Hydroxychloroquine (Plaquenil)| MOA, Uses,Side effects, and Dosage

Hydroxychloroquine is a synthetic antimalarial agent derived from chloroquine. While it retains activity against *Plasmodium* species, it is more commonly used for autoimmune diseases due to its **anti-inflammatory and immunomodulatory effects** .

Indications

FDA-Approved Uses

- **Malaria** : Treatment and prophylaxis of *Plasmodium vivax* , *P. ovale* , *P. malariae* , and *chloroquine-sensitive P. falciparum* .
- **Systemic Lupus Erythematosus (SLE)** : Reduces skin lesions, fatigue, joint pain, and prevents disease flares.
- **Rheumatoid Arthritis (RA)** : DMARD used to control inflammation and prevent joint damage.
- **Porphyria Cutanea Tarda**

Off-Label Uses

- **Juvenile Idiopathic Arthritis**
- **Primary Sjögren's Syndrome**

Hydroxychloroquine and COVID-19: Summary of Evidence

- Early in the COVID-19 pandemic, hydroxychloroquine was proposed as a potential treatment due to in vitro antiviral activity against SARS-CoV-2.
- **Mechanism hypothesized:**
  - Interfered with endosomal pH needed for viral entry and replication.
  - Inhibited binding of viral spike protein to ACE2 receptors.
- **2020 Recovery Trial (UK)** and other RCTs found no clinical benefit.
- **FDA revoked Emergency Use Authorization (EUA)** in June 2020 due to lack of efficacy and risk of QT prolongation and cardiac arrhythmias.

  Key Point: Hydroxychloroquine is *not* recommended for the prevention or treatment of COVID-19.

Mechanism of Action

Hydroxychloroquine has **multiple mechanisms** depending on the condition treated:

In Autoimmune Disorders:

- Increases **lysosomal pH** in antigen-presenting cells ? impairs antigen processing and presentation.
- Inhibits **toll-like receptors (TLR 7 and TLR 9)** on plasmacytoid dendritic cells ? ? interferon release.
- Reduces neutrophil chemotaxis and eosinophil activity.
- Suppresses **autoantigen presentation** , dampening immune activation.

In Malaria:

- Prevents the **biocrystallization of heme into hemozoin** in the parasite's food vacuole.
- Accumulation of free heme is **toxic** to the parasite ? lysis and death.

Pharmacokinetics

Parameter	Details
Absorption	Rapid and complete GI absorption
Bioavailability	~67–74%
Peak Plasma Time	1–3 hours
Protein Binding	~55%
Metabolism	Hepatic (CYP2D6, 2C8, 3A4/5) ? N-desethylhydroxychloroquine
Excretion	Renal (partially unchanged); long half-life (40–50 days)

Pharmacodynamics

- Lipophilic weak base ? accumulates in lysosomes.
- Increases lysosomal pH ? disrupts protein degradation and immune signaling.
- Alters MHC class II antigen processing.
- Inhibits intracellular pathways related to immune activation.

Onset and Duration

- **Onset of Action** : Typically 4–6 weeks; may take up to 6 months for full effect in autoimmune diseases.
- **Duration of Action** : Prolonged due to tissue accumulation (esp. skin, retina).

Therapeutic Benefits in Autoimmune Diseases

Hydroxychloroquine is considered **first-line therapy in SLE** due to:

- **Antithrombotic properties** : Decreases lupus-associated thrombosis.
- **Glycemic control** : Improves insulin sensitivity.
- **Lipid profile improvement** : ? LDL and triglycerides.
- ? Disease flares and long-term organ damage.

Adverse Effects

System	Adverse Effect
Ocular	Retinopathy (dose-dependent; screen annually)
Cardiac	QT prolongation, cardiomyopathy (rare but serious)
GI	Nausea, diarrhea, abdominal pain
Dermatologic	Hyperpigmentation, rash
Hematologic	Bone marrow suppression (rare)
CNS	Headache, dizziness

> Retinopathy risk increases with daily doses >5 mg/kg of actual body weight and long-term use (>5 years).

Contraindications

- Hypersensitivity to 4-aminoquinoline compounds
- Retinal or visual field changes
- Pre-existing maculopathy

Monitoring Parameters

- **Ophthalmologic exam** : Baseline + annually after 5 years of use (or earlier if risk factors)
- CBC and LFTs if long-term use
- Baseline ECG if other QT-prolonging drugs are used