What can visual caregivers expect with patients treated for SARS-CoV-2? An analysis of ongoing clinical trials and ocular side effects

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Introduction

Coronavirus disease 2019 (COVID-19) has been labelled as a Public Health Emergency of International Concern by the WHO. Nowadays, there is no known specific, effective, proven, pharmacological treatment.(1) The international health authorities’ efforts are focused on rapid diagnosis and isolation of patients and on the search for therapies able to counter the severe effects of the disease. Different drugs are being investigated,(2) and evidence of their safety, efficacy and effectiveness should be generated quickly,(3–6) according to the seriousness of the possible consequences of the virus.(7)

Used worldwide for over 70 years, Chloroquine (CQ) and Hydroxychloroquine (HCQ) are two antimalarial agents that have been proposed as a treatment for COVID-19, with toxic retinopathy being their most undesirable ocular side effect.(8–10) HCQ has largely supplanted CQ lately, with the added advantage of lower toxicity and higher effectiveness.(8,11) At present, HCQ is broadly used in the treatment of autoimmune diseases. However, the margin between the therapeutic and toxic doses is narrow and, therefore, its use should be subject to strict rules.(12,13) For CQ analogues, relatively few adverse effects at the standard doses have been described.(13) Withal, acute toxicity can be most frequently encountered when therapeutic or high doses are administered rapidly by parenteral routes.(14)

Public Health Emergencies require fast clinical decision-making, especially in the first phases of the pandemic. Evidence-based medicine should always be advocated to guide clinical decisions, unfortunately, within the emergency context, the dose calculations may not have been adjusted as required, or the ophthalmological screening recommendation previous to treatment might have been overlooked.

This review aims to assess the ocular adverse effects of the drugs used in the current treatment of patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), according to the recommendations published by the WHO and to evaluate the doses of CQ and HCQ that are being applied in ongoing clinical trials (CT). The results collected will allow visual caregivers to anticipate upcoming issues and hopefully be one step ahead of this pandemic.

Methods

The list of therapeutics recommended for the treatment of SARS-CoV-2 published by the WHO(15) was the starting point of our research (Table 1). After checking their Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval status, repurposed drugs and investigational products were identified. Their individual ocular side effects were analyzed. Only drugs that could have a significant visual impact in the medium/long term, were considered to create the search strategies. Detailed search strategies on their side effects were
conducted in EMBASE, MEDLINE, SCOPUS and WOS Core Collection in April 2020. The same approach, including chloroquine, adverse effects, poisoning, and toxicity, was adapted to the different databases. Only reviews that have addressed the possible ocular side effects of the selected drugs, written in English, French or Spanish language and published in the last 5 years were considered.

Moreover, two open access CT databases were consulted: the database of clinical studies conducted worldwide [https://clinicaltrials.gov/] and, taking into account the pandemic outbreak of COVID-19 arose in Wuhan, China,(7,16) the Chinese registry of clinical trials [http://www.chictr.org.cn/]. CQ was used as a search term and a date restriction from November 2019 to 21st April 2020 applied. Cancelled CT were excluded. We analysed the proposed doses, related to treatment, prevention or prophylaxis, the duration, the routes of administration and their ophthalmological considerations if any. The total cumulative dose was calculated where possible. CTs were classified into CQ (when CQ was considered in one arm of the CT), HCQ (if HCQ was considered in one arm of the CT), BOTH DRUGS (both drugs were considered), CQ DOSE (different doses of CQ), HCQ DOSE (different doses of HCQ) and those related to prevention or prophylaxis. The original articles already published on this topic were also reviewed.

In the end, 22 reviews were included, all of which confirmed that CQ and HCQ may have ocular side effects. Figure 1 summarizes the flow relative to both search strategies.

**Results**

**COVID-19 and CQ derivatives**

More than 3 million SARS-CoV-2 cases have been reported in 185 countries to date and, according to the International Coalition of Medicines Regulatory Authorities (ICMRA) report published on 2nd April 2020, no specific treatment has yet demonstrated efficacy.(1) Visual caregivers must be informed about the possible ocular side effects of the given treatments. From the lists of drugs considered for the treatment of SARS-CoV-2, and summarized in Table 1, CQ and HCQ seem to be the only ones that could have a significant visual impact in the medium/long term,(15) with retinal damage being their most threatening ocular consequence.

These drugs were originally intended for malaria treatment and prophylaxis, but their clinical indications keep growing.(10,17,18) Recently, early clinical observations reported their potential benefit in SARS-CoV-2 patients, with a decrease in viral load and carriage duration.(19,20)

Therapeutic properties of CQ and HCQ are not fully understood yet,(21) but they are considered drugs with anti-inflammatory, immunomodulating, anti-infective, antithrombotic, and metabolic properties.(17) They have an antiproliferative effect on T cells and reduce the production of pro-
inflammatory cytokines, such as Interferon-C, interleukin (IL)-1, IL-6, and IL-2. Moreover, CQ stimulates the production of nitric oxide in human endothelial cells, a putative mechanism explaining partly its antiproliferative effect.\(^{(17)}\) Their benefit in COVID-19 may be mainly attributed to their broad-spectrum antiviral effects;\(^{(22–24)}\) whether their immunomodulatory properties also play a role remains yet unknown.\(^{(22)}\)

**Ocular Impact of CQ and HCQ**

CQ and HCQ are melanotropic drugs, i.e. they accumulate mainly in the structures containing melanin. Within the eye, they create deposits in the iris, ciliary body, retinal pigment epithelium (RPE) and the choroid,\(^{(18,25)}\) and their effects can be divided into reversible and irreversible.

**Reversible ocular side effects**

Deposition of CQ/HCQ in the cornea can appear within the first 2-3 weeks of treatment. Intraepithelial deposits (corneal verticillate or vortex keratopathy), can be observed in 90% of the patients receiving CQ and in approximately 5% of those treated with HCQ. They are not associated with visual loss and are not an indication to stop the treatment, although patients might report symptoms (e.g. halos, photosensitivity). Deposits are usually reversible on drug discontinuation within 6-8 weeks without any residual corneal damage regardless of the duration of therapy.\(^{(10,26–28)}\)

Difficulty with accommodation may occur soon after administration of CQ and probably also with HCQ. These symptoms may disappear despite the continuation of therapy or after reduction of the dose.\(^{(27,28)}\) Finally, temporary treatment-induced diplopia has also been described in the early phases.\(^{(29)}\)

**Irreversible ocular side effects**

Retinopathy caused by HCQ was first described in 1963.\(^{(9)}\) Traditionally, a ring of depigmentation in the parafovea termed “Bull’s eye retinopathy” was considered the distinctive sign of CQ retinopathy.\(^{(28)}\) However, novel detection methods have deepened our understanding of the early stages, typically asymptomatic and not detectable by fundoscopic examination or visual acuity assessments.

Early studies on the incidence of HCQ or CQ retinopathy were based on patients with severe visual field loss or Bull’s Eye on fundoscopy, so the true incidence of retinopathy was underreported,\(^{(28)}\) and thought to be around 1%.\(^{(9)}\) In 2014, Melles and Marmor found a rate of 7.5%.\(^{(30)}\)

Animal experiments have shown that pathologic changes related to toxic retinopathy occur in all layers of the neural retina; the photoreceptors and ganglion cells are the first to be
affected. In clinical practice, the primary damage to photoreceptors is followed by a secondary disruption of the RPE in the later phases, as the outer nuclear layer degenerates.

The first signs of retinopathy (premaculopathy) are subtle changes at the macula, with pigmentary stippling. Loss of fundus image, ringed foci discolouration and the loss of foveal reflex have been described in this phase, as well as red vision and visual field loss to red test object only. Patients are normally asymptomatic since central fixation is preserved and recovery in this early stage is still possible with the cessation of the treatment.

Early maculopathy is characterized by patchy damage within the parafoveal zone and modest visual acuity and visual field loss. Moderate stage presented a 50–100% parafoveal ring of damage and marked thinning of the inner parafoveal retina on SD-OCT before evidence of structural RPE damage. If the retinopathy progresses, different pigmentary patterns can be observed, with no known correlation between the anatomic features of the retina and the pattern of damage. These patterns are similar and bilateral in both CQ and HCQ, but they are less common with HCQ. A Bull’s Eye lesion in the macula may develop and is characterized by an irregular foveolar island of pigment surrounded by a depigmented zone of RPE atrophy, which is itself encircled by a hyperpigmented ring. In the final stage, widespread RPE atrophy surrounds the fovea. The atrophy of the RPE cells may be complicated by secondary cystoid macular oedema, epiretinal membrane and other sequelae.

Damage in the macular area may cause peripheral field narrowing or paracentral scotomas and patients may have trouble reading, although they can keep good central vision. Besides photophobia, photopsia and alterations in colour vision, when toxicity affects the fovea, there may be a substantial decrease in visual acuity and/or deterioration in night vision. Severe intoxication might also result in slower pupillary reaction to light, pupillary asymmetry, or afferent pupillary defect.

HCQ/CQ retinopathy in different ethnicities is variable, although not thought to be associated solely to ocular pigmentation. Caucasians generally exhibit a parafoveal pattern (2–6° from the fovea), while Asians frequently manifest an extramacular or pericentral pattern (>8° from the fovea). Black and Hispanic patients demonstrated a predominantly parafoveal distribution of disease.

Once retinopathy is diagnosed, discontinuation of medication is recommended, but progression can continue long after; the persistence of CQ and HCQ tissue deposition is so long that patients may be exposed to their toxic effect months after discontinuation.
Assessment and diagnosis of toxic retinopathy

Before 2014 the risk of CQ/HCQ retinopathy was believed to be low,(30,31) but recent studies have shown that state of the art technology can detect earlier changes e.g. automated 10–2 visual field assessment (VFA), spectral-domain optical coherence tomography (SD-OCT) and multifocal electroretinography (mfERG),(27,31,33) with the last being the most sensitive. Screening alternatives can be found in Table 2.(34,35) However, mfERG is not widely available and requires expertise. Alternatively, VFA is widely available but it is subjective and is known to have considerable variability when retesting the same patient.(28)

The proposed dosage of HCQ/CQ for SARS-CoV-2

Despite the limited evidence available to date,(36–40) some organizations have already recognized the utility of CQ and HCQ (Table 3). Preliminary in vitro results of CQ/HCQ antiviral activity for SARS-CoV-2 have been published.(41–43) The first human trial ever conducted with CQ used in the treatment of COVID-19 was a Chinese study involving more than 100 patients.(20) At present, there are almost 150 CT including these drugs in at least one of their arms of treatment, being mostly the ones in China those with preliminary published results.

Of the 135 interventional CT considered in our study (Supplementary file A), 53% were Phase III and Phase IV trials according to their descriptions in the corresponding databases. Oral administration was specified in 60 CT. Parenteral administration was not indicated in any of the specifications. Merely 48% (65 /135) considered a pre-existing retinal disease as exclusion criteria. However, just one study refers to an eye exam before study entry.

In those studies, classified as CQ (N=18) whose total dose was calculable (N=4), the maximum cumulative dose (MCD) administered was 7000mg (4300 ± 1871 mg) in a period of 9.5 ± 4.8 days. An MCD of 10000 mg of CQ was found in one study that analysed both drugs; 12000 mg was the MCD among the DOSE CQ studies. For those CT classified as HCQ (N=67, dose calculable in 56) the MCD was 18000 mg (4514 ± 2847 mg) within a period of 7.9 ± 3.5 days. None of the DOSE HCQ or BOTH DRUGS studies exceeded this dose.

For those CT related to prevention or prophylaxis (N=36, MCD calculable in 27), 72000 mg was the MCD for HCQ and 22500mg for CQ within a treatment period of 55.1 ± 51.9 days. Typically, the doses were 2-5 times greater than the AAO recommendation (adjusted to weight) (Table 4).
Table 3. Dosage guidelines for CQ and HCQ in treatment of COVID-19

<table>
<thead>
<tr>
<th>STUDY/GUIDELINES/COUNTRY</th>
<th>DOSE (ADULTS)</th>
<th>EXCLUSION CRITERIA</th>
</tr>
</thead>
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<tr>
<td>The Society of Critical Care Medicine and the European Society of Intensive Care Medicine (44)</td>
<td>There is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19 at this point of time</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
| Spanish Agency for the Drugs and Healthcare Products (AEMPS) (45) | Hydroxychloroquine Sulphate: for 5 days:  
• Day 1: Hydroxychloroquine sulphate 400 mg twice daily  
• Days 2nd-5th: Hydroxychloroquine sulphate 200 mg twice daily on days 2-5  
Chloroquine Phosphate: for 5 days:  
• Day 1: 620 mg of chloroquine base followed by a dose of 310 mg chloroquine base twice daily  
• Days 2nd-5th: 310 mg of chloroquine base twice daily | Unknown |
| Italian Society of Infectious and Tropical Diseases (46) | Mild to moderate COVID-19:  
• Lopinavir/ritonavir plus Chloroquine 500 mg twice/day  
• Hydroxychloroquine 200 mg per day for 5-20 days  
Severe or critical COVID-19:  
• Remdesivir plus Chloroquine 500 mg twice daily or  
• Hydroxychloroquine 200 mg per day for 10-20 days | Unknown |
| Haut Conseil de la Santé Publique (HCSP) France (47) | Hydroxychloroquine 600 mg daily for 10 days | A known allergy to HCQ or CQ, retinopathy, G6PD deficiency and QT prolongation |
Clinical guidance for patients with suspected or confirmed COVID-19 in Belgium (48)

Mild/Moderate/Severe COVID-19:
- Hydroxychloroquine 400 mg at diagnosis, 400 mg 12 h later, followed by 200 mg twice daily for 5 days, or
- Chloroquine 600 mg at diagnosis and 300 mg 12 h later followed by 300 mg twice daily for 5 days
- Consider lopinavir 400 mg/ritonavir 100 mg twice daily for 14 days as a second choice only if HCQ and CQ is contraindicated, provided it can be administered within 10 days after onset of symptoms

Critical COVID-19:
- Remdesivir 200 mg loading dose i.v. within 30 min followed by 100 mg a day for 2-10 days
- Hydroxychloroquine is the second option if Remdesivir is unavailable

The Dutch Centre for Disease Control (49)

600 mg of Chloroquine base followed by 300 mg after 12 h on day 1. Then 300 mg twice daily per person on days 2-5

Public Health England (50)

Chloroquine and hydroxychloroquine are not licensed to treat COVID-19 related symptoms or prevent infection. They should only be used for this purpose within a clinical trial.

Centre for Disease Control and Prevention, Atlanta, MICC (51)

URTI plus positive PCR:
- Chloroquine phosphate 500 mg twice daily for 5 days
- Oseltamivir 150 mg twice daily for 5 days

COVID-19 Pneumonia:
- Chloroquine phosphate 500 mg twice daily for 5 days plus Darunavir 800 mg/ Cobicistat 150 mg a day for 15 days

Food and Drug Administration (FDA) (52) Emergency Use Authorization (EUA)

For adults and adolescents who weigh > 50 kg:
- Hydroxychloroquine sulphate 800 milligrams on the first day
- 400 milligrams daily for 4-7 days

Chinese Centre for Disease Control and Prevention (53)

Chloroquine phosphate (for adults (18-65 years old):
- If weight >50kg, 500 mg each time, twice a day for 7 days
- If weight <50kg, 500 mg each time and twice a day on the first and second days, 500 mg each time and once a day for the third to seventh days

CQ is contraindicated in patients with heart disease
It is not recommended to use 3 or more antiviral medications at the same time
| **Central Clinical Task Force, Korea**<sup>(54)</sup> | Moderate to severe COVID-19:  
- Lopinavir 400mg/Ritonavir 100 mg twice daily or  
- Chloroquine 500 mg orally per day or  
- Hydroxychloroquine 400 mg orally per day for 7-10 days | Unknown |
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<tr>
<td><strong>Pan American Health Organization (PAHO)</strong>&lt;sup&gt;(55)&lt;/sup&gt;</td>
<td>There is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19 at this point of time</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
| **Indian Council for Medical Research**<sup>(56)</sup> | For prophylaxis:  
- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks  
- Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 3 weeks | The drug is not recommended for prophylaxis in children under 15 years of age. It is contraindicated in persons with known case of retinopathy, known hypersensitivity to hydroxychloroquine, 4-aminoquinoline compounds |

Discussion

What can visual caregivers expect?

Retinal toxicity has been previously reported in patients treated for 5-7 years and related to HCQ doses >5 mg/kg.\(^{(29,57)}\) Even though the CT doses analyzed here are high and, in general, have not been adjusted to weight, they have been prescribed for a brief time. High-dose HCQ, i.e. 1200 mg/day for 6 weeks, has been used in the past with no visual loss reported, although no detailed ophthalmological exam was performed.\(^{(58)}\) Up to date, retinopathy associated with use <1 month of HCQ has not been reported, but extreme doses can accelerate retinal toxicity even in patients with no RPE or photoreceptors affection, although within a time course of some months.\(^{(59)}\) Therefore, in SARS-CoV-2 patients treated with HCQ/CQ, no signs of retinal toxicity or an early (reversible) stage should be expected.

An ophthalmological screening previous to administration of CQ/HCQ is appealing,\(^{(60)}\) since the retinal disease is a relative contraindication for the use of these drugs\(^{(28)}\) (although isolated drusen with proper photoreceptor function are not).\(^{(8)}\) However, within the context of COVID-19 emergency, this consideration might have been overlooked: only 48% of the CT considered a pre-existing retinal disease as exclusion criteria.

COVID-19 has had devastating effects, especially among the elderly with comorbidities.\(^{(7,61–65)}\) Age-related macular degeneration, affecting photoreceptors and RPE, is common within this age-group. How CQ and HCQ, even in moderated doses and short-term periods, may interact with a concomitant retinal disease is unknown. A comprehensive ophthalmological examination (including automated 10–2 VFA, SD-OCT and mfERG, when available)\(^{(66)}\) in this subgroup might shed some light in these yet unknown aspects of HCQ/CQ treatment. However, our study was based on the descriptions of the ongoing CT on databases, since most of them do not have published results to date, and this should be acknowledged as a limitation. If these have been the doses used outside clinical trials, if an ophthalmological examination has been performed previous to initiation of treatment or if patients with a known retinal disease have been treated with CQ and HCQ is unknown.

To conclude, ophthalmologists should also be aware that self-prescription of CQ/HCQ as SARS-CoV-2 prophylaxis is a harsh reality these days. Without medical supervision of the administered doses or the consideration of risk factors, such as renal impairment, retinal toxicity should be considered as an option in the differential diagnosis.

Conclusions

How CQ and HCQ treatment may interact with a previous retinal condition is still poorly understood. Since 52% of the worldwide SARS-CoV-2 CT have not considered a retinal
disease as an exclusion criterion for treatment, a comprehensive ophthalmological examination 6 months post-treatment is recommended in those patients with a previous retinal condition.

**Abbreviations**


**Availability of data and materials**

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Not applicable.

**Conflict of interests**

The authors declare that there is no conflict of interest

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Not applicable.

**Author’s contribution**

IF-M and MJ-G were involved in the conception and design and draft the manuscript.

The rest of the authors reviewed and analysed the articles. All the authors revised and approved the final document.

**References**


33. Chhablani PP, Ambiya V, Nair AG, Bondalapati S, Chhablani J. Retinal Findings on OCT in...


Tables and Figures

Figure 1. Flow charts showing the review procedure

Chloroquine (CH), adverse effects, poisoning and Toxicity

Reviews after removing duplicates (N = 44) (April 2020)

Selected reviews (n=44)

Reviews excluded (n=5)
3 Case report
1 No humans (plant)
1 Polish language

Full-text reviews assessed for eligibility (n=39)

Reviews full text excluded (n=17)
4 lupus disease
4 sarcoidosis disease
3 rheumatic disease
2 heart disease
1 cancer
1 liver disease
1 lung disease
1 study other medications

Reviews included (n=22)

Identification of CQ and HCQ clinical trials as COVID-19 treatment

Clinical trials identified (N=147) (21st April 2020)

Cancelled clinical trials (n=6)
4 by the investigator
2 due to lack of patients

Not using CQ / HCQ (n=6)

Analysed Clinical Trials (n=135)
67 HCQ
36 Prevention / Prophylaxis
18 CQ
6 HCQ and CQ
6 Dose HCQ
2 Dose CQ

Databases consulted:
EMBASE MEDLINE, SCOPUS and WOS Core Collection

Databases of clinical trials consulted:
https://clinicaltrials.gov/ and
http://www.chictr.org.cn/

Figure 1. Flow charts showing the review procedure
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<tr>
<th>COVID TREATMENT</th>
<th>ORIGINAL INDICATION</th>
<th>PHARMACOLOGIC CATEGORY</th>
<th>KNOWN OCULAR SIDE-EFFECTS</th>
<th>FDA</th>
<th>EMA</th>
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<tr>
<td>CHLOROQUINE AND HYDROXYCHLOROQUINE</td>
<td>Anti-malarial</td>
<td>Aminoquinoline (Antimalarial)</td>
<td>Frequency not reported: Maculopathy; macular degeneration; irreversible retinal damage; retinopathy; double vision; visual disturbances (blurred vision, focusing or accommodation difficulty); decreased visual acuity; color-vision defects; nystagmus; scotomatous vision with field defects of paracentral, pericentral ring types, and typically temporal scotomas, (e.g., difficulty in reading with words tending to disappear, seeing half an object, misty vision, fog before the eyes); pigmentary retinopathy; corneal deposits; keratopathy; decreased corneal sensitivity; corneal edema; reversible corneal opacities.</td>
<td>YES</td>
<td>National</td>
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<td>LOPINAVIR/RITONAVIR (LPV/R)</td>
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<td>Antiretroviral, Protease Inhibitor (Anti-HIV)</td>
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<tr>
<td>REMDESIVIR (INVESTIGATIONAL)</td>
<td>Ebola</td>
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### OTHER DRUGS, NOT PRIORITISED FOR RANDOMIZED CONTROLLED TRIAL

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<th>Class</th>
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<td><strong>BALOXAVIR MARBOXIL</strong></td>
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<td><strong>BARICITINIB</strong></td>
<td>Rheumatoid arthritis</td>
<td>Antirheumatic Miscellaneous</td>
<td>ONLY SHORT TERM OR UNCOMMON (0.1% - 1%)</td>
<td>Blurred vision (1% to 10%)</td>
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<td>Antirheumatic, Disease Modifying</td>
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<td>Uncommon (0.1% to 1%): Cataract</td>
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<td>ONLY SHORT TERM OR RARE (&lt;0.1%)</td>
<td>Conjunctivitis, abnormal vision, eye pain, lacrimal gland disorder (1-10%) or very rare (0.01% to 0.1%)</td>
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<td>Biological Response Modulator</td>
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<td>Blurred vision (When combined with interferon)</td>
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<td>Corneal ulcer (&lt;1%)</td>
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<td>Conjunctivitis</td>
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<td>Retinal Detachment reported post-marketing</td>
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<th>Graft-versus-host disease, acute Myelofibrosis, Polycythemia vera</th>
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<tr>
<th><strong>SIROLIMUS</strong></th>
<th>Lymphangioleiomyomatosis, Renal transplantation (rejection prophylaxis)</th>
<th>Immunosuppressant Agent mTOR Kinase Inhibitor</th>
<th>ONLY SHORT TERM</th>
<th>YES</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Eyelid edema (Frequency not reported)</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>TENOFOVIR DISOPROXIL (+ EMTRICITABINE)</th>
<th>HIV-1 infection, treatment Chronic hepatitis B</th>
<th>Antihepadnaviral, Reverse Transcriptase Inhibitor, Nucleotide (Anti-HBV) Antiretroviral, Reverse Transcriptase Inhibitor, Nucleotide (Anti-HIV)</th>
<th>NO</th>
<th>YES</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOCILIZUMAB</td>
<td>Giant cell arteritis Rheumatoid arthritis Juvenile idiopathic arthritis, etc.</td>
<td>Antirheumatic, Disease Modifying Interleukin-6 Receptor Antagonist</td>
<td>ONLY SHORT TERM. Conjunctivitis (1-10%)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>BASIC</td>
<td>DISCRETIONARY</td>
<td>NOT RECOMMENDED</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Visual Acuity</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Fundoscopy</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Static Perimetry</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD-OCT</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mfERG</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Fundus Autofluorescence</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Color Vision Testing</td>
<td></td>
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<tr>
<td>Amsler Grid</td>
<td></td>
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<tr>
<td>EOG</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Full Field ERG</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Fluorescein Angiography</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>AAO 2016</td>
<td>AAO 2011</td>
<td>AAO 2020: Update for COVID-19</td>
<td>Details</td>
<td></td>
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<td>--------------------------------</td>
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<tr>
<td><strong>Age</strong></td>
<td>Not specified</td>
<td>&gt;65 years old</td>
<td></td>
<td>Patients should be informed of the potential for macular toxicity before starting therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Duration</strong></td>
<td>&gt;5 years</td>
<td>&gt;5 years</td>
<td></td>
<td>Minimal risk if &lt;5 years use; rise if 10–25 years of use</td>
<td></td>
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<tr>
<td><strong>Daily Dose</strong></td>
<td>HCQ: &gt;5.0 mg/kg ABW/day, CQ: &gt;2.3 mg/kg ABW/day</td>
<td>HCQ: &gt;6.5 mg/kg IBW/day (&gt;400 mg/day), CQ: &gt;3 mg/kg IBW/day (&gt;250 md/day)</td>
<td>The risk of irreversible maculopathy at these higher doses for short periods of time is unknown</td>
<td>Largest study suggests that ABW- based dosing offers improved prediction of retinopathy risk. Might additionally predict retinopathy, particularly in obese patients (controversial).</td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative Drug Dose</strong></td>
<td>Not specified</td>
<td>HCQ: &gt;1000g total, CQ: &gt;460g total</td>
<td></td>
<td>Some studies suggest increased risk with &gt;600–1,000g exposure</td>
<td></td>
</tr>
</tbody>
</table>

**OTHER RISK FACTORS**

| **Ocular Disease**             | Maculopathy | Maculopathy | Retinal Disease | Decisions should be made on an individual basis, taking into consideration any pre-existing retinal disease | Some studies suggest Diabetic Retinopathy could be a relative contraindication |
| **Systemic Disease**           | Renal Impairment | Renal Impairment | Hepatic Impairment |                             | Increased risk associated with stage 3, 4, or 5 chronic kidney disease. |
| **Concurrent Drugs**           | Tamoxifen | Not specified |                             | Increased risk associated with concomitant tamoxifen use for >6 months. |
| **Ethnicity**                  | Asian patients show a different pattern of damage in the retina | Not specified |                             |                             |
Genetic | Not specified | Not specified | Individuals with mutations in the ABCA4 gene (which causes Stargardt macular dystrophy and cone dystrophy) may affect the risk of HCQ retinopathy

<table>
<thead>
<tr>
<th>Screening Frequency</th>
<th>Baseline: Fundus examination (first year). If abnormalities: Visual fields and spectral domain optical coherence tomography (SD-OCT) Annual screening begins after 5 years of use (sooner if major risk factors)</th>
<th>Baseline: Fundus examination (first year) Annual screening begins after 5 years of use</th>
<th>Baseline, unknown in cases with high doses over a relatively short duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic screening protocol</td>
<td>Non-Asian patients: • 10-2 visual fields • SD-OCT Asian patients: • 24-2 or 30-2 visual fields • Widefield SD-OCT</td>
<td>Ocular examination 10-2 visual fields with white target</td>
<td>Sensitivity: mild to moderate retinopathy (combining both methods)</td>
</tr>
<tr>
<td>Discretionary screening protocol</td>
<td>Multifocal electroretinography (mfERG) Fundus Autofluorescence (widefield in Asian eyes)</td>
<td>mfERG Fundus Autofluorescence SD-OCT</td>
<td>mfERG: objective corroboration for suspected visual field abnormalities fundus autofluorescence is to detect only advanced stages of retinopathy</td>
</tr>
<tr>
<td></td>
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<td>ERG, prior to placing a patient for treatment is likely unnecessary due to the short treatment duration</td>
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