DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

Hydroxychloroquine Prescribing Guideline

Hydroxychloroquine is **GREEN** - after consultant/specialist initiation in Derbyshire

The consultant/ specialist initiating hydroxychloroquine is responsible for referring patients to ophthalmology for **annual retinal screening*** after 5 years of therapy, or after 1 year if additional risk factors** present

There is no routine ongoing blood monitoring requirements by GP

Background

Hydroxychloroquine is an antimalarial and a disease modifying anti-rheumatic drug (DMARD). New evidence suggests that the prevalence of hydroxychloroquine (HCQ) related retinopathy is higher than previously thought, estimated at around 7.5%, increasing to 20-50% in those who have been on HCQ for >20 years. Evidence also suggests that doses exceeding 5mg/kg/day (actual weight), concomitant tamoxifen therapy and renal impairment can further increase the risk of developing HCQ related retinopathy. Early stages of retinal toxicity tend to be asymptomatic. The aim of retinal screening is to help identify early stages of ocular toxicity, as advanced retinopathy can eventually lead to irreversible central vision loss. Furthermore, retinal toxicity can continue after the discontinuation of HCQ. Detection in early to moderate stages of retinopathy can help limit the level of macular damage associated with post-drug toxicity.

This prescribing guide is based on Royal College of Ophthalmologists (RCOphth) recommendations, and in line with national shared care protocol for HCQ. Consultant/ specialist in this document refer to the clinician initiating/ overseeing hydroxychloroquine treatment e.g., rheumatologist, dermatologist. Where referring to retinal screening ophthalmology is specified.

Consultant/ specialist responsibility

- Assess the patient and provide diagnosis, discuss the benefits and risks of the treatment. Obtain and document patient consent and provide appropriate counselling. Assess for contraindications and cautions and interactions.
- Conduct required baseline investigations and initial monitoring; Initiate and optimise treatment.
- Contact patient's GP to request continuing prescribing. Provide GP with diagnosis, current and ongoing dose, and baseline test results. Include contact information.
- Annually conduct the required reviews - after each review, advise primary care whether treatment should be continued and confirm the ongoing dose.
- **When approaching five years treatment with hydroxychloroquine, refer for ophthalmology monitoring*. Patients who are at higher risk** of retinal toxicity need to be referred after 1 year.**

*spectral-domain optical coherence tomography (SD-OCT)/ widefield fundus autofluorescence imaging (FAF)

** additional risk factors include concomitant tamoxifen; renal impairment eGFR<60ml/min/1.73^2; hydroxychloroquine dose >5mg/kg/day (actual body weight).

GP responsibility

- Prescribe ongoing treatment as detailed in the specialist's request taking into any account potential drug interactions. Adjust the dose of hydroxychloroquine prescribed or stop treatment as advised by the specialist.
- Assess for possible interactions with hydroxychloroquine when starting new medicines; manage any adverse effects and discuss with specialist team when required.
- **Stop hydroxychloroquine and discuss urgently with the specialist if retinopathy or cardiomyopathy are confirmed.**
- Ensure the patient is offered an annual flu vaccination.

Patient responsibility

- Take hydroxychloroquine as prescribed and do not stop taking it without speaking to their primary care prescriber or specialist.
- Attend regularly for monitoring and review appointments with primary care, specialist, and ophthalmology. Be aware that medicines may be stopped if they do not attend appointments.
- Stop taking the drug immediately and seek the advice of their prescribing doctor if any disturbances of vision are noted, including abnormal colour vision.

Local contacts

Chesterfield Royal Hospital NHS Foundation Trust
Contact the referring consultant/nurse via switchboard: 01246 277271
Rheumatology nurse advice line: 01246 513097 Available Mon-Thurs 9am-4:30pm, Fri 9am- 12:30pm
Dermatology- 01246513106

University Hospital of Derby and Burton NHS Foundation Trust

Derby sites
Rheumatology helpline: 01332 787710
Dermatology- Consultant/specialist nurse via switchboard: 01332 265500

Burton Sites
Switchboard: 01283 511511/566333
Rheumatology Dr R Laximinarayan ext. 3167 Dr S Das/ Dr D Ray ext. 3211/3247
Clinical Rheumatology Nurse Specialist ext. 4112 bhft.rheumatologynurses@nhs.net

Resources

- General information: https://patient.info/medicine/hydroxychloroquine-tablets-quinoric
- Rheumatology: https://www.versusarthritis.org/about-arthritis/treatments/drugs/hydroxychloroquine/
- British Association of Dermatologists via www.bad.org.uk/for-the-public/patient-information-leaflets
- Patient information leaflets https://www.medicines.org.uk/emc/search?q=hydroxychloroquine
- Clinical Guidelines Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring, The Royal College of Ophthalmologists, December 2020, https://www.rcophth.ac.uk/wp-content/uploads/2020/12/Hydroxychloroquine-and-Chloroquine-Retinopathy-Monitoring-Guideline.pdf

References

British National Formulary 76, https://bnf.nice.org.uk/drug/hydroxychloroquine-sulfate.html
Clinical Guidelines Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring, The Royal College of Ophthalmologists, December 2020, accessed 7/11/22, https://www.rcophth.ac.uk/wp-content/uploads/2020/12/Hydroxychloroquine-and-Chloroquine-Retinopathy-Monitoring-Guideline.pdf
National shared care protocol: Hydroxychloroquine for patients within adult services, Version 1, Specialist Pharmacist Service/ NHSE, assessed 7/11/22 https://www.england.nhs.uk/publication/shared-care-protocols/

Produced by Derbyshire Guideline group in consultation with UHDBFT & CRHFT.

Appendix 1- Hydroxychloroquine Clinical information

Indications

Licensed

- Active rheumatoid arthritis
- Systemic and discoid lupus erythematosus
- Dermatological conditions caused or aggravated by sunlight

Off-label use

- Rheumatology (e.g., inflammatory arthritis, connective tissue disease, Sjögren's syndrome, myositis)
- Dermatology (e.g., urticaria, other inflammatory skin diseases

Dose & administration

Oral hydroxychloroquine sulfate 200mg tablets- 200mg to 400 mg daily, taken with food.

- **The risk of significant toxicity increases with doses above 5 mg/kg/day (based on actual body weight).** BNF max. dose 6.5mg/kg/day.
- 300mg hydroxychloroquine do not offer a clinical advantage and are not preferred. Alternate day dosing with 200 mg and 400 mg may be used.
- Consider dose adjustment and caution in renal or hepatic impairment.
- Oral antacids should be avoided for 4 hours before and after the dose.
- If necessary, tablets may be crushed and dispersed in water (unlicensed).

Adverse effects

Refer to the SPC for a full list of adverse effects & further information http://www.medicines.org.uk
Clinician should review severity of side effect and contact specialist for advice if needed. Below is advice on how to manage some of the adverse effects.

Vision disturbances including blurred vision, changes in visual acuity or abnormal colour vision	Refer to optometrist/ ophthalmologist; discuss with specialist team
Symptoms or signs of cardiomyopathy e.g., breathlessness, swelling in the abdomen and ankles, palpitations, cardiac conduction disorders and ECG changes.	Review for reversible causes. Discuss with specialist team urgently and consider withholding. If cardiomyopathy occurs due to hydroxychloroquine treatment, hydroxychloroquine must be withheld
Headache, gastrointestinal disturbances e.g., abdominal pain, nausea, diarrhoea, vomiting	Review for reversible causes; discuss with specialist team if persistent or severe
Skin and subcutaneous tissue disorders e.g., pruritic erythematous macular rash occurring soon after treatment commenced, blue-black pigmentation of the skin, bleaching of skin & hair	Withhold and discuss with specialist team
Skeletal muscle myopathy or neuromyopathy	Review for reversible causes; withhold and discuss with specialist team
Signs and symptoms of bone marrow suppression e.g., sore throat, oral ulceration, abnormal bleeding/bruising, signs of infection	Review for reversible causes. Be aware that the underlying condition may contribute to bone marrow suppression. Although the risk is low, if bone marrow suppression is suspected, discontinue treatment, and obtain an urgent FBC and other bloods as appropriate. Discuss with specialist team.

Monitoring Requirements

A useful aide memoir for HCQ is the 5 x 5 rule (ideally keep dosage < 5mg/kg/day and monitor after five years of drug use).

Consultant/ specialist (e.g., rheumatologist, dermatologist)

- Baseline investigations:
  - Bloods - U&Es, CrCl, ALT and/or AS, and albumin, FBC
  - Weight, height, and blood pressure (if indicated)
  - Assess for co-morbidities which may influence DMARD choice, including risk factors for retinopathy (e.g., concomitant tamoxifen use, eGFR <60 mL/min)
  - ECG if concerns exist regarding the QT-interval.
- No routine ongoing laboratory monitoring is required for hydroxychloroquine. Monitoring may be required if the patient is prescribed an additional DMARD.
- Annually review the patient and advise the GP promptly on when to adjust the dose, stop treatment or consult with the specialist.
- **When approaching 5 years treatment with hydroxychloroquine, refer to ophthalmology for annual monitoring for retinopathy.**
- **Patients who are at higher risk of retinal toxicity will need to be referred after 1 year.**
  - concomitant tamoxifen use
  - impaired renal function (eGFR <60mL/min/1.73m^2)
  - hydroxychloroquine dose (>5mg/kg/day)

GP

Risk factors may change over time; primary care should discuss with specialist overseeing treatment if new risk factors that are 'high risk' are identified before the five-year mark.

Action to be taken

Possible retinopathy	Consider whether withholding is in the best interests of the patient specialist overseeing treatment to be informed and to determine follow-up plan
Definite retinopathy	primary care to ensure **withheld** pending urgent discussion between patient and specialist overseeing treatment.

Advice on Immunisation

- Annual influenza vaccinations are recommended.
- COVID-19 vaccination is safe and recommended
- Patients aged 70-79 years old could be eligible for the shingles vaccine (herpes zoster). For patients who are immunosuppressed (e.g., those taking prednisolone at a dose of 10 mg or more for more than 4 weeks in the prior 3 months, or 20 mg or more for more than 10 days in the prior month) a non-live vaccine should be used. Specialist input may be required. If patient is taking additional DMARDs, check advice for all drugs.

Clinically relevant drug interactions

Refer to the SPC for more detailed information on drug interactions http://www.medicines.org.uk.

Do not prescribe the following drugs without consultation with the specialist:

- Drugs that can prolong the QT interval: for example, amiodarone, moxifloxacin, quinine, citalopram. Avoid concomitant use; possible increased risk of QT prolongation/ventricular arrhythmias.
- Antidiabetic drugs and/or insulin: hypoglycaemic effect may be enhanced, may need dose adjustment of antidiabetic medication.
- Cimetidine: possible increase in plasma concentration of hydroxychloroquine.
- Ciclosporin: possible increase in plasma concentration of ciclosporin (combination used by some specialists).

- Digoxin: possible increase in plasma concentration of digoxin.
- Mefloquine and other drugs known to lower the convulsion threshold: possible increased risk of convulsions.
- Penicillamine: possible increased risk of haematological toxicity.
- Tamoxifen: increased risk of retinal toxicity, necessitates annual ophthalmic monitoring

The following drugs may be prescribed with caution:

- Antacids and calcium carbonate-containing supplements: may reduce absorption of hydroxychloroquine; separate administration by at least four hours. Other calcium salts do not appear to interact.
- Antiepileptics: activity of antiepileptic drugs may be impaired with hydroxychloroquine. Additionally, hydroxychloroquine may lower the seizure threshold.
- Neostigmine and pyridostigmine: effects may be antagonised by hydroxychloroquine.
- Intra-dermal rabies vaccine: possible reduced antibody response
- Topiramate – increased risk of toxicity when co-administered with valproate, monitor for signs and symptoms of encephalopathy or hyperammonaemia

Contra-indications/ cautions

Refer to the SPC for more detailed information

MHRA drug safety update Feb 2022- Hydroxychloroquine, chloroquine: increased risk of cardiovascular events when used with macrolide antibiotics; reminder of psychiatric reactions

Contraindications

- Hypersensitivity to hydroxychloroquine or 4-aminoquinoline compounds
- Pre-existing maculopathy

Cautions

- Concurrent use of medicines which may cause adverse ocular or skin reactions
- Diabetes mellitus, and those taking anti-diabetic drugs (including SGLT-2 inhibitors) for any indication (hydroxychloroquine treatment may lower blood glucose)
- Glucose-6-phosphate dehydrogenase deficiency
- Increased risk of retinopathy with high doses (>5 mg/kg/day), long-term treatment (>5 years), eGFR <60 mL/min/1.73m2 or concurrent tamoxifen use.
- Myasthenia gravis or psoriasis (may exacerbate)
- Porphyria cutanea tarda, and other acute porphyria's
- Renal or hepatic disease and concurrent use of drugs known to affect these organs
- Sensitivity to quinine
- Severe gastrointestinal, neurological (especially for those with a history of epilepsy – may lower the seizure threshold), or blood disorders
- Significant cardiac arrhythmias due to the risk of QT interval prolongation

Pregnancy, paternal exposure, and breastfeeding

Pregnancy

Hydroxychloroquine can be continued throughout pregnancy.
https://www.medicinesinpregnancy.org/Medicine--pregnancy/Hydroxychloroquine/

Breastfeeding

Hydroxychloroquine is compatible with breastfeeding, though does pass into breast milk in small quantities. https://www.sps.nhs.uk/medicines/hydroxychloroquine/