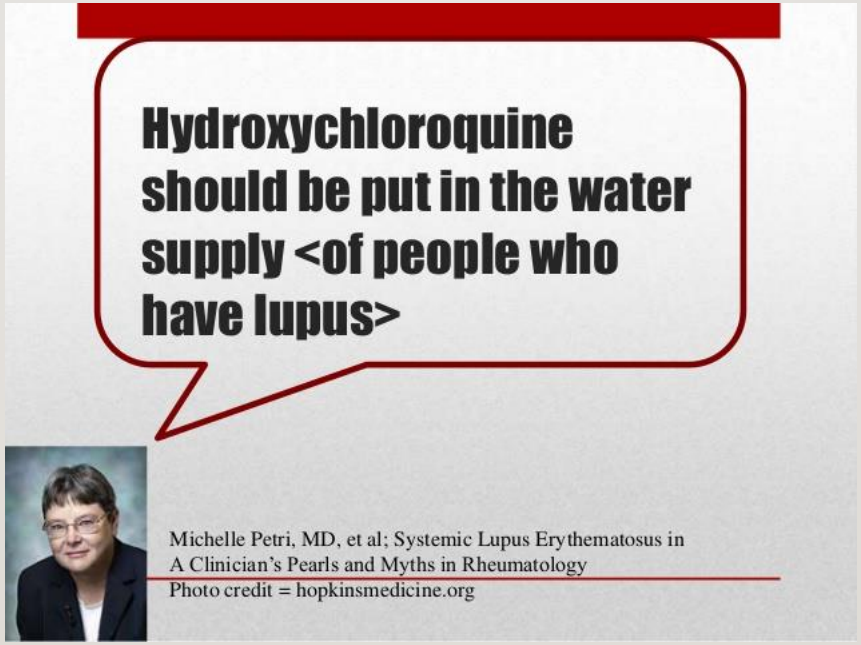
UNDERSTANDING PLAQUENIL IN THE TREATMENT OF LUPUS

AILDA NIKA, MD

ASSISTANT PROFESSOR

RUSH UNIVERSITY LUPUS CLINIC

PETRI PEARL!!!


Hydroxychloroquine should be put in the water supply <of people who have lupus>
Michelle Petri, MD, et al; Systemic Lupus Erythematosus in A Clinician's Pearls and Myths in Rheumatology
Photo credit = hopkinsmedicine.org

LUPUS

- Lupus is a complex Multi-Systemic Autoimmune Disorder:
  - Dysregulation of the immune system activation
  - Loss of tolerance of immune system to one's body, resulting in inflammation and tissue damage.
  - Environmental Factors implicated: UV light, chemicals, drugs (Bactrim), infections (Parvovirus, CMV, HCV), smoking
  - Abnormal estrogen metabolism
    - In animal studies estrogen worsens disease activity and causes early mortality

LUPUS

- The female to Male ratio is 9:1 during childbearing years
  - Closer to 2:1 during childhood and after menopause, suggesting hormonal influence
  - Disease in males is can be more severe

- 70% of SLE: females between ages 15-45 (children can get it too)
  - 10% present age >60

LUPUS TREATMENT

Drugs used in SLE

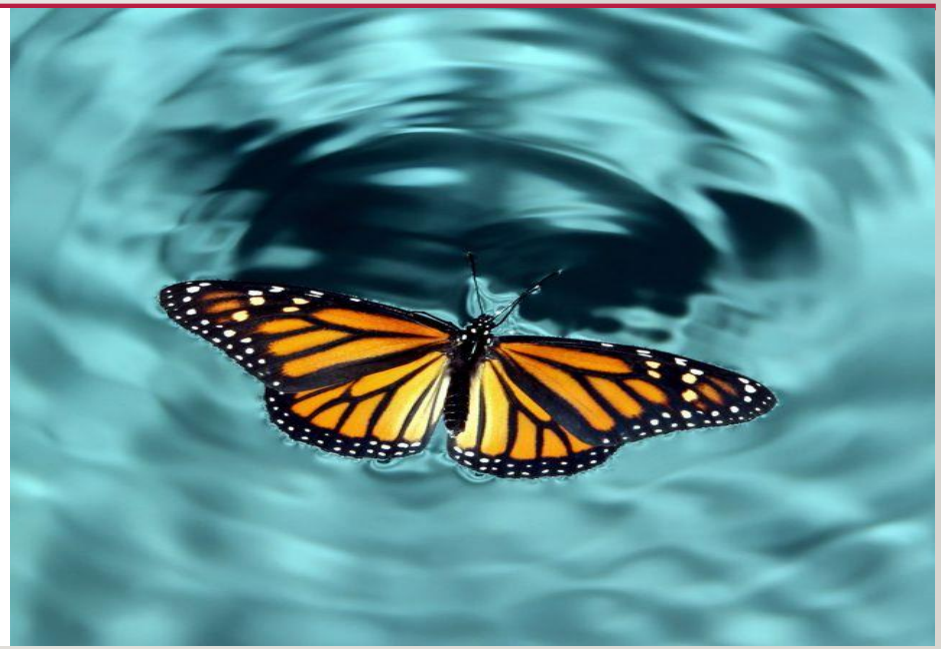
a) **Antimalarials -** Hydroxychloroquine sulfate (Plaquenil)

b) **NSAIDs -** Ibuprofen (Advil, Motrin), Naproxen (Aleve, Anaprox, Naprosyn)

c) **DMARDS, Immunomodulators –** Cyclophosphamide, Methotrexate (Otrexup, Rasuvo)

d) **Rheumatologics -** Belimumab (Benlysta)

e) **Corticosteroids -** Methylprednisolone (A-Methapred, Medrol, Solu-Medrol, Depo-Medrol)



ANTIMALARIALS

- Anti-malarials were originally used to prevent or treat malaria.
- During World War II it was also found that these medications were effective in treating the symptoms of lupus.
- Anti-malarial medications have shown to improve all of the lupus symptoms
- These medications also prevent lupus from spreading to major organs, such as the kidney and central nervous system (your brain and spinal cord)
- May also help to reduce flares by as much as 50%.
- Anti-malarials are the key to controlling lupus long term, and some lupus patients may be on Plaquenil for the rest of their lives.
- You can think of anti-malarials as a sort of “lupus life insurance.”

MORE HISTORY

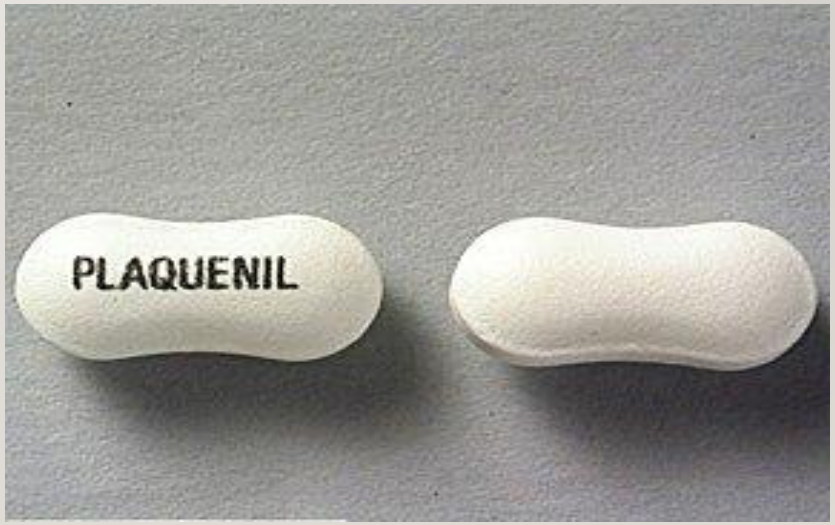
- **Quinine** was first used to treat cutaneous lupus in 1834.
- In the mid-1940s, both hydroxychloroquine (HCQ) and chloroquine (CQ) had been synthesized.
- In 1955 HCQ was shown to be effective for both systemic lupus and rheumatoid arthritis.
- **In 1956, the U.S. Food and Drug Administration approved HCQ for symptoms of lupus and rheumatoid arthritis, particularly skin inflammation, hair loss, mouth sores, fatigue, and joint pain.**

HOW DO ANTI-MALARIAL DRUGS CONTROL LUPUS SYMPTOMS?

- Anti-malarial medications help to control lupus in several ways by modulating the immune system without predisposing you much to infections.
- They can protect against UV light and improve skin lesions that do not respond to treatment with topical therapy (ointments).
- They work in the innate immune system, by preventing activation of plasmacytoid dendritic cells, a component of the immune system that is responsible for making interferon.

PLAQUENIL

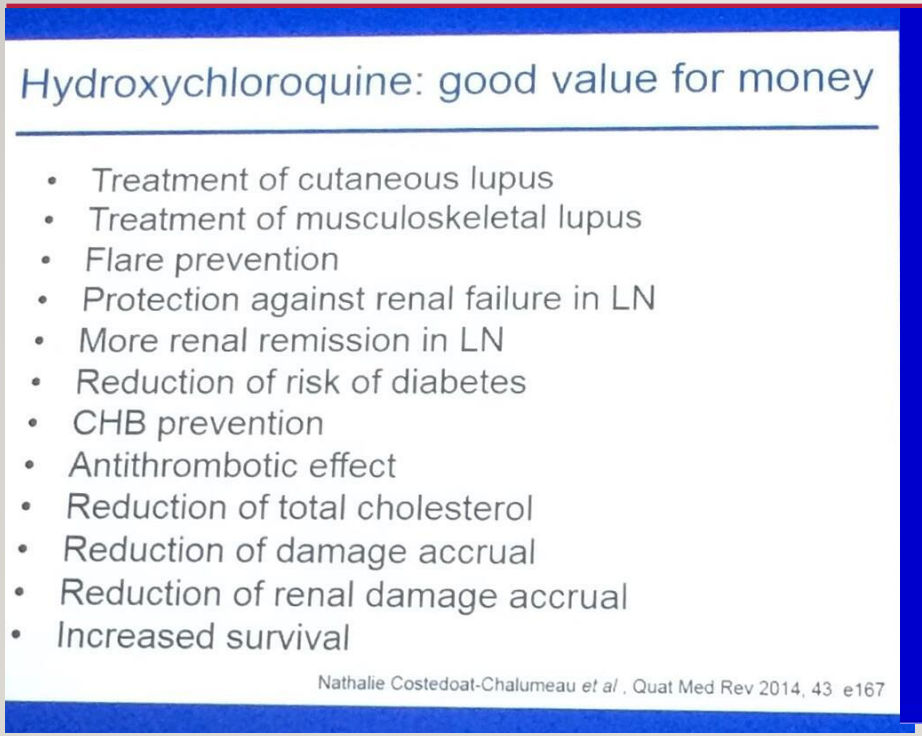
PLAQUENIL tablets are white.
Each tablet contains 200 mg hydroxychloroquine coated tablets imprinted “PLAQUENIL” on one face (equivalent to 155 mg base).
Bottles of 100 tablets

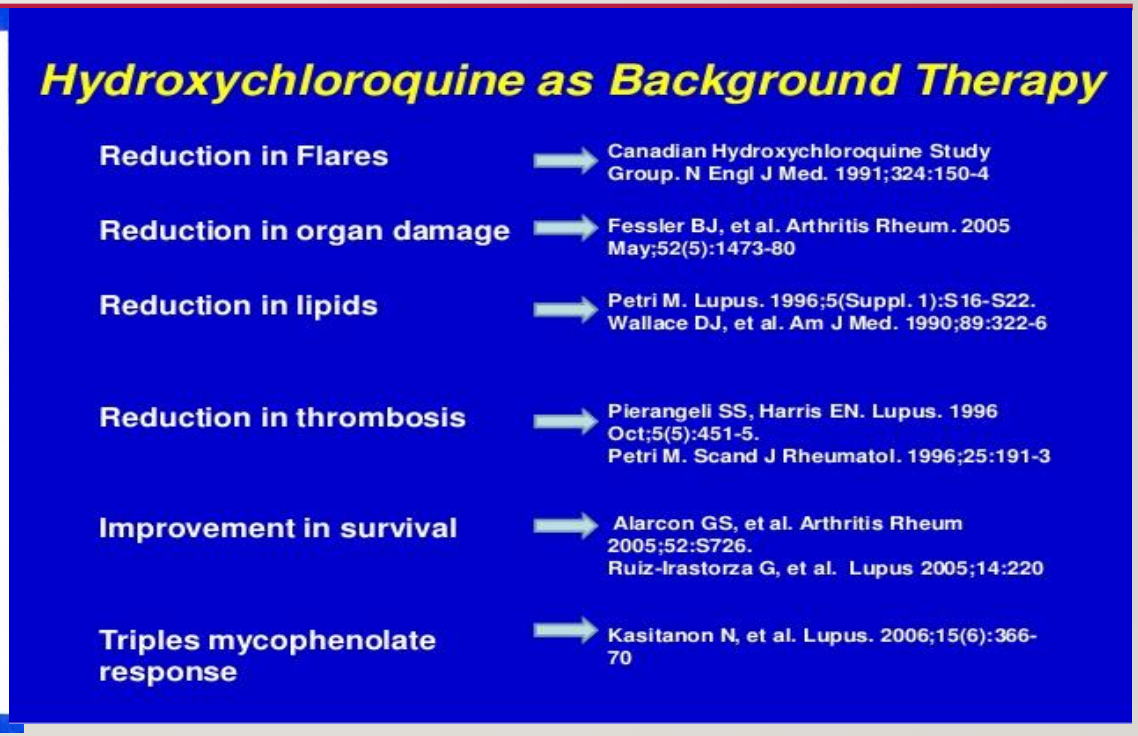


WHAT ANTI-MALARIAL DRUGS ARE COMMONLY PRESCRIBED FOR LUPUS?

- 3 anti-malarial drugs have been prescribed for lupus symptoms.
- Hydroxychloroquine (Plaquenil) is the most commonly prescribed because it is generally believed to cause fewer side effects of them all.
- Chloroquine (Aralen) has a reputation for more serious side effects, but it may be prescribed in situations where hydroxychloroquine cannot be used/tolerated.
- Quinacrine (Atabrine) is another alternative, but it is prescribed less often because it can sometimes cause a yellow discoloration of the skin. Quinacrine tablets are **no longer manufactured** and can only be obtained through a compounding pharmacist.

PLAQUENIL


Hydroxychloroquine: good value for money
• Treatment of cutaneous lupus
• Treatment of musculoskeletal lupus
• Flare prevention
• Protection against renal failure in LN
• More renal remission in LN
• Reduction of risk of diabetes
• CHB prevention
• Antithrombotic effect
• Reduction of total cholesterol
• Reduction of damage accrual
• Reduction of renal damage accrual
• Increased survival
Nathalie Costedoat-Chalumeau et al , Quat Med Rev 2014, 43 e167


Hydroxychloroquine as Background Therapy
Reduction in Flares
Canadian Hydroxychloroquine Study Group. N Engl J Med. 1991;324:150-4
Reduction in organ damage
Fessler BJ, et al. Arthritis Rheum. 2005 May;52(5):1473-80
Reduction in lipids
Petri M. Lupus. 1996;5(Suppl. 1):S16-S22.
Wallace DJ, et al. Am J Med. 1990;89:322-6
Reduction in thrombosis
Pierangeli SS, Harris EN. Lupus. 1996 Oct;5(5):451-5.
Petri M. Scand J Rheumatol. 1996;25:191-3
Improvement in survival
Alarcon GS, et al. Arthritis Rheum 2005;52:S726.
Ruiz-Irastorza G, et al. Lupus 2005;14:220
Triples mycophenolate response
Kasitanon N, et al. Lupus. 2006;15(6):366-70

PLAQUENIL

- PLAQUENIL is indicated for the treatment of malaria
- prophylaxis of malaria
- Lupus Erythematosus
- PLAQUENIL is indicated/approved for the treatment of chronic discoid lupus erythematosus and systemic lupus erythematosus in adults.
- Rheumatoid Arthritis
- Or overlap of Lupus+ RA (coined under the term Rheupus)

DOSAGE

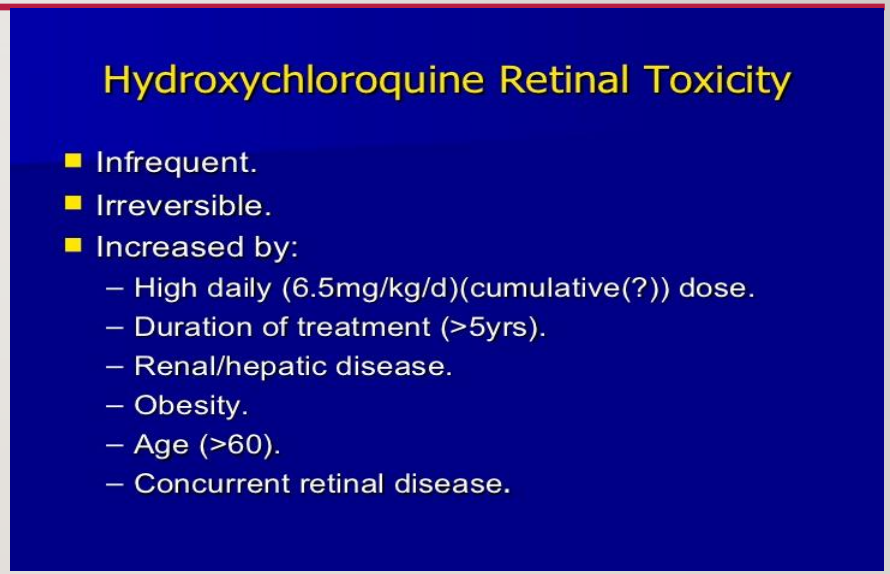
- The recommended adult dosage is < 6.5 mg/kg (ideal body weight) or 5 mg/kg actual body weight
- usually 200 to 400 mg (155 to 310 mg base) daily, administered as a single daily dose or in two divided doses.
- Doses above 400 mg a day are rarely recommended.
- Do not crush or divide PLAQUENIL film-coated tablets
- Suggested to take PLAQUENIL with a meal or a glass of milk.

PLAQUENIL

- The absorption half-life is approximately 3 to 4 hours and terminal half-life 40 to 50 days.
- The long half-life attributed to extensive tissue uptake.
- Metabolized in the liver and excreted through kidneys
- May take several weeks to start working (up to 3 months)

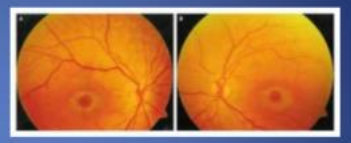
SIDE EFFECTS

- **Eye disorders** :
- retinopathy, pigmentation (bull's eye appearance),
- visual field defects
- macular degeneration,
- decreased dark adaptation,
- color vision abnormalities,
- corneal changes/ deposition with or without accompanying symptoms
- (halo around lights, photophobia, blurred vision).



OCULAR MANIFESTATIONS

Drugs affecting retina



ANTIMALARIALS:

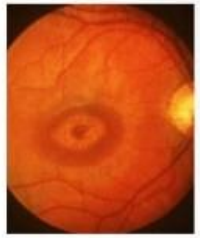
Drugs

Antimalarials- melanotropic drugs.

- **Chloroquine** retinotoxicity- related to the total cumulative dose(>300g), Rx duration > 3y
- **Hydroxychloroquine** - much safer than chloroquine

The risk of toxicity is increased if a daily dose over 6.5 mg/kg is administered for longer than 5 years, although even then the risk is still very small.

Plaquenil: Ocular Manifestions



- Corneal Verticillata
  - superficial whorl-like deposits of the corneal
  - visually asymptomatic
  - reversible with cessation
- Bilateral Pigmentary Retinopathy
  - Early
    - Typically asymptomatic
  - Subtle paracentral scotoma (loss of vision around the central area of focus)
- Bull's Eye Maculopathy (ring of pigment loss around the central area of the retina)
  - Central vision depression
- Wide Spread Retinal Pigment & Retina Cell Atrophy (cell death)
  - Central vision Loss
  - Peripheral vision Loss
  - Nyctalopia (difficulty with night vision)

WHAT SHOULD WE KEEP IN MIND WHEN TAKING ANTI-MALARIAL DRUGS?

- Damage to the retina, the light sensitive portion of the inner eye, can occur with long-term use.
- A baseline ocular examination is recommended **within the first year** of starting PLAQUENIL.
- Rare - 1 out of 5,000 people who take the drug for five years or more, no cumulative dose know though .
- If your ophthalmologist does find some Plaquenil deposits, s/he will request that you stop taking the medication.

OCULAR

- Risk factors for retinal damage include:
- Daily doses greater than 6.5 mg/kg (5 mg/kg base) of body weight, durations of use greater than 5 years, subnormal kidney function, use of some drugs such as tamoxifen and concurrent macular disease.
- Studies show that the annual risk after an examination showing no evidence of toxicity in patients using no more than 5 mg/kg was less than 1% during the first 10 years of use,
- And almost 4% per year after 20 years.
- For individuals without significant risk factors, annual exams can usually be deferred until five years of treatment.

SIDE EFFECTS

- Blood and lymphatic system disorders : anemia, aplastic anemia, leukopenia, and thrombocytopenia.
- Hemolysis reported in individuals with glucose-6- phosphate dehydrogenase (G-6-PD) deficiency.
- Cardiac disorders : Cardiomyopathy , may prolong the QT interval. Ventricular arrhythmias (extremely rare)
- Ear and labyrinth disorders : Vertigo, tinnitus, nystagmus, nerve deafness
- Gastrointestinal disorders : Nausea, vomiting, diarrhea, and abdominal pain.

SIDE EFFECTS

- Hepatic disorders : Liver function tests abnormalities
- Urticaria, angioedema, bronchospasm
- Metabolism: Decreased appetite, hypoglycemia, weight decreased.
- Musculoskeletal : myopathy or neuromyopathy leading to progressive weakness of muscle groups

SIDE EFFECTS

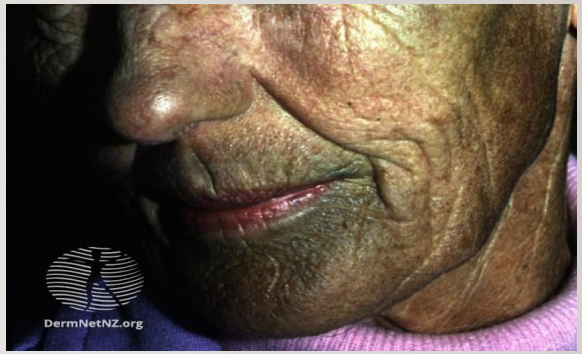
- Nervous system disorders : Headache, dizziness, seizure, tremor
- Psychiatric disorders : Affect/emotional lability, nervousness, irritability,
- Skin: rash, pruritus/itching, pigmentation disorders in skin and mucous membranes, hair color changes, hair loss (also treats alopecia)
- May precipitate attacks of psoriasis.

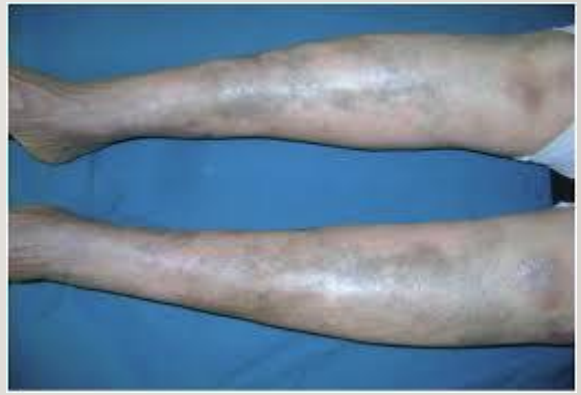
CARDIAC EFFECTS, INCLUDING CARDIOMYOPATHY AND QT PROLONGATION

- Cardiomyopathy have been reported with use of PLAQUENIL as well as with use of chloroquine.
- ECG findings may include arythmias, atrioventricular, right or left bundle branch block.
- Chronic toxicity should be considered when conduction disorders (bundle branch block/atrioventricular heart block) or biventricular hypertrophy are diagnosed(ECHO).
- If cardiotoxicity is suspected, prompt discontinuation of PLAQUENIL may prevent life-threatening complications.

SKIN DISCOLORATION

Can be slowly reversible with time with drug discontinuation





DRUG INTERACTIONS

- Digoxin- Concomitant PLAQUENIL and digoxin therapy may result in increased serum digoxin levels
- Insulin Or Antidiabetic Drugs- As PLAQUENIL may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin may be required.
- Drugs That Prolong QT Interval And Other Arrhythmogenic Drugs
- PLAQUENIL can lower the seizure threshold.
- Antiepileptics

DRUG INTERACTIONS

- Cyclosporine - An increased plasma cyclosporine level was reported when cyclosporine and PLAQUENIL were co-administered.
- Antacids -Antacids can reduce absorption of chloroquine; an interval of at least **4 hours between intake of these agents** and chloroquine should be observed.
- Cimetidine- Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level. Concomitant use of cimetidine should be avoided.

OTHER

- Worsening Of Psoriasis
- Use of PLAQUENIL in patients with psoriasis may precipitate a severe attack of psoriasis.
- When used in patients with porphyria the condition may be exacerbated.
- The preparation should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the possible hazard.

PREGNANCY/ NURSING

- No known teratogenic Effects
- Human pregnancies resulting in live births have been reported in the literature and no increase in the rate of birth defects has been demonstrated.
- Nursing Mothers
- Caution should be exercised when administering PLAQUENIL to nursing women. It has been demonstrated that hydroxychloroquine administered to nursing women is excreted in human milk

OVERDOSE

- Plaquenil is very rapidly and completely absorbed after ingestion
- Accidental over-dosage, or rarely with lower doses in hypersensitive patients, toxic symptoms may occur within 30 minutes.
- Symptoms may include headache, drowsiness, visual changes, convulsions, arrhythmias, potentially respiratory and cardiac arrest.
- In that case treatment must be prompt.
- Immediate gastric lavage
- activated charcoal within 30 minutes of ingestion

- diazepam may be beneficial in reversing chloroquine and hydroxychloroquine cardiotoxicity.
- Respiratory support as necessary.

OTHER PEARLS

- **Do not smoke** while taking anti-malarial medications, since smoking actually reduces the benefits of these drugs. In fact, people with lupus should not smoke at all due to their increased risk of cardiovascular disease.
- You should always **take your anti-malarial medications with food** to prevent stomach upset. If a stomachache does occur, it is usually temporary.
- However, if you experience stomach upset while taking generic hydroxychloroquine, ask your doctor about trying name-brand Plaquenil instead.
- Your doctor can ensure that you receive this version of the medication by writing “do not substitute” on your script.

BLOOD LEVELS

- There are available laboratory tests to check levels of HCQ and its metabolites, but the role of routine testing in clinical care is uncertain.
- There has been an increased interest in blood level testing to identify patients who are non-adherent with therapy.
- Adherence in systemic lupus erythematosus (SLE) has been estimated to be as low as 20 percent in some studies
- In one study, in which adherence was defined as the presence of a therapeutic drug level (at least 500 ng/mL), the measurement of the HCQ blood level, together with counseling regarding dosing and repeated testing, resulted in an increase in adherence from 56% (at baseline) to 80% (after 3 or more visits at which levels were assessed)
- No studies have correlated HCQ levels with ocular toxicity.

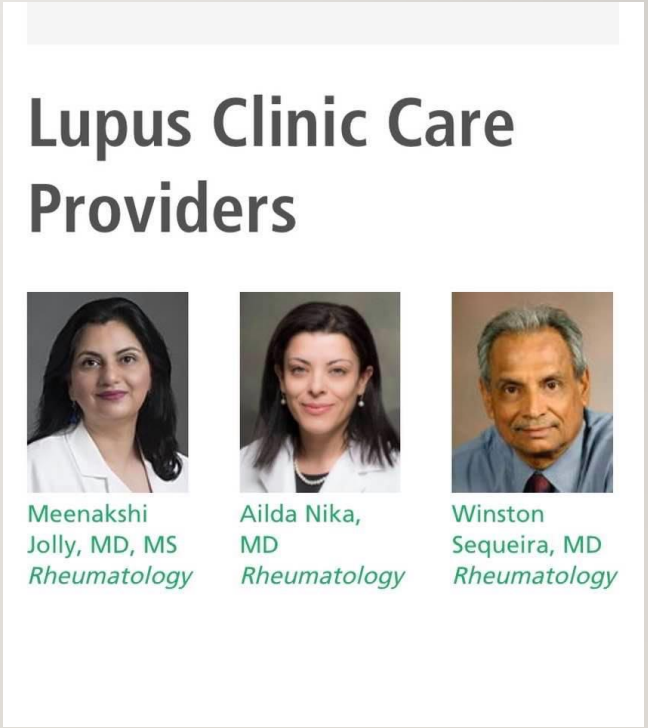
- Lastly, remember that even though you may feel the benefits of anti-malarial therapy after about a month of treatment, it may take up to three months for the full benefits of the drug to manifest.
- If you experience any serious adverse effects, notify your doctor.
- **Can I stop taking anti-malarials suddenly?**
- Long-term anti-malarial use is normally safe. However, if you stop taking your anti-malarial drugs, you may experience a lupus flare.

POTENTIAL ADDED BENEFITS OF ANTI-MALARIAL DRUGS

- Anti-malarial drugs may have additional health benefits for some people.
- Potential benefits include **lower cholesterol** and **blood glucose** levels.
- These benefits may be especially helpful for people taking steroids.
- In addition, individuals with antiphospholipid antibodies, such as the lupus anticoagulant and anti-cardiolipin antibodies, may experience a decreased likelihood of blood clots.

QUESTIONS

- ? ? ?


Lupus Clinic Care Providers
Meenakshi Jolly, MD, MS
Rheumatology
Ailda Nika, MD
Rheumatology
Winston Sequeira, MD
Rheumatology

THANK YOU!
RUSH LUPUS TEAM!!!!