Case 3

Let’s deal with our next case. A 31 year old Hispanic male comes in looking for a second opinion on a uveitis. He’d gone to his primary care physician with a painful red eye. The doctor had diagnosed him with uveitis, but really wanted him to see an eye care professional to confirm that was what it really was. Medication-wise, the patient is only on Omega-3 supplements.

His VA is 20/30 in both eyes, and after refraction we get him to 20/25+. We find a bunch of cyl there. Entrance skills were unremarkable, but as the Intern was working this patient up, they decided to do confrontation visual fields and realized there was a significant reduction in confrontation visual fields in both eyes.

Slit lamp shows that there is some injection in that right eye. The anterior chamber is deep and quiet, with no cells or flare noted in either eye. Pressures are 12 and 11. I will show you the fundus photos in just a second.

Because of that reduced confrontational visual fields, the intern decided that he wanted to do a visual field on the patient. We did a Humphrey Visual Field on the patient, and Figure 1 shows our results. Right eye and left eye obviously have significantly reduced visual fields, looking closely at the pattern standard deviation in both eyes.

In looking at these visual fields, I want you to quantify for me, or give me an estimation of how much continuous visual field this patient has.

1. Approximately, how much continuous visual field does the patient have remaining centrally in each eye?
   a. 6 degrees
   b. 12 degrees
   c. 18 degrees
   d. 24 degrees
Let’s see what the doctors said when this was last polled. The correct answer is 3. Looking at the visual fields, remember that each subunit is approximately 6 degrees worth of visual field. Figure 2 shows boxes around the usable visual fields. You are getting about 3 in the left eye, and just a little bit more than 3 in the right eye, so each of those being 6, we have about 18 to 20 degrees worth of visual field. In Oregon, you need 120 degrees of continuous visual field to qualify for a driver’s license, so unfortunately we had to file the forms to have the patient’s driver’s license revoked. Obviously this is devastating for a 31 year old who came in, interestingly enough, with his
cousin who had two kids with her, and after showing the patient and her the patient’s visual fields, she actually called her husband to drive her home. Again, very devastating to that patient to have to have his driver’s license revoked.

Here’s our next question. I’m ultimately thinking you probably know what this condition is, but:

2. Which of the following are you NOT expecting to find on the fundus?
   a. Waxy pallor to the ONH
   b. Bone spicules
   c. Vertically elongated ONH cupping
   d. Arteriolar construction (reduced A/V ratio)

(scroll down for answer)

The correct answer is 3 – the vertically elongated C/D ratio, this is RP. The things we expect to see with RP are waxy pallor to the optic nerve, A/V constriction, and bone spicules. Be a little bit careful with bone spicules, though, as we tend to associate that with RP, but there is also RP Sans Pigmentosa, where the patient doesn’t have the pigmented bone spicules. Thus, that pigmentation is not essential to the diagnosis of RP.

Figure 3 is the fundus photos. They are not the best photos, but you can see the bone spicules towards the periphery, a waxy pallor to the optic nerve, and a reduced A/V ratio in this patient.

This patient had received an eye exam about 7 years previously, and had been told that he had some problem with his peripheral vision, but wasn’t told what condition it was. Unfortunately, we had to tell him that he had RP, and that this might still be progressive on him, and had to file to have his driver’s license revoked. He went through the whole bargaining process, asking if he could take a pill, undergo surgery, and was truly devastated.
On to our fourth case: We have a 33 year old Hispanic female that presents with a painful red right eye that started a few days ago. There is a deep, boring pain. She has tried Visine, but that hasn’t helped, surprisingly enough. All patients seem to try Visine, and it doesn’t ever solve their problem, but we do have to remember with that Visine that the redness that the patient is presenting with may not be as red as the patient’s eye actually is. We need to make sure to take that into consideration that the patient is on Visine.

**Case: Gonzalez**

- 33 HF presents with a painful, red right eye
  - Started a couple of days ago, deep boring pain
  - Has tried Visine but hasn’t helped the redness
- PMHx: patient reports she experiences joint pain and has been “diagnosed” with rheumatoid arthritis for 3 years
  - Takes Celebrex for the joint pain
  - Patient reports she occasionally gets a skin rash when she is outdoors in the sun
- POHx: unremarkable
- PMHx: mother has rheumatoid arthritis
She reports that she experiences joint pain, and has been
diagnosed with RA. I put in ‘air quotes’ that she was diagnosed
with RA because we are not really too sure how she was
diagnosed with RA, as the patient has only told us that she has
joint pain, has been diagnosed with RA, and is taking Celebrex.
She also reports that she occasionally gets a skin rash when
she goes outside in the sun.

Ocular history is unremarkable. As far as her medical history
goes, her mother does have RA.

Her vision is 20/30 in the affected eye, 20/20 in the left. For entrance skills, her pupils are
unremarkable, confrontation visual fields are full to finger count (FTFC), EOM’s are full range of motion.
Her blood pressure is 130/85.

On slit lamp exam, we can see in Figure 4 (top) that her eye is very red and injected. This isn’t our
patient’s eye, but it looked very similar to how her eye appeared with this deep injection. The
anterior chamber showed a 2+ cell, plus a mild flare. Her pressures are 16 and 16.

The bottom picture in Figure 4 is our patient’s
fundus photo. What we see here are some cotton
wool spots (CWS).

I want you to think, based on this patient who is a
33 year old Hispanic female. With CWS in a red
eye, where are those cotton wool spots coming from? Some of us would think either diabetes or
hypertension, but looking at her blood pressure, it’s certainly not elevated to the point to be
considering that she’s got hypertension. If you
look at her fundus, you notice that there are really
no other changes to her fundus beyond the CWS.
Cotton wool spots are an indication of ischemia. If
we are looking for hypertension or diabetes, we
would expect either changes in the A/V ratio, 90
degree crossings, nicking, or with diabetes dot-blot
hemorrhages or microaneurysms. As we are not
seeing any of those on the fundus, that for me excludes those as possible findings. We really need to
think, “Why does this patient have cotton wool spots when she’s young and doesn’t have high blood
pressure or diabetes?”
We have to start thinking that this may be an autoimmune disease. Conditions like Lupus can certainly cause findings like this. RA doesn’t result in CWS, but Lupus does, and this patient fits more of the demographic for Lupus than she does that for RA. RA tends to be a little bit older, certainly female and our patient does have that family history, but primarily RA affects more Caucasian females than African-American or Hispanic. Lupus again fits that African-American/Hispanic demographic. Also it fits with a younger female. Now we go back and re-consider that skin rash that she gets when she goes out in the sun, and we have a much stronger indication for Lupus than we do for RA.

Back to that lesion that is on the patient’s eye. What would you diagnose that patient’s lesion as?

1. What is the “nodular” lesion on the patient’s right eye?
   a. Pinguecula
   b. Episcleritis
   c. Scleritis
   d. Scleromalacia perforans

(Scroll down for the answer)

The correct answer is 3, scleritis. Looking at a pinguecula, certainly you can get that redness and irritation that goes along with it, but you’re not going to get an anterior chamber reaction or that deep, boring pain. The same thing goes along with an episcleritis – you will not get an anterior chamber reaction, and you are not likely to get the deep, boring pain. Scleromalacia perforans is not a bad answer, particularly for someone with longstanding RA. That is, in fact, a pathognomonic sign for RA. Ultimately, it’s usually long-standing RA, and our patient does not have RA.

We sent this patient off for more of a workup, and she was diagnosed with Lupus. Our screening test for Lupus is ANA, antinuclear antibodies, and it’s a great screening test for Lupus. 99% of patients who have
Lupus are going to test positive for ANA, so you have less than 1% chance of being diagnosed with Lupus and testing negative. That’s our first screening test, then we go on to do anti-DNA antibodies. They also do what’s called Compliment C4 levels. Those all confirm the diagnosis of Lupus.

She also had RF levels tested for rheumatoid factor, and also joint x-rays done. Those are diagnostic for Rheumatoid Arthritis, looking at what is being affected in RA: your fingers and toes initially, then it moves towards the trunk. She had tests done to look at her peripheral joints, and they found no changes in her peripheral joints.

She was taken off of her Celebrex and was put on Plaquenil (hydroxychloroquine) 400 mg PO QD. When she was tested, they noted that she had changes to other organs in her body, not just her scleritis, but she had two or three other organs that were affected.

The typical treatment for scleritis is oral NSAIDs. Interestingly enough, she is already on Celebrex, so why wasn’t the Celebrex working for her? Celebrex is a COX2 inhibitor, and you do need the actual COX1 enzyme inhibition to treat scleritis. Thus, something like indomethacin or ibuprofen would be a much better treatment option for her than the Celebrex. After you do the oral NSAIDs, then the next option is systemic steroids, and then we move to immunosuppressive agents. Because this patient already had changes to other organs, they bypassed the steroids and went directly to immunosuppressive agents. The patient already has a sight-threatening condition, and her other organs are already affected.

As I said before, she was put on the Plaquenil 400 mg to manage her joint pain, and any skin lesions that showed up. Plaquenil is great for managing pain – it does a great job of increasing mobility and function for patients. It has a mild DMARD (disease-modifying antirheumatic drug) effect, so if a patient does have RA, or in this case Lupus, it can mildly slow down joint destruction. What it really does well is increases mobility and function in patients.

I wanted to talk to you a little bit about the new screening guidelines for Plaquenil. The screening guidelines changed almost three years ago now, and I think it’s important for you to know the new guidelines. OCT becomes especially important in those new guidelines.

The usual dose for Plaquenil is 200-400 mg per day. It takes 2-4 months for the drug to take effect. We are really not seeing people on doses over 400 mg anymore. The only time we see someone outside of this dosing range is occasionally when we get someone on less than 200 mg, if someone tends to be really, really tiny. Plaquenil loves pigmented tissue, so any tissue that is pigmented will have more of the drug accumulated in that tissue. This is why we get concerned about the RPE and the photoreceptors, because a buildup of Plaquenil can cause a toxic response in that tissue.

Plaquenil has a really slow excretion rate out of the body. We used to think that it would accumulate in adipose tissue, but we now know that it doesn’t. It just takes a really long time for the body to process that medication through. There have been reports of continuing secondary changes due to Plaquenil two to five years after stopping the medication, so it takes a long time for the body to process that medication out.
Here is your next question.

2. Based off of the following OCT’s, which OCT would you tend to think is a patient undergoing hydroxychloroquine or Plaquenil toxicity?

(Scroll down for answer)

The correct answer is 3. This first image is the development of a neovascular net. If I remember correctly, this was due to the patient having ocular histoplasmosis syndrome. Image number two is a full-thickness macular hole. Image three is Plaquenil. Remember that Plaquenil tends to affect the paracentral area, which is what we are seeing here, as well as a disruption to the RPE. We are actually seeing the beams from the OCT penetrating down into the choroid. Image number four is a patient with AMD with drusen that are forming.
With Plaquenil, and all the antimalarials, especially chloroquine, we are concerned about the Whorl Keratopathy a patient can get. (Fig 5) Both chloroquine and hydroxychloroquine can give you those RPE changes shown in Figure 6, as well as the development of a Whorl Keratopathy.

If you have a patient who shows up and has a Whorl Keratopathy but is not on any medications, what condition are you concerned about for your patient? The answer is Fabry’s Disease. The Whorl Keratopathy shows up very early in Fabry’s Disease – it shows up in their early teens. Optometrists tend to be the professionals that diagnose Fabry’s Disease the earliest because that Whorl Keratopathy shows up so early. Genzyme is the company that has a medication for this. They are really hitting hard in optometry to make sure that optometrists recognize this sign because optometrists tend to find this condition early, and it’s important that patients get treatment for this as early as possible.

The original screening guidelines for Plaquenil came out in 2002. The new recommendations came out in March of 2011. In those new guidelines, they look at all the reports out there for toxicity issues, prevalence, incidence, and the rest of it. We found that the prevalence is probably a little higher than we thought. This is still a rare condition, but with the addition of having newer technologies, I think we’re going to find more and more patients who are having toxicity. I’m not a big fan of you having to remember numbers, but there is one number I want you to remember, and that is 1%. A patient’s risk of toxicity approaches 1% in those patients who exceed 5 years of exposure. Plaquenil is considered as a cumulative dose, so we are looking at 5 years’ exposure and above. The toxicity risk goes a little bit higher after the 5 year mark, but still covers about 1% of patients.

So, do you think the patient’s primary care physician or rheumatologist has told the patient that their risk of toxicity is 1%? No – what they’ve told the patient is that they want the patient to be screened before starting the medication, then screened every 6 months to a year after that. Also, they tell the patients that they have the potential to go blind. Ultimately, I think it’s really important for us to tell our patients that this is a relatively safe medication. If you are going to Vegas, and you had a 99% chance that you were going to win, you would certainly take those odds. Thus, I think it’s important that we
communicate to our patients that their overall risk is 1% of running into problems. Yes, we are still going to monitor them very closely and if we see any changes, we can do something about that, but their overall risk is still very low.

Taking a look at all of the different tests that are listed, all of the following tests were considered acceptable tests under the original screening guidelines. Under the new screening guidelines, which of the following tests are still considered acceptable tests for screening for Plaquenil Maculopathy?

3. Under the new screening guidelines for hydroxychloroquine retinopathy, which of the following is still considered an acceptable screening test?
   a. Amsler grid
   b. 10-2 visual field
   c. Time domain OCT (e.g. Stratus)
   d. Color vision testing
   e. A, B, C
   f. All of the above are still acceptable screening tests

(Scroll down for the correct answer)

The correct answer is #2. This group of polled doctors did not necessarily do very well on this question. The only test that is still an acceptable test from this list is the 10-2 visual field. The new screening guidelines really look at the 10-2 visual field, in addition to one of the following three:

- Multifocal ERG
- Spectral domain OCT
- Fundus Autofluorescence

These are our new screening guidelines. Looking back at the tests offered in the above question, Amsler Grid is no longer considered an acceptable test. It is not equivalent to a 10-2 visual field. Your Time
domain OCT is still a part of the guideline, but it’s not the Stratus anymore, it’s one of your SD-OCT’s. Color vision can certainly be done, but it’s not considered an appropriate screening test anymore.

Revised Recommendations on Screening for Retinopathy

- Amsler grid testing removed as an acceptable screening technique
  - NOT equivalent to threshold VF testing
- Strongly advised that 10-2 VF screening be supplemented with sensitive objective tests such as:
  - Multifocal ERG
  - Spectral domain OCT
  - Fundus autofluorescence

To the left is a breakdown of the new screening guidelines for Plaquenil Maculopathy. You need a 10-2 visual field, in addition to one of the three objective tests listed. Those are the new guidelines.

In respect to your visual field, it’s still the 10-2 visual field, which is the same as before, but now it’s also a white-on-white visual field. You don’t have to do any of the red stimuli anymore.

Now you will start your screening, before the patient starts taking their medication, and really our concern level is at 5 years and above. At that point, we get a cumulative dose of 1000 grams, and at that point we get really concerned whether or not patients will start running into toxicity issues. When you do your screening, you will find what their baseline is, and hopefully there are no defects in their 10-2 visual field. Then, say that they come back in 6 years, and at that time there is a paracentral scotoma that shows up. That is usually the very first type of visual field defect we tend to see in Plaquenil Toxicity – that paracentral scotoma. If they have a defect in the paracentral zone, you need to repeat that visual field within the next couple of weeks, because you don’t ever want to say, “Oh, this is just you taking that test.” We do this all the time when we do visual fields, such as for glaucoma. With glaucoma, patients should not be missing any spots because that is their central vision. You need to repeat that visual field, and if the defect is repeatable, then that needs to be reported to the rheumatologist or primary care provider.

Yes, a repeatable visual field defect could be an indication of toxicity, but we should not tell the patient they are going to come off of their medication, because sometimes that doesn’t happen. Remember that Plaquenil is really good for increasing the mobility and function of patients. Say your patient is 85 years old. If you take them off of Plaquenil, what is the alternative for them getting around? It would probably be a steroid, and we know there are lots of complications to that. Thus, make sure you indicate to the patient that you’re going to talk to their primary care physician, or their rheumatologist, and then there will be a discussion between the patient and their managing physician whether or not they come off of that medication.

Paracentral scotomas (Fig 7) are those first field defects we tend to see in Plaquenil Toxicity patients.
With the SD-OCT, and I will show you those images, what we are looking for is changes in the PIL (Photoreceptor Integrity Line). That is the junction between the inner and outer photoreceptor segments. We do not see that on the Time domain OCT because that didn’t give us enough detail. But on the SD-OCT, we find that this junction, although it is not a true junction, is an artifact that is being picked up. With the PIL, it is very important for us to look to see if the PIL is intact or not. If it is intact, then patients tend to have good vision. If the PIL is not intact, they tend to not have good vision.

The other objective test we can look at is Fundus Autofluorescence. We know that as there’s damage to the RPE cells, there is a production of Lipofuscin, and that Lipofuscin tends to auto fluoresce. An increase in the amount of fluorescence indicates an increase in the amount of damage to the RPE cells. As patients undergo Plaquenil Toxicity, they get damage to the RPE cells, more fluorescence, and more damage, until eventually you get the destruction of the RPE cells and no fluorescence.

A classical diagnosis can come from Multifocal-ERG (MF-ERG), which gives you not only a subjective, but an objective assessment as to what’s going on in the retina, as well. There is a lot of difficulty in obtaining a MF-ERG. There are now more commercial products out there that are making access to that more readily available, but still not quite as readily available as your SD-OCT.

Figure 8 shows a picture of an SD-OCT. Again, we want to look at it in the grey scale, but the article only had it in the colored images. In the upper right, we have our MF-ERG, with our foveal peak. The upper left shows the Time domain-OCT. You can see in the TD-OCT, we just don’t get the detail that we do in our SD-OCT.

What we are looking for in the SD-OCT is changes in the Outer Nuclear Layer, the white band that is marked in the picture. In addition we want to look at the (top red) PIL line. Figure 8 is our normal retina. Figure 9 shows us the results we get on an abnormal retina.
Figure 8: OCT, ERG image of a normal retina

Figure 9: Test results from a patient with mild Plaquenil Toxicity
The upper right hand corner on Fig 9 shows us that we are starting to get paracentral scotomas that are starting to form. We still have a foveal peak on the MF-ERG because remember in Plaquenil Toxicity, the fovea is affected last. The patient still has 20/20 vision, but we have a suppressed area surrounding the foveal peak.

Going down to our OCT, we can see a very reduced PIL line, that is only remaining under the fovea, which is why our patient still has 20/20 vision, but it's disappeared past there. We also have a much reduced Outer Nuclear Layer.

Figure 10: Advanced Bull’s Eye Maculopathy

Figure 10 shows us advanced Plaquenil Toxicity. We have dense paracentral as well as central scotomas in our visual field. Looking at the fundus photo, we have some visual atrophy that we call Bull’s Eye Maculopathy. Our MF-ERG has a flattened foveal peak, with it pretty much gone. Looking at our OCT, we are really only left with a tiny remnant of the PIL. We have no Outer Nuclear Layer left, and now it looks like the image I showed you in that question before, where now we have the paracentral defects in the RPE and the beams from the OCT are actually penetrating down into the choroid.

I want you to take a look at Figures 8 through 10 again, because I think it’s very important that you know and understand what you are looking at.
In the new guidelines, it’s important to note that looking at the fundus is not part of the new guidelines. (Table 1) Your risk goes up from duration of use, so 5 years or greater, and a cumulative dose of 1000 grams or more. If you have a patient who is taking more than 400 mg/day, that puts them at a higher risk. Any patient who is elderly, although the report doesn’t really classify what ‘elderly’ is, I tend to say 65 years old and above, but I will let you come up with your own definition. Many of my interns seem to think that I am elderly. Any systemic disease that results in a decreased ability for the patient to process the drugs through the system puts the patient at a higher risk, such as kidney or liver disease.

The other one that I thought was interesting that they included in the report was any ocular disease. Remember that patients can have other concurrent conditions going on with the retina. Say, for example, that your patient has Macular Degeneration. They’ve already got a disrupted function of the retina, and potentially already have Lipofuscin that is being produced. In this case, I would think that Fundus Autofluorescence would not be the best test for you to use, because how do you differentiate between the fluorescence that is coming from the drusen compared to that coming from the Plaquinil? Any of the fundus conditions put the patient at higher risk, and ultimately the patient’s rheumatologist and/or primary care physician probably doesn’t know that they have drusen, diabetic macular edema, etc. Those changes in the fundus could probably predispose that patient to greater changes in the fundus due to Plaquinil, and in addition to the fact that it might mask other issues that may be going on. Remember that the criterion for Plaquenil Toxicity is your SD-OCT, in addition to your 10-2 visual field.

I think that’s about it from me. I hope that from this presentation you got an indication of how important the imaging equipment is, not only in looking for glaucoma and progression of glaucoma, but also looking for your retinal conditions. I know that all of you are seeing patients who are on Plaquinil, and under the new guidelines, you need to be using an SD-OCT and a 10-2 visual field. If you are not doing it, you are not following the new guidelines. I want you to have access to this equipment, as well as an understanding of the importance of this technology for your practice.

I appreciate your time, and hope that I have answered all of your questions.