Appropriate Use of Hydroxychloroquine in Lupus

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Do	• Do prescribe hydroxychloroquine (HCQ) to **all lupus patients** unless contraindicated.[1,2,3,4,5] • Do recommend **concomitant administration** of HCQ along with other medications (e.g., immunosuppressives or biologic therapies).[1,2] • Do recommend that HCQ use **before and during pregnancy and breastfeeding is safe**.[1,4,6,7] • Do counsel patients that HCQ can take between **3 – 6 months** to demonstrate efficacy.[8] • Do continue HCQ use in the case of **infection or cardiovascular events**.[5,9] • Do prescribe HCQ at 5 mg/kg/day of **actual body weight** up to **400 mg/day**.[1,8,10]
Stop	• Stop HCQ use if there is proven **retinopathy**.[8] • Stop HCQ in the case of **allergic reactions** and consider desensitization therapy.[8]
Consider	• Consider **dose reduction** of HCQ in patients undergoing long-term remission who are clinically and serologically inactive.[1] • Consider the potential for **QT prolongation** in those with underlying cardiac disease or those taking other QT-prolonging medications.[1,8,11,12,13] • Consider exercising caution in patients with **retinal conditions**, i.e., macular degeneration, before recommending HCQ.[8] • Consider 50% dose reduction in patients with **renal dysfunction** (i.e., eGFR <30).[8,10]

Background

Originally used in the treatment of malaria, **hydroxychloroquine** (HCQ), also known as Plaquenil®, is an anti-inflammatory and immunomodulatory medication used as an essential component of the treatment of lupus. Benefits of HCQ include decreased disease activity, prevention of disease flares, reduced risk of cardiovascular and thrombotic events (including in patients with anti-phospholipid antibodies), and improved patient survival.[4,7]

HCQ is indicated for the treatment of systemic lupus erythematosus (SLE) and cutaneous lupus. HCQ is considered to be an "anchor" therapy and should be considered for all patients with a diagnosis of SLE, unless contraindicated. HCQ is not an immunosuppressant therapy and does not increase the risk of infection. Other medications to control lupus disease activity may be added (e.g., immunosuppressives or biologic therapies). Contraindications to HCQ include pre-existing retinopathy.[1,3,4,8]

Further, HCQ may be used with caution in patients with renal impairment. Dose adjustment may be required. HCQ interacts with a number of concomitant medications (e.g., tamoxifen, citalopram, ciprofloxacin) and may require monitoring, therapy modification, or avoidance.[8,10]

Dosing Considerations

When calculating the recommended dosage of HCQ, prescribe 5 mg/kg/day of **actual body weight**, up to 400 mg/day. Exceeding recommended daily dosage increases the risk of retinal toxicity and cardiac arrhythmia.[1,8,10] Variable or alternate day dosing (e.g., 400/200 mg every other day) may be considered to achieve ideal dosing.

For prolonged maintenance therapy, the dosage may be decreased if the patient is clinically and serologically inactive.[1,6,8]

For patients with renal impairment, dosage should be lowered to <5 mg/kg/day depending on the severity of renal impairment.[8,10] Reduce HCQ dosage by 50% in those with eGFR <30.[1]

Safety

HCQ is considered to be a very safe medication, however, requires monitoring, as do all therapies. In most patients, the benefits gained from HCQ use far outweigh any potential risks.[7]

Side effects of HCQ include headache, nausea, diarrhea, loss of appetite, confusion, drug hypersensitivity, and rash. Uncommon side effects include dizziness, tinnitus, hyperpigmentation, muscle weakness, psychosis, or severe hypoglycemia.[4,8,10,14]

Some patients on HCQ may develop a hypersensitivity reaction. Allergic reactions may occur within 2-33 days and typically manifest as cutaneous reactions or anaphylaxis. If allergic reaction occurs, consult with an allergist to consider HCQ desensitization.[8,15]

The potential exists for retinal toxicity and cardiac toxicity. (See screening and monitoring section for specifics).[1,7,8]

Hyperpigmentation

Blue-grey hyperpigmentation may occur after long-term or high-dose use of HCQ. Incidence is approximately 7%, however may be higher in darker-skinned individuals (e.g., southeast Asian ethnicity). HCQ should only be discontinued if patient has cosmetic concerns.[14]

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Use in Pregnancy and Breastfeeding

Use of HCQ is recommended and considered to be safe before and during pregnancy and breastfeeding. Many studies support maternal and pregnancy benefits of HCQ and it is considered low risk for mother and fetus, with no significant negative outcomes in children exposed to HCQ during pregnancy.[1,4,6,7,16,17]

Screening and Monitoring

Potential toxic effects of HCQ include retinal and cardiac toxicity (e.g., cardiomyopathy). While the overall risk is considered to be low, certain ocular and cardiac assessments prior to the initiation of HCQ may be recommended. When prescribed and managed appropriately in the context of guideline-approved management, toxicity is infrequent. Studies have found the risk of HCQ-related retinopathy is <2% for usage up to 10 years. Acute cardiovascular toxicities can manifest as QT interval prolongation and arrhythmia. QTc prolongation occurred in 0.7% of HCQ users and the duration of use was not a significant predictor.[5,8,11,12,13,18]

Retinal toxicity considerations

Retinopathy may occur and has a greater likelihood of occurring in those on **long-term** (i.e., >5 years) or **high-dose** (i.e., ≥5 mg/kg actual body weight) HCQ and monitoring for retinal toxicity is important. Further progression of retinopathy may be prevented if identified early and requires cessation of HCQ. If retinopathy develops, there may be a risk of progression even after treatment withdrawal.

Risk factors for retinal toxicity include: [1,4,8,10,18]

- Duration of treatment.
- Dose exceeding recommendations.
- Kidney impairment.
- Pre-existing retinal or macular disease.
- Concurrent use of tamoxifen citrate.

For those patients at higher risk, consultation with an ophthalmologist to assess the risk: benefit ratio of HCQ use is recommended prior to treatment initiation. Concerns regarding retinopathy should be confirmed by a retinal specialist.[18,19]

Recommended retinal monitoring schedule[1,18]

It is recommended that all patients on HCQ undergo screening for HCQ toxicity by an ophthalmologist or optometrist, including:

- Optical coherence tomography (OCT) at **baseline**, repeated **within the first year** of treatment, then **every 5 years.**
- Visual fields assessment **annually**.

Cardiac toxicity considerations

Both traditional and disease-related factors increase cardiovascular risk in SLE. Cardiovascular risk assessment is recommended upon diagnosis of lupus. Low disease activity should be maintained to reduce risk of cardiovascular events, which may be assisted through treatment with HCQ.[1,5,6,10,20]

- **Cardiomyopathy** is an uncommon side effect of long-term use of HCQ (i.e., after 10 years of therapy). Cardiac toxicity is rare with conventional dosing for the treatment of lupus.
- However, HCQ use may prolong the QT, PR, and/or QRS intervals, especially in patients with underlying risk factors.
- Cardiac assessment (e.g., baseline electrocardiogram) is only required in patients at elevated risk,[5,8,21,22] such as:
    - Higher risk of **QT prolongation**, including those on concomitant antidepressants (e.g., citalopram, venlafaxine), or QTc, PR, or QRS interval prolonging drugs (e.g., azithromycin, haloperidol).
    - Comorbid conditions, including hypokalemia, bradycardia, or hepatic/renal impairment.

*While chloroquine is not readily available, its use should be carefully considered due to amplified toxicity.[4]

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