorescence (FAF). The risk to vision remains low as long as the foveal anatomy is good, and the RPE is not involved.

Proper dose (<5 mg/kg of HCQ) is the key to minimizing toxicity, and both patients and rheumatologists, need to be educated about dose and about the importance of regular annual screening after the first 5 years (as well as high risk if the kidneys fail). With proper management these are remarkably safe drugs, and our job as ophthalmologists is to show how they can be safely maintained as well as to safeguard vision over the long run.

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