Welcome!

Other Conventional DMARDs

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INDIAN + COUNTRY ECHO

AMERICAN COLLEGE of RHEUMATOLOGY *Empowering Rheumatology Professionals*

UCSF Health

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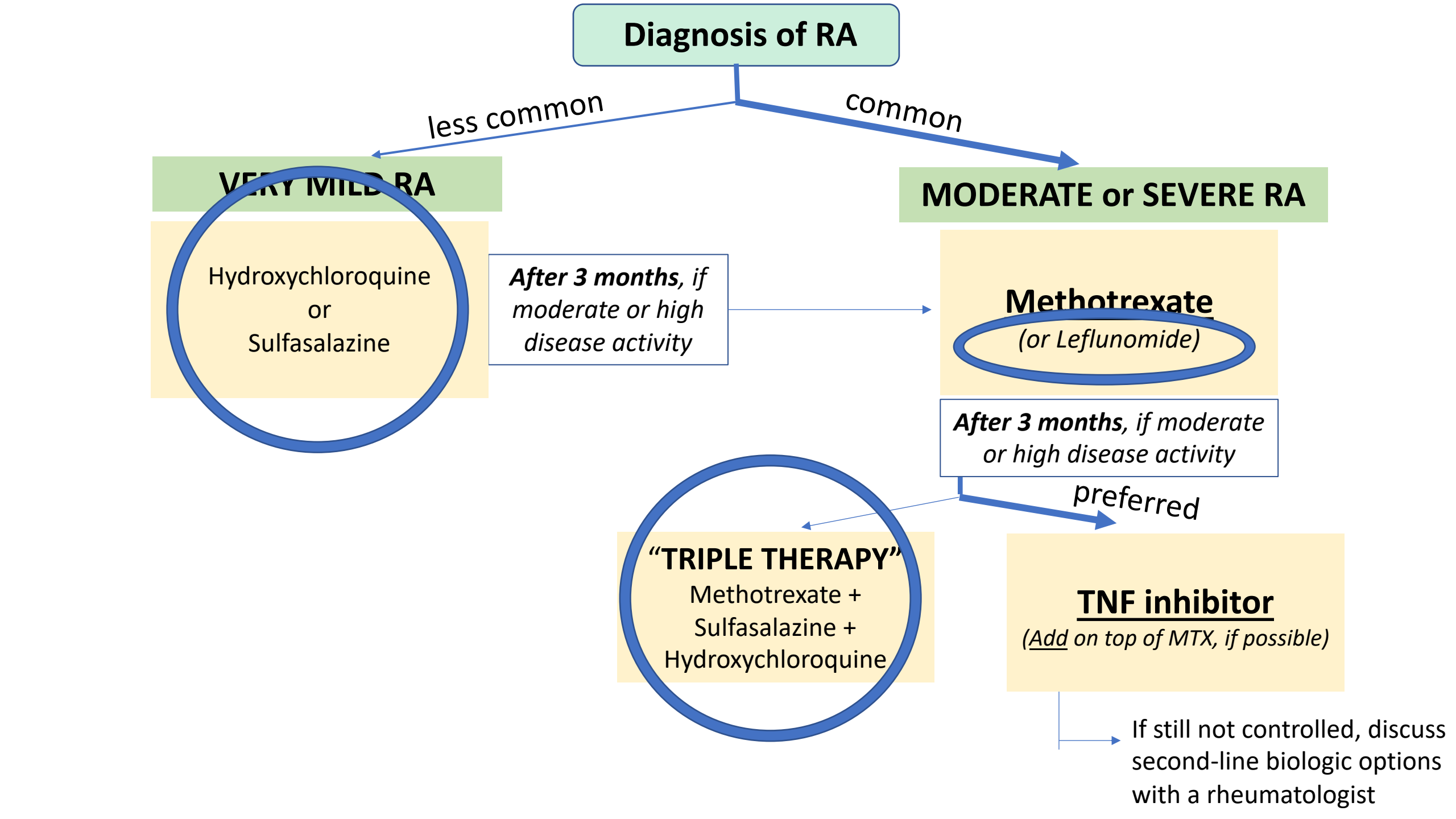
Planners Jennifer Mandal, MD, Leslie Dexheimer Gleason, RN, and Tabitha Carroway, MPH have stated they have no relationships to disclose. Speaker Wendy Grant, MD has stated she has no relationships to disclose.


Diagnosis of RA
less common
common
VERY MILD RA
MODERATE or SEVERE RA
Hydroxychloroquine
or
Sulfasalazine
After 3 months, if moderate or high disease activity
Methotrexate
(or Leflunomide)
After 3 months, if moderate or high disease activity
preferred
"TRIPLE THERAPY"
Methotrexate +
Sulfasalazine +
Hydroxychloroquine
TNF inhibitor
(Add on top of MTX, if possible)
If still not controlled, discuss second-line biologic options with a rheumatologist

Hydroxychloroquine

Hydroxychloroquine (Plaquenil)

- Anti-malarial
- First-line therapy for **very mild RA** (low disease activity, no extra-articular manifestations, no erosions), or can be used in combination w/ MTX+sulfasalazine (“triple therapy”) in more severe/refractory RA
- Also used in SLE, MCTD, Sjogrens

Hydroxychloroquine (Plaquenil)

- 1638: the wife of the Viceroy of Peru, Countess Cinchona, was cured of a febrile illness (malaria) by an Incan healer using a powder from the bark of a native tree (now known as the Cinchona tree)
- Shipped in large quantities back to Spain and controlled by the Jesuits for 200 years
- Quinine isolated in mid 1800's – popular folk remedy for "malaise"
- Chloroquine developed during WWII for its antimalarial effect
- Hydroxychloroquine developed in 1950's – less toxic than chloroquine
- Benefits for lupus and RA recognized in the 1950's

Hydroxychloroquine (Plaquenil)

- Unlike most other DMARDs, **HCQ is not immunosuppressive**
- Mechanisms of actions are poorly understood. Inhibitory effect on toll-like receptors (TLRs), many other proposed mechanisms
- **Can take months to have effect** (full effect typically by 6 months)
- Long terminal half-life (1-2 months)

Hydroxychloroquine: Dosing

- Once daily pill
- Calculate dose based on weight: **5mg/kg, then round down to nearest 100.** (Only comes in 200mg tablets. Ok to cut pills.)
  - Dose >5mg/kg is associated with increased risk of irreversible retinal toxicity
- Dose should be lowered in setting of severe renal impairment
  - HD: 200mg 3x/week after HD

Example:

70kg patient:

70kg x 5mg/kg = 350mg

→ Round down to 300mg.

Dose = 300mg (1.5 pills) per day

Hydroxychloroquine: Adverse Effects

- **Retinal toxicity**
- GI upset (cramping, nausea)
- Skin hyperpigmentation
- Transient blurry vision
  - early; not associated with ↑ risk for retinal toxicity
- Neuromyotoxicity (rare)
  - painless proximal muscle weakness, CK normal or slightly elevated
- Cardiotoxicity (rare at dose <5mg/kg)
  - QTc prolongation, arrythmias
  - Cardiomyopathy resulting in CHF

What monitoring is recommended for a patient on hydroxychloroquine?

A. Ophthalmology exam every 5 years
B. Ophthalmology exam every year
C. Ophthalmology exam every 5 years + CBC/CMP every year
D. Ophthalmology exam every year + CBC/CMP every year

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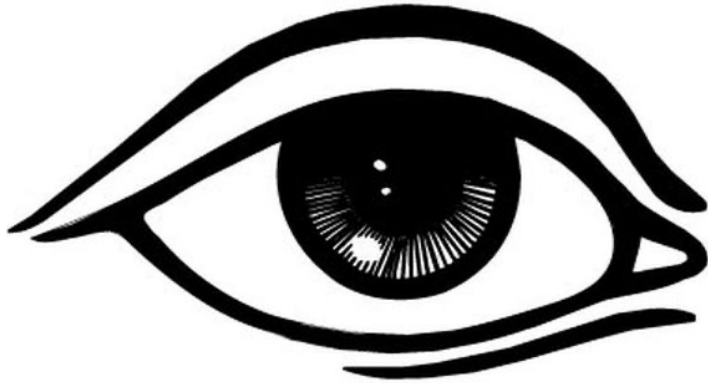
Hydroxychloroquine: Retinal Toxicity



- Vision-threatening, irreversible retinal toxicity
- **Risk depends heavily on duration of HCQ use**
  - <2% risk in the first 5 years
  - But rises to 20% with >20 years of use
- Screening: Annual ophthalmology exam (visual acuity screening is not enough) while on HCQ
- Discontinue HCQ immediately if any sign of retinal toxicity

How to reduce the risk of hydroxychloroquine associated retinal toxicity:

- Make sure your patients are getting their annual ophthalmology exam (with dilation and full retinal exam)
- Limit dose to <5mg/kg
- Do not combine hydroxychloroquine with chloroquine
- If an ophthalmology exam reveals any retinal toxicity (even mild) stop hydroxychloroquine immediately and do not restart (list it as allergy/contraindicated in the patient's chart)

Hydroxychloroquine: Monitoring

- Annual retinal exam
- No routine lab monitoring required

Sulfasalazine

Sulfasalazine

- Used in RA since the 1980s
- Can be used as an alternative to HCQ in mild RA (low disease activity), or in combination with MTX+HCQ (“triple therapy”) in more severe/refractory disease

Sulfasalazine: Dosing & Monitoring

- Pre-treatment testing: CBC, LFTs, Cr
  - Consider testing for G6PD deficiency (increased risk of hemolytic anemia)
- Typically start with 500mg daily → then increase dose by 500mg weekly (w/ lab checks) until target dose of 2g – 3g daily (divided BID) is achieved
- Monitoring: Check labs (CBC, LFTs, Cr) ~1 week after each dose increase. Once on a stable dose, can check labs q 3 months

Sulfasalazine: Adverse Effects

- GI upset
- Hepatotoxicity
- Leukopenia (usually mild, but life-threatening agranulocytosis can rarely occur, typically within first 3 months of starting tx)
- Hemolytic anemia (usually in setting of G6PD deficiency)
- Men: reversible oligospermia (Avoid in men who are trying to conceive.)

Safe in pregnancy & breastfeeding

What is “Triple Therapy” for RA?

A. Methotrexate + Leflunomide + Hydroxychloroquine

B. Methotrexate + Hydroxychloroquine + Sulfasalazine

C. Methotrexate + Sulfasalazine + Prednisone

D. Methotrexate + Hydroxychloroquine + Prednisone

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RA “Triple Therapy”: MTX + HCQ + Sulfasalazine

- For patients who have inadequate response to MTX alone, options for escalating therapy include:
  - 1) Adding a biologic DMARD such as TNFi (preferred)
  - 2) Starting triple therapy (PO)

Complex oral regimen with heavy pill burden…

1-2 pills of HCQ once daily
2-6 pills of sulfasalazine daily (divided BID)
1 folic acid pill daily
6-10 methotrexate pills (or SQ injection) once a week

34 – 73 pills per week, just for RA!

RA “Triple Therapy”: MTX + HCQ + Sulfasalazine

Reasons to choose Triple Therapy over a Biologic DMARD:

- Patient strongly prefers pills over injections (ex: needle phobia)
  - Note: JAK inhibitors are another potential option for patients who will only take pills

- Cost: Triple therapy is MUCH less expensive that TNFi (and other biologics). Depends on insurance coverage.

- “Don’t Rock the Boat”: Patient has been stable on triple therapy for a long time and doesn’t want/need to change.

Leflunomide

Quick Pearls: Leflunomide

- Oral conventional DMARD
- Sometimes used as an alternative to MTX (ex: pt in whom daily dosing is strongly preferred)
- Very similar side effect profile to MTX (GI upset, hepatotoxicity, teratogenic), same lab monitoring guidelines
  - CBC, Cr, LFTs: monthly until stable dose, then q3 months
- Typical dose = 20mg daily (can decrease to 10mg daily if side effects)

A 41 year old woman with RA on leflunomide discovers that she is 8 weeks pregnant. She wishes to continue the pregnancy. In addition to stopping leflunomide, what is the most appropriate next step:

A. Start methotrexate

B. Counsel her that termination of the pregnancy is recommended due to high risk of maternal mortality

C. Start cholestyramine

D. Refer to high risk OB for serial fetal echocardiograms throughout the pregnancy

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Quick Pearls: Leflunomide

- EXTREMELY LONG HALF-LIFE: Can linger in the body for **<u>up to 2 years</u>** after discontinuation!
  - **Avoid in women of childbearing age!**
  - In case of serious adverse event or accidental pregnancy, there is a (very unpleasant) accelerated drug elimination protocol: cholestyramine 8g PO TID for 11 days

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