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

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.(28,31) 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.(27,31)

The first signs of retinopathy (premaculopathy) are subtle changes at the macula, with pigmentary stippling.(26,29) Loss of fundus image, ringed foci discolouration and the loss of foveal reflex have been described in this phase,(26) as well as red vision(29) and visual field loss to red test object only.(12) Patients are normally asymptomatic since central fixation is preserved and recovery in this early stage is still possible with the cessation of the treatment.(18,26,29)

Early maculopathy is characterized by patchy damage within the parafoveal zone and modest visual acuity and visual field loss.(31) 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.(31) If the retinopathy progresses, different pigmentary patterns can be observed,(18) with no known correlation between the anatomic features of the retina and the pattern of damage.(27) These patterns are similar and bilateral in both CQ and HCQ, but they are less common with HCQ.(26) A Bull's Eye lesion in the macula may develop and is characterised 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.(9,27) The atrophy of the RPE cells may be complicated by secondary cystoid macular oedema, epiretinal membrane and other sequelae.(8,10,27)

Damage in the macular area may cause peripheral field narrowing or paracentral scotomas,(8,28) and patients may have trouble reading, although they can keep good central vision.(9,18) 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.(10,28) Severe intoxication might also result in slower pupillary reaction to light, pupillary asymmetry, or afferent pupillary defect.(10,28)

HCQ/CQ retinopathy in different ethnicities is variable, although not thought to be associated solely to ocular pigmentation.(8) Caucasians generally exhibit a parafoveal pattern (2–6º from the fovea), while Asians frequently manifest an extramacular or pericentral pattern (>8º from the fovea).(8,10) Black and Hispanic patients demonstrated a predominantly parafoveal distribution of disease.(8)

Once retinopathy is diagnosed, discontinuation of medication is recommended, but progression can continue long after:(32) the persistence of CQ and HCQ tissue deposition is so long that patients may be exposed to their toxic effect months after discontinuation.(12,17,30)

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

STUDY/GUIDELINES/COUNTRY	DOSE (ADULTS)	EXCLUSION CRITERIA
The Society of Critical Care Medicine and the European Society of Intensive Care Medicine (44)	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	Unknown
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	Unknown
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	Unknown
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.	Unknown
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	Unknown
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	Unknown
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(54)	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
Pan American Health Organization (PAHO) (55)	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	Unknown
Indian Council for Medical Research(56)	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

SARS-CoV-2: severe acute respiratory syndrome, COVID-19: coronavirus disease 2019, CQ: chloroquine, HCQ: hydroxychloroquine, CT: clinical trials, FDA: Food and Drug Administration, EMA: European Medicines Agency, ICMRA: International Coalition of Medicines Regulatory Authorities, IL: interleukin, RPE: retinal pigment epithelium, VFA: visual field assessment, SD-OCT: spectral-domain optical coherence tomography, mfERG: multifocal electroretinography,

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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Conflict of interests

The authors declare that there is no conflict of interest

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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

1. International Coalition of Medicines Regulatory Authorities. Global regulatory workshop on COVID-19 therapeutic development [Internet]. 2020. Available from: http://www.icmra.info/drupal/sites/default/files/2020-03/First regulatory COVID-19 workshop - meeting report_March 2020.pdf
2. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol [Internet]. 2020 May 1 [cited 2020 Apr 15];92(5):479–90. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2004372238

3. Huang M, Tang T, Pang P, Li M, Ma R, Lu J, et al. Treating COVID-19 with Chloroquine. Wu J, editor. J Mol Cell Biol [Internet]. 2020 Apr 1; Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631416180

4. Perinel S, Launay M, Botelho-Nevers É, Diconne É, Louf-Durier A, Lachand R, et al. Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients. Clin Infect Dis [Internet]. 2020 Apr 7 [cited 2020 Apr 15]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32255489

5. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. [Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi [Internet]. 2020 Feb 12 [cited 2020 Apr 15];43(0):E019. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32164085

6. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study Running title: Hydroxychloroquine-Azithromycin and COVID-19. IHU-Méditerranée Infect [Internet]. 2020 Apr 11 [cited 2020 Apr 15];8:101663. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1477893920301319

7. Kakodkar P, Kaka N. A Comprehensive Literature Review on the Clinical Presentation , and Management of the Pandemic Coronavirus Disease 2019 History of the outbreak. Cureus [Internet]. 2020 Apr 6 [cited 2020 Apr 15];12(4):e7560. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32269893

8. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. Eye [Internet]. 2017 Jun 10;31(6):828–45. Available from: http://dx.doi.org/10.1038/eye.2016.298

9. Abdulaziz N, Shah AR, McCune WJ. Hydroxychloroquine: Balancing the need to maintain therapeutic levels with ocular safety: An update. Curr Opin Rheumatol. 2018;30(3):249–55.

10. Wiącek M, Bobrowska-Snarska D, Lubiński W, Brzosko M, Modrzejewska M. What is new in recommendations on ophthalmological screening in patients treated with chloroquine and hydroxychloroquine? Update and literature review. Vol. 20, Nigerian Journal of Clinical Practice. 2017. p. 919–23.

11. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents [Internet]. 2020 Mar [cited 2020 Apr 15]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0924857920300881

12. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology [Internet]. 2015 Oct 6;23(5):231–69. Available from: http://link.springer.com/10.1007/s10787-015-0239-y

13. Onodera H, Sasaki S, Otake S, Tomohiro M, Shibuya K, Nomura M. General considerations in ocular toxicity risk assessment from the toxicologists' viewpoints. J Toxicol Sci [Internet]. 2015;40(3):295–307. Available from: https://www.jstage.jst.go.jp/article/jts/40/3/40_295/_article

14. Al-Bari AA. Chloroquine analogues in drug discovery: New directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J Antimicrob Chemother. 2014;70(6):1608–21.

15. World Health Organization. Landscape analysis of therapeutics as 21st March 2020 [Internet]. 2020 [cited 2020 Apr 20]. p. 1–49. Available from: https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf

16. European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: Cluster of pneumonia cases caused by a novel coronavirus, Wuhan, China [Internet]. European Centre for Disease Prevention and Control. 2020 [cited 2020 May 3]. p. 1–10. Available from: https://www.who.int/health-topics/coronavirus.

17. Plantone D, Koudriavtseva T. Current and Future Use of Chloroquine and Hydroxychloroquine in Infectious, Immune, Neoplastic, and Neurological Diseases: A Mini-Review. Clin Drug Investig

[Internet]. 2018 Aug 8;38(8):653–71. Available from: https://doi.org/10.1007/s40261-018-0656-y

18. Dettoraki M, Moschos MM. The Role of Multifocal Electroretinography in the Assessment of Drug-Induced Retinopathy: A Review of the Literature. Ophthalmic Res [Internet]. 2016;56(4):169–77. Available from: https://www.karger.com/Article/FullText/446321

19. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents [Internet]. 2020 Mar;105949. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32205204

20. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends [Internet]. 2020 Feb 29 [cited 2020 Apr 15];14(1):72–3. Available from: https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/_article

21. Hong W, W. H. Combating COVID-19 with Chloroquine. J Mol Cell Biol [Internet]. 2020 Apr 1 [cited 2020 Apr 15]; Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631415962

22. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clin Immunol [Internet]. 2020 May 1 [cited 2020 Apr 15];214. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2005410159

23. Fantini J, Di Scala C, Chahinian H, Yahi N. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents [Internet]. 2020 Apr [cited 2020 Apr 15]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0924857920301102

24. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses [Internet]. 2020 Mar 27 [cited 2020 Apr 15];12(4):372. Available from: https://www.mdpi.com/1999-4915/12/4/372

25. Rimpelä A-K, Reinisalo M, Hellinen L, Grazhdankin E, Kidron H, Urtti A, et al. Implications of melanin binding in ocular drug delivery. Adv Drug Deliv Rev [Internet]. 2018 Feb;126:23–43. Available from: https://doi.org/10.1016/j.addr.2017.12.008

26. Ding HJ, Denniston AK, Rao VK, Gordon C. Hydroxychloroquine-related retinal toxicity. Rheumatology [Internet]. 2016 Jun;55(6):957–67. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kev357

27. Conigliaro P, Cesareo M, Chimenti MS, Triggianese P, Canofari C, Barbato C, et al. Take a look at the eyes in Systemic Lupus Erythematosus: A novel point of view. Autoimmun Rev [Internet]. 2019 Mar;18(3):247–54. Available from: https://doi.org/10.1016/j.autrev.2018.09.011

28. Costedoat-Chalumeau N, Dunogué B, Leroux G, Morel N, Jallouli M, Le Guern V, et al. A Critical Review of the Effects of Hydroxychloroquine and Chloroquine on the Eye. Clin Rev Allergy Immunol [Internet]. 2015 Dec 12;49(3):317–26. Available from: http://link.springer.com/10.1007/s12016-015-8469-8

29. Haładyj E, Sikora M, Felis-Giemza A, Olesińska M. Antimalarials – are they effective and safe in rheumatic diseases? Reumatologia/Rheumatology [Internet]. 2018;56(3):164–73. Available from: https://www.termedia.pl/doi/10.5114/reum.2018.76904

30. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132(12):1453–60.

31. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy — implications of research advances for rheumatology care. Nat Rev Rheumatol [Internet]. 2018 Dec 6;14(12):693–703. Available from: http://dx.doi.org/10.1038/s41584-018-0111-8

32. Pandya H, Robinson M, Mandal N, Shah V. Hydroxychloroquine retinopathy: A review of imaging. Indian J Ophthalmol [Internet]. 2015;63(7):570. Available from: http://www.ijo.in/text.asp?2015/63/7/570/167120

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

Systemic Conditions. Semin Ophthalmol [Internet]. 2018 May 19;33(4):525–46. Available from: https://doi.org/10.1080/08820538.2017.1332233

34. Tsang AC, Ahmadi Pirshahid S, Virgili G, Gottlieb CC, Hamilton J, Coupland SG. Hydroxychloroquine and Chloroquine Retinopathy. Ophthalmology [Internet]. 2015 Jun;122(6):1239-1251.e4. Available from: http://dx.doi.org/10.1016/j.ophtha.2015.02.011

35. Couturier A, Giocanti-Aurégan A, Dupas B, Girmens J-F, Le Mer Y, Massamba N, et al. Mise à jour des recommandations sur la toxicité rétinienne des antipaludéens de synthèse. J Fr Ophtalmol [Internet]. 2017 Nov;40(9):793–800. Available from: http://dx.doi.org/10.1016/j.jfo.2017.08.002

36. Singh AKA, Singh AKA, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr Clin Res Rev. 2020 May;14(3):241–6.

37. Lu CC, Chen MY, Chang YL. Potential therapeutic agents against COVID-19: What we know so far. J Chin Med Assoc. 2020;

38. Shah S, Das S, Jain A, Misra DP, Negi VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in Coronavirus Disease-19 (COVID-19). Int J Rheum Dis [Internet]. 2020 Apr 13 [cited 2020 Apr 15]; Available from: http://doi.wiley.com/10.1111/1756-185X.13842

39. Gbinigie K, Frie K. Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review. BJGP open [Internet]. 2020 Apr 7 [cited 2020 Apr 15]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32265182

40. Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents [Internet]. 2020 Mar 1 [cited 2020 Apr 15];55(3):105924. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0924857920300674

41. Li X, Zhang C, Liu L, Gu M. Existing bitter medicines for fighting 2019-nCoV-associated infectious diseases. FASEB J [Internet]. 2020 Apr 13 [cited 2020 Apr 15];fj.202000502. Available from: http://doi.wiley.com/10.1096/fj.202000502

42. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis [Internet]. 2020 Mar 9;2:1–25. Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa237/5801998

43. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Vol. 30, Cell Research. Springer Nature; 2020. p. 269–71.

44. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med [Internet]. 2020 [cited 2020 Apr 16]; Available from: http://guidecanada.org/

45. Agencia Española de medicamentos y productos sanitarios. Tratamientos disponibles para el manejo de la infección respiratoria por SARS-CoV-2 - Agencia Española de Medicamentos y Productos Sanitarios. Minist Sanid [Internet]. 2020 [cited 2020 Apr 16]; Available from: https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid-19/tratamientos-disponibles-para-el-manejo-de-la-infeccion-respiratoria-por-sars-cov-2/?lang=gl

46. Rizzi Malattie Infettive M, Francesco Castelli Malattie Infettive B, Nicola Latronico Anestesia Rianimazione B, Redazione Susanna Capone Malattie Infettive B, Sergio Cattaneo Anestesia Rianimazione B, Antonella BD, et al. Vademecum per la cura delle persone con malattia da COVI-19. SIMIT. 2020.

47. The French National Agency for Medicines and Health Products Safety (ansm). Plaquenil et Kaletra : les traitements testés pour soigner les patients COVID-19 ne doivent être utilisés qu'à l'hôpital - Point d'information - ANSM : Agence nationale de sécurité du médicament et des produits de santé [Internet]. [cited 2020 Apr 16]. Available from: https://ansm.sante.fr/S-

informer/Points-d-information-Points-d-information/Plaquenil-et-Kaletra-les-traitements-testes-pour-soigner-les-patients-COVID-19-ne-doivent-etre-utilises-qu-a-l-hopital-Point-d-information

48. Van Ierssel S, Dauby N, Bottieau E, Huits R. Interim clinical guidelines for patients suspected of/confirmed with COVID-19 infection in Belgium [Internet]. 2020 [cited 2020 Apr 19]. Available from: www.notifieruneffetindesirable.be

49. Vollaard A, Gieling E, Linden P van der, Sihna B, Boer M de. Medicamenteuze behandelopties bij patiënten met COVID-19 (infecties met SARS-CoV-2)le [Internet]. SWAB. 2020 [cited 2020 Apr 16]. p. 1. Available from: https://swab.nl/nl/covid-19#to_6

50. Chloroquine and Hydroxychloroquine not licensed for coronavirus (COVID-19) treatment - GOV.UK [Internet]. [cited 2020 Apr 16]. Available from: https://www.gov.uk/government/news/chloroquine-and-hydroxychloroquine-not-licensed-for-coronavirus-covid-19-treatment

51. Protocol For Treatment of Confirmed COVID-19 [Internet]. [cited 2020 Apr 16]. Available from: https://www.medcampus.io/mnotes/protocol-for-treatment-of-confirmed-covid-19-5e5e2781e86c5d0001f77303

52. FDA. Fact sheet for health care providers emergency use authorization (eua) of chloroquine phosphate supplied from the strategic national stockpile for treatment of covid-19 in certain hospitalized patients. 2020 [cited 2020 Apr 30];1–7. Available from: https://dailymed.nlm.nih.gov/dailymed/.

53. National Health Commission. Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (7th edition) [Internet]. 2020 [cited 2020 Apr 30]. p. 9. Available from: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html

54. Sung-sun K. Physicians work out treatment guidelines for coronavirus - Korea Biomedical Review [Internet]. 2020 [cited 2020 Apr 16]. Available from: http://www.koreabiomed.com/news/articleView.html?idxno=7428

55. PAHO. Guideline for critical care of seriously ill adult patients with coronavirus (COVID-19) in the Americas. 2020; Available from: https://www.paho.org/en/documents/guidelines-critical-care-seriously-ill-adult-patients-coronavirus-covid-19-americas-short

56. Indian council of medical research. Recommendation for empiric use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection. Indian Counc Med Res [Internet]. 2020 [cited 2020 May 23];1(1):2. Available from: https://www.icmr.gov.in/pdf/covid/techdoc/HCQ_Recommendation_22March_final_MM_V2.pdf

57. Garcia-Cremades M, Solans BP, Hughes E, Ernest JP, Wallender E, Aweeka F, et al. Optimizing hydroxychloroquine dosing for patients with COVID-19: An integrative modeling approach for effective drug repurposing. Clin Pharmacol Ther [Internet]. 2020 Apr 14 [cited 2020 Apr 15]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32285930

58. Marmor MF. COVID-19 and Chloroquine/Hydroxychloroquine: is there Ophthalmological Concern? Am J Ophthalmol [Internet]. 2020 Mar [cited 2020 Apr 15];19–20. Available from: https://doi.org/10.1016/j.ajo.2020.03.028

59. Leung LSB, Neal JW, Wakelee HA, Sequist L V., Marmor MF. Rapid Onset of Retinal Toxicity from High-Dose Hydroxychloroquine Given for Cancer Therapy. Am J Ophthalmol [Internet]. 2015;160(4):799-805.e1. Available from: http://dx.doi.org/10.1016/j.ajo.2015.07.012

60. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF, Lum F. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology [Internet]. 2016 Jun 1 [cited 2020 Apr 30];123(6):1386–94. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642016002013

61. Xie M, Chen Q. Insight into 2019 novel coronavirus — an updated intrim review and lessons from SARS-CoV and MERS-CoV. Int J Infect Dis [Internet]. 2020;94:119–24. Available from: https://doi.org/10.1016/j.ijid.2020.03.071

62. Singhal T, T. S. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr [Internet]. 2020 Apr 13 [cited 2020 Apr 15];87(4):281–6. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2004450978

63. Lai C-CC, Liu YH, Wang C-YY, Wang Y-HH, Hsueh S-CC, Yen M-YY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect [Internet]. 2020 Mar [cited 2020 Apr 15];2(xxxx). Available from: https://doi.org/10.1016/j.jmii.2020.02.012

64. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract [Internet]. 2020 Apr 9 [cited 2020 Apr 15];162:108142. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822720303922

65. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020 Mar;105955.

66. Yusuf IH, Foot B, Galloway J, Ardern-Jones MR, Watson S-L, Yelf C, et al. The Royal College of Ophthalmologists recommendations on screening for hydroxychloroquine and chloroquine users in the United Kingdom: executive summary. Eye [Internet]. 2018 Jul 11;32(7):1168–73. Available from: http://dx.doi.org/10.1038/s41433-018-0136-x

Tables and Figures

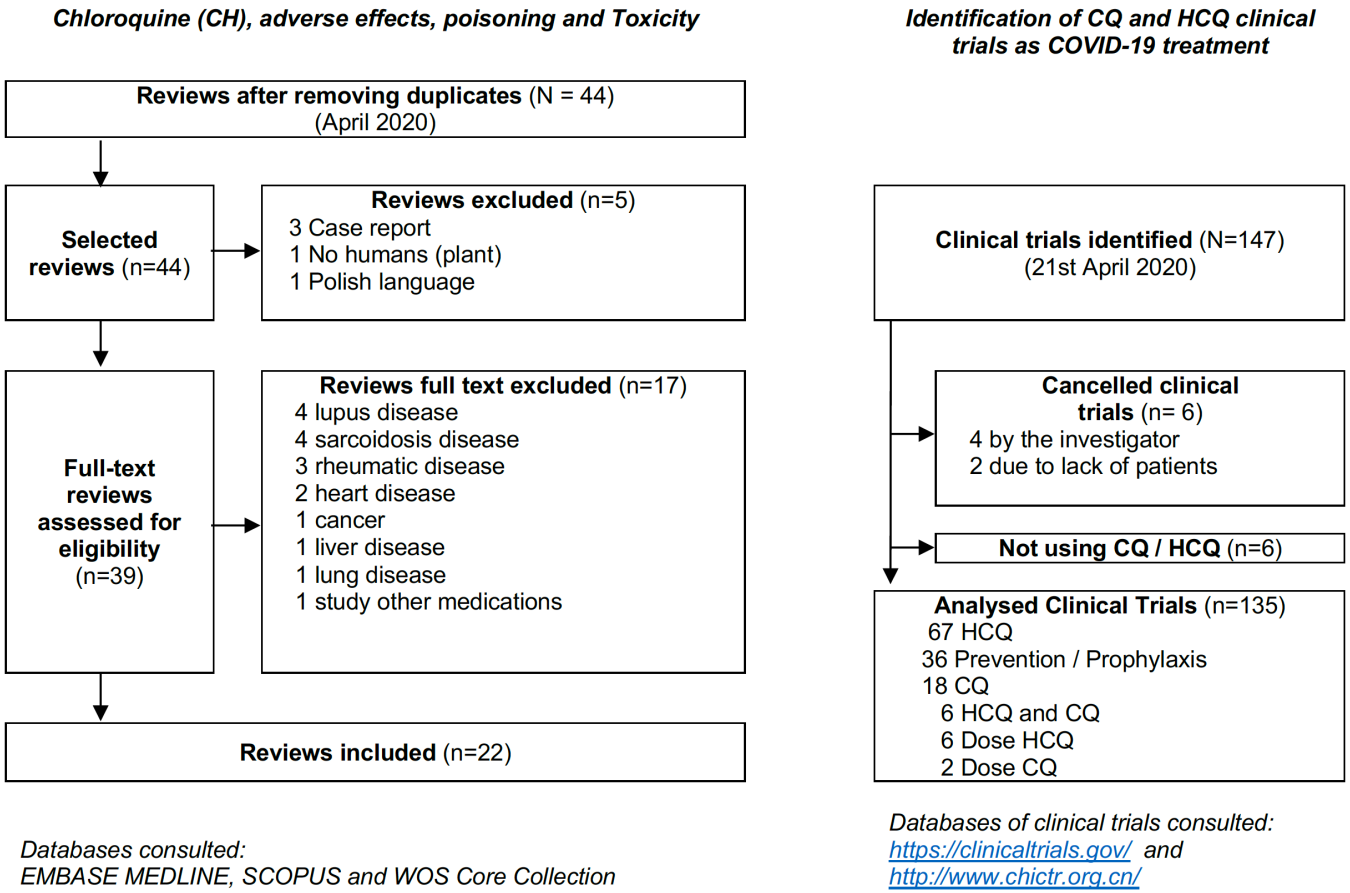

Figure 1. Flow charts showing the review procedure

Table 1. Selected drugs for SARS-CoV-2 (WHO), ocular side effects and approval status

COVID TREATMENT	ORIGINAL INDICATION	PHARMACOLOGIC CATEGORY	KNOWN OCULAR SIDE-EFFECTS	FDA	EMA
PRIORITISED FOR INCLUSION IN LARGE WELL-DESIGNED RANDOMIZED CONTROLLED TRIAL ACCORDING TO WHO ANALYSIS					
CHLOROQUINE AND HYDROXYCHLOROQUINE	Anti-malarial Autoimmune disease	Aminoquinoline (Antimalarial) Antimalarial Agent	**YES** 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; nyctalopia; 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 .	YES	National
LOPINAVIR/ RITONAVIR (LPV/R)	HIV	Antiretroviral, Protease Inhibitor (Anti-HIV)	NO	YES	YES
REMDESIVIR (INVESTIGATIONAL)	Ebola	Investigational antiviral	UNKNOWN	NO	NO

OTHER DRUGS, NOT PRIORITISED FOR RANDOMIZED CONTROLLED TRIAL					
BALOXAVIR MARBOXIL	Influenza, seasonal, treatment	Antiviral Agent Endonuclease Inhibitor	NO	YES	NO
BARICITINIB	Rheumatoid arthritis	Antirheumatic Miscellaneous Antirheumatic, Disease Modifying Janus Associated Kinase Inhibitor	ONLY SHORT TERM OR UNCOMMON (0.1% - 1%) Blurred vision (1% to 10%) Uncommon (0.1% to 1%): Cataract	YES	YES
DARUNAVIR	HIV	Antiretroviral, Protease Inhibitor (Anti-HIV)	NO	YES	YES
EMTRICITABINE	HIV	Antiretroviral, Reverse Transcriptase Inhibitor, Nucleoside (Anti-HIV)	NO	YES	YES
FAVIPIRAVIR (INVESTIGATIONAL)	Ebola	Investigational antiviral	UNKNOWN	NO	NO
INTERFERON BETA-1B	Multiple sclerosis, relapsing	Interferon	NO	YES	YES
INTERFERON ALFA-2B	AIDS-related Kaposi sarcoma Chronic hepatitis B, etc.	Antineoplastic Agent, Biological Response Modulator Biological Response Modulator Interferon	ONLY SHORT TERM OR RARE (<0.1%) Conjunctivitis, abnormal vision, eye pain, lacrimal gland disorder (1-10%) or very rare (0.01% to 0.1%)	YES	YES

RIBAVIRIN	Respiratory syncytial virus	Antiviral Agent	ONLY SHORT TERM OR UNCOMMON (0.1% - 1%) Blurred vision (When combined with interferon) Corneal ulcer (<1%) Conjunctivitis Retinal Detachment reported post-marketing.	YES	YES
RUXOLITINIB	Graft-versus-host disease, acute Myelofibrosis Polycythemia vera	Antineoplastic Agent, Janus Associated Kinase Inhibitor Antineoplastic Agent, Tyrosine Kinase Inhibitor Janus Associated Kinase Inhibitor	NO	YES	YES
SARILUMAB	Rheumatoid arthritis	Antirheumatic, Disease Modifying Interleukin-6 Receptor Antagonist Monoclonal Antibody	NO	YES	YES
SILTUXIMAB	Castleman disease	Antineoplastic Agent, Monoclonal Antibody Interleukin-6 Inhibitor	NO	YES	YES
SIROLIMUS	Lymphangioleiomyomatosis Renal transplantation (rejection prophylaxis)	Immunosuppressant Agent mTOR Kinase Inhibitor	ONLY SHORT TERM Eyelid edema (Frequency not reported)	YES	YES

TENOFOVIR DISOPROXIL (+ EMTRICITABINE)	HIV-1 infection, treatment Chronic hepatitis B	Antihepadnaviral, Reverse Transcriptase Inhibitor, Nucleotide (Anti-HBV) Antiretroviral, Reverse Transcriptase Inhibitor, Nucleotide (Anti-HIV)	NO	YES	YES
TOCILIZUMAB	Giant cell arteritis Rheumatoid arthritis Juvenile idiopathic arthritis, etc.	Antirheumatic, Disease Modifying Interleukin-6 Receptor Antagonist	ONLY SHORT TERM. Conjunctivitis (1-10%)	YES	YES

Table 2. Screening Protocol in patients with HCQ and CQ treatment			
	SCREENING		
	BASIC	DISCRETIONARY	NOT RECOMMENDED
Visual Acuity	X		
Fundoscopy	X		
Static Perimetry	X		
SD-OCT	X		
mfERG		X	
Fundus Autofluorescence		X	
Color Vision Testing			X
Amsler Grid			X
EOG			X
Full Field ERG			X
Fluorescein Angiography			X

Table 4. American Academy Ophthalmology GUIDELINES 2016 VS 2011

	AAO 2016	AAO 2011	AAO 2020: Update for COVID-19	Details
Age	Not specified	>65 years old	Patients should be informed of the potential for macular toxicity before starting therapy	
Drug Duration	>5 years	>5 years		Minimal risk if <5 years use; rise if 10–25 years of use
Daily Dose	HCQ: >5.0 mg/kg ABW/day CQ: >2.3 mg/kg ABW/day	HCQ: >6.5 mg/kg IBW/day (>400 mg/day) CQ: >3 mg/kg IBW/day (>250md/day)	The risk of irreversible maculopathy at these higher doses for short periods of time is unknown	Largest study suggests that ABW- based dosing offers improved prediction of retinopathy risk. Might additionally predict retinopathy, particularly in obese patients (controversial).
Cumulative Drug Dose	Not specified	HCQ: >1000g total CQ: >460g total		Some studies suggest increased risk with >600–1,000g exposure
		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
		SCREENING		
Screening Frequency	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)	Baseline: Fundus examination (first year) Annual screening begins after 5 years of use	Baseline: unknown in cases with high doses over a relatively short duration	
Basic screening protocol	Non-Asian patients: • 10-2 visual fields • SD-OCT Asian patients: • 24-2 or 30-2 visual fields • Widefield SD-OCT	Ocular examination 10-2 visual fields with white target		Sensitivity: mild to moderate retinopathy (combining both methods)
Discretionary screening protocol	Multifocal electroretinography (mfERG) Fundus Autofluorescence (widefield in Asian eyes)	mfERG Fundus Autofluorescence SD-OCT	ERG, prior to placing a patient for treatment is likely unnecessary due to the short treatment duration	mfERG: objective corroboration for suspected visual field abnormalities fundus autofluorescence is to detect only advanced stages of retinopathy