Welcome!

Initial Therapy: Glucocorticoids, NSAIDs, and Other Conventional DMARDs

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NSAIDs: The Basics

NSAIDs - Key Points

- They are widely used in RA and are effective for treating inflammation and pain
- They do not reduce levels of acute phase reactants or prevent radiographic progression (ie, they are not DMARDs)
- All work by blocking production of prostaglandins via the cyclo-oxygenase enzyme (COX)
- Prostaglandins play a key role in the inflammatory response BUT are also protective in certain tissues

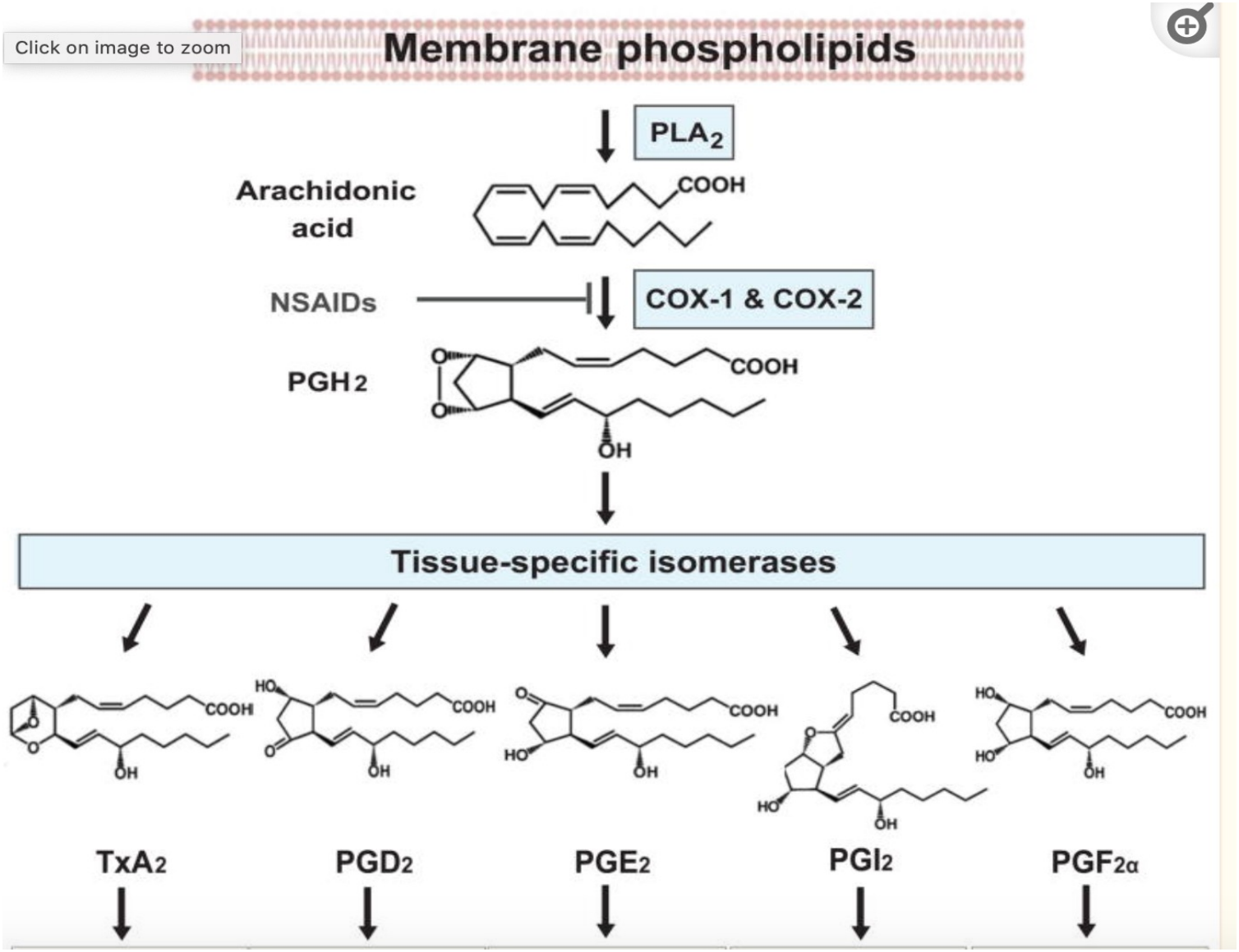
NSAIDs: The Basics

NSAIDs - Key Points

- COX-1: expressed under basal conditions
  - Platelets (thromboxane A2 is a PG that signals platelet aggregation)
  - GI mucosa (PGs have a protective effect)
  - Kidney (renal tubules; PGs help maintain perfusion)

- COX-2: expressed during inflammation/stress

Click on image to zoom



NSAIDs: The Basics

NSAIDs - Key Points

NSAIDs are grouped according to:

- **chemical structure**
- **half life**

”short acting” (< 6 hrs): IBU, diclofenac, ketoprofen, indomethacin

“long acting” (> 6 hrs): naproxen, celecoxib, meloxicam, nabumetone, piroxicam

- **COX-1 vs COX-2 selectivity**

NSAIDs
The Basics

Major Structural Class	Subclass	Examples
Carboxylic Acids	Acetylated	ASA
	Acetic Acids	indomethacin, sulindac, diclofenac
	Propionic Acids	ibuprofen, naproxen
	Pyrollizine Derivatives	ketorolac
Enolic Acids	Oxicams	meloxicam
COX-2 Inhibitors		celecoxib

NSAIDs
The Basics

Short acting (< 6 hrs)

IBU
diclofenac
ketoprofen
indomethacin

Long acting (> 6 hrs)

naproxen
celecoxib
meloxicam
nabumetone
piroxicam

NSAIDs
The Basics

INHIBITION	Examples
COX-1 Specific	ASA (irreversibly binds/inhibits COX-1)
COX Nonselective	ibuprofen, naproxen, indomethacin
COX-2 Selective	meloxicam, diclofenac
COX-2 Highly Selective	celecoxib

NSAIDs: The Basics

NSAIDs - Key Points

Most NSAIDs inhibit both COX-1 and COX-2, with variable relative potency for these targets

NSAIDs tend to accumulate in synovial fluid; anti-inflammatory effect may last longer than the ½ life suggests

Overall, efficacy of different NSAIDs is about equal although individual responses may vary

Toxicities are largely related to COX-1 effects but also to bioavailabilty, individual patient risk factors

NSAIDs
The Basics

NSAIDs: Complications

GI: dyspepsia, esophagitis, ulcers, erosions, strictures, colitis

Renal: Na retention, edema, HTN, ARF, RTA, AIN, accelerated CKD

CV: CHF exacerbation, MI, stroke

Hepatic: transaminase elevations

CNS: headache, confusion, seizures, aseptic meningitis

Allergic: ASA-exacerbated asthma; rash

Bone: delayed healing

NSAIDs
The Basics

NSAIDs: Mitigation Strategies

< 65 years, uncomplicated (no GI, renal or CV risk; no ASA or anticoag)

- traditional NSAID; short acting and lowest dose possible

< 65 years, intermediate risk

- Traditional NSAID + PPI or misoprostol or **high dose** H2 blocker
- If on ASA→ Celecoxib + PPI

NSAIDs
The Basics

NSAIDs: Mitigation Strategies

> 65 years, or otherwise high risk
- intermittent, low-dose, short half-life
- avoid chronic NSAIDs if possible
  if required:
    CV risk > GI risk: use naproxen/IBU + PPI
    GI risk > CV risk: use Celecoxib + PPI
- acetaminophen < 3 gm/day
- Topical NSAIDs (diclofenac gel)

NSAIDs
The Basics

NSAIDs in RA

- Avoid concomitant use with glucocorticoids (increased GI tox)
- MTX & NSAIDs: theoretically NSAIDs may increase MTX plasma concentrations. However, a 2012 Cochrane review concluded that NSAID + MTX was safe
- Monitor CMP/CBC annually in chronic use

NSAIDs
The Basics

NSAIDs in Pregnancy

- **Safe up to 20 weeks**
- **Possible increased risk of oligohydramnios at 20-30 weeks**
- **Avoid > 30 weeks (premature closure of the PDA)**

Glucocorticoids: The Basics

Glucose metabolism + adrenal cortex + steroid structure =

Glucocorticoids

”Corticosteroids” = glucocorticoids + mineralocorticoids

GCs bind to intracellular GC receptor and inhibit a broad range of immune responses; inhibit synthesis of almost all pro-inflammatory cytokines

Addison used adrenal extracts in the 19th C to treat “Addison’s disease”

1940’s push to isolate active compounds from adrenals

1948: first therapeutic use of glucocorticoids (compound E) in human disease

Glucocorticoids: The Basics

GCs - Key Points

- both ACR and EULAR's guidelines advocate for using the lowest dose (10 mg or 7.5 mg) for the shortest time possible

- recommended to use with initiation of DMARD therapy with plan for taper off by 3 months (US) or 6 months (EU) and for flares

= clear data that GCs reduce disease activity in the short term

- medium and long term benefit? Some studies show decreased radiographic progression at 2 years in GC + MTX vs PBO + MTX

Glucocorticoids: The Basics

DURATION	GLUCOCORTICOID	POTENCY	MINERALOCORTICOID
Short Acting	Hydrocortisone	1	1
Intermediate Acting	Prednisone	4	0.25
	Prednisolone	4	0.25
	Methylprednisolone	5	+/-
Long Acting	Dexamethasone	40	+/-

Glucocorticoids: The Basics

GCs - RA

- Initial: 10 - 15mg QD, then taper to 5 mg while introducing DMARD therapy
- For flares:
  - Multiple options but if treating for 3-10 days, no need to taper
  - Unusual to require > 15 mg for flare
  - Consider IM methylpred at 80-120 mg; self-taper over 2 weeks
- Chronic low-dose (5mg or less) used, rarely, as chronic therapy

Glucocorticoids: The Basics

Toxicities are generally related to dose and duration

Very low dose GC (3 mg/d) = low increased risk of toxicities at 7 years

- *Endocrine:* osteoporosis
- *Infectious:* any infection
- *GI*: gastritis/erosion/ulcers
- *Endo*: Risk of adrenal insufficiency at 3-5wks
- *Endo*: Risk of insulin resistance incr. at >10 pred/day
- *CV*: Fluid retention/hypertension; cardiovascular events
- *Integument:* skin fragility

Glucocorticoids: The Basics

Glucocorticoids: Mitigation Strategies

Lowest dose, shortest duration

Ca/Vit D supplementation

Screening/treatment for osteoporosis (bone loss is most pronounced in the first few months of treatment; GCs associated with higher fracture risk and at higher BMD)

GI protection

PJP prophylaxis for prednisone > 20 mg x 4 weeks

increased risk with baseline lymphopenia, pulse steroids, cyclophosphamide use

GCs and NSAIDs
The Basics

SUMMARY

- NSAIDs treat pain and inflammation - but are NOT effective DMARDs in RA
- GCs at low dose may have some DMARD effects but are generally not used in this fashion, given other effective therapies
- NSAID and GC treatment-related AEs common but often manageable with proper screening/mitigation

Opioids and RA

Any benefit in treating RA pain?

- Trials are of short duration
- Benefit is neutral/modest in these trials
- Most evidence does not support the use of opioids in chronic non-cancer pain

Opioids and RA

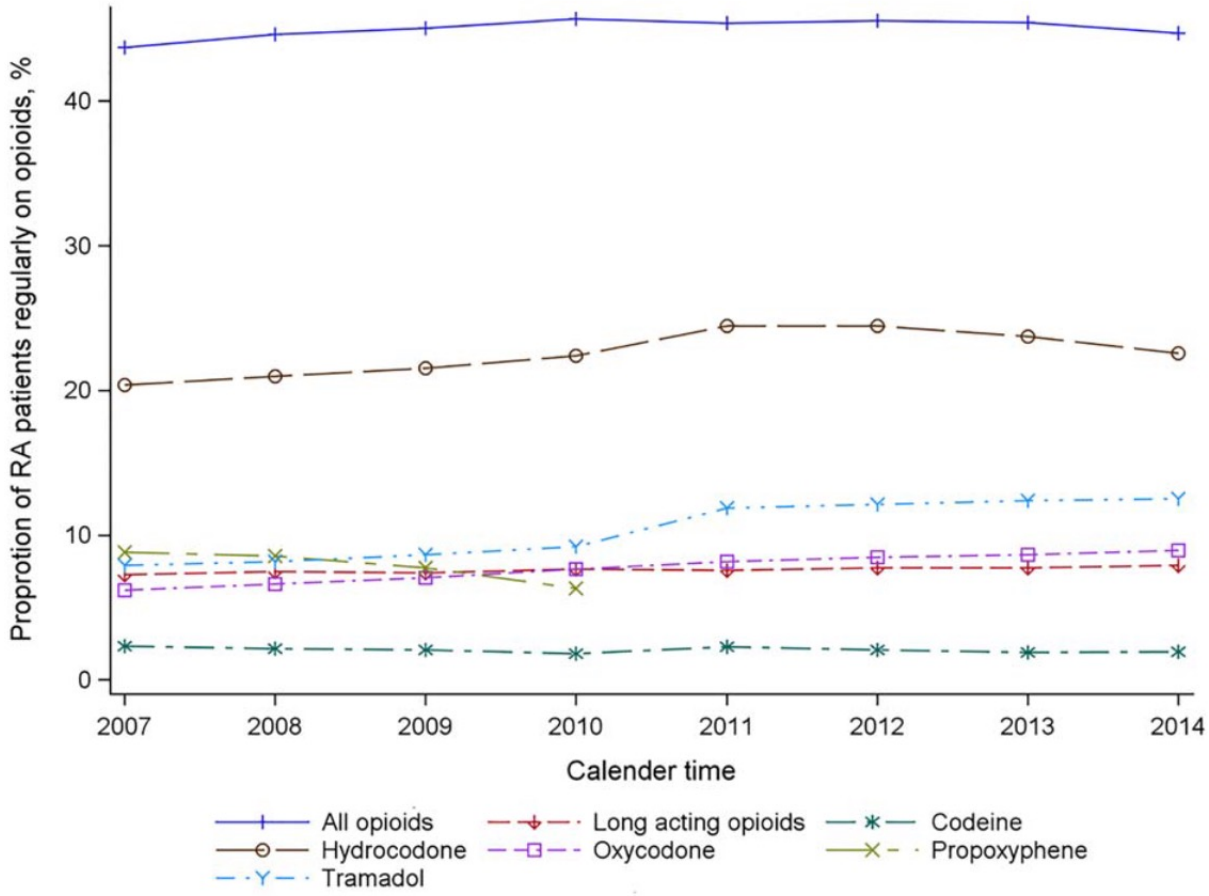


Figure 1. Trends in regular opioid receipt (defined as ≥3 filled prescriptions or at least 90 days of cumulative use in each 12-month calendar interval) in patients with rheumatoid arthritis (RA).

Curtis et al. Arthritis and Rheumatology. Vol 69, No 9, Sept 2017; 1733-1740

Opioids and RA

Regular opioid use was associated with

- female sex
- fibromyalgia
- depression/anxiety
- back pain
- use of durable medical equipment

In a separate study, 25% of regular opioid use among RA patients was associated with obesity

Curtis et al. Arthritis and Rheumatology. Vol 69, No 9, Sept 2017; 1733-1740

What about Diet?

Altered microbiome postulated as possible etiology in pathogenesis of RA

Foods purported to promote/exacerbate inflammation:

- refined sugar/sugary drinks
- preservatives
- saturated and trans fats
- red/processed meats
- highly processed foods

What about Diet?

Most trials of diet in RA are small (15-30 patients)

Short term benefits found in:

- Subtotal fasting → vegan diet
- Vegan diet
- Mediterranean diet
- ITIS diet (Mediterranean plus)

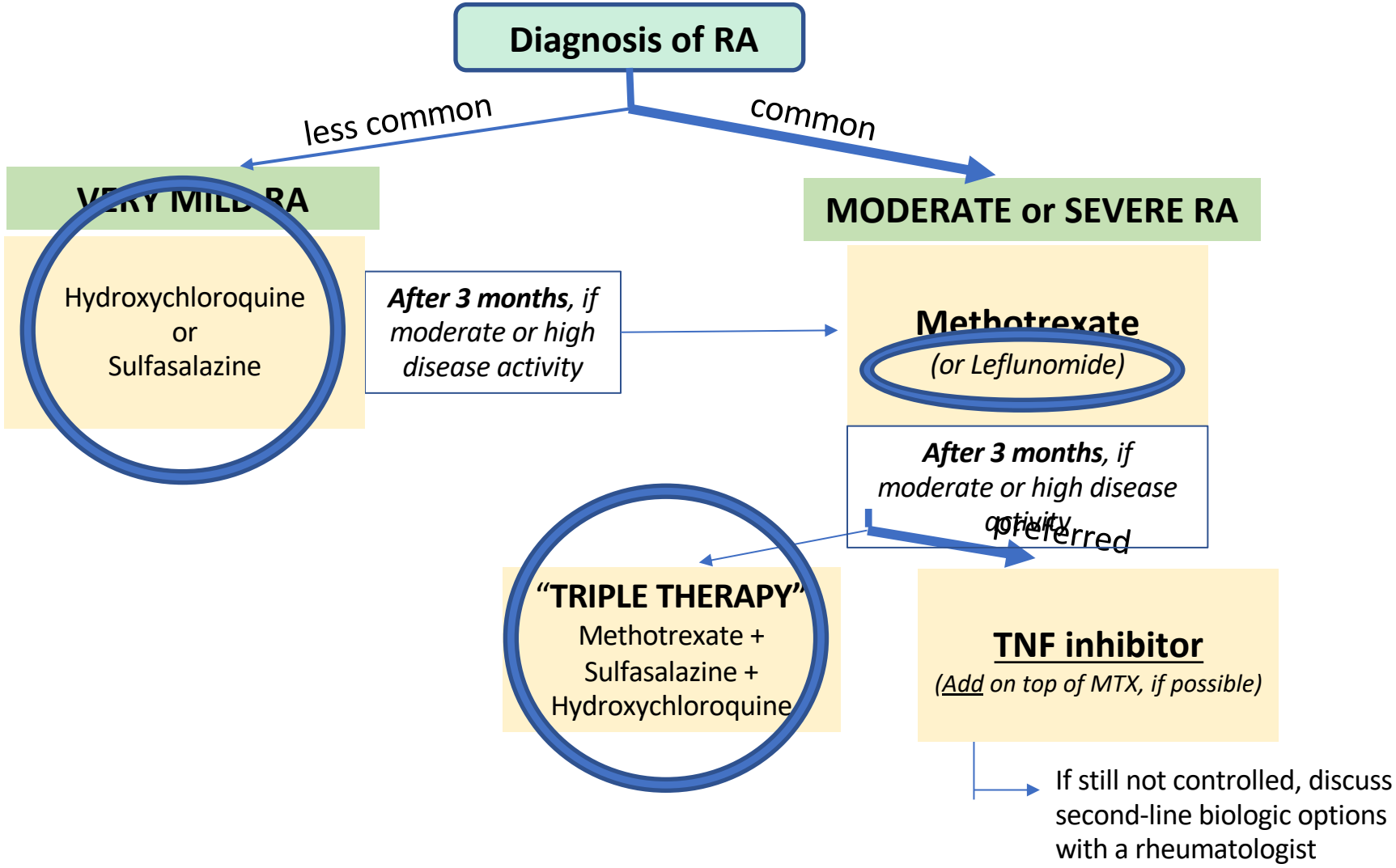
Obesity and RA

- Higher disease activity scores
- Higher pain scores
- Reduced remission rates
- Decreased response to c/b DMARDs

Weight loss effects

In 53 patients who underwent bariatric surgery, 68% achieved remission at 6 months

Other Conventional DMARDs


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 dosing
- 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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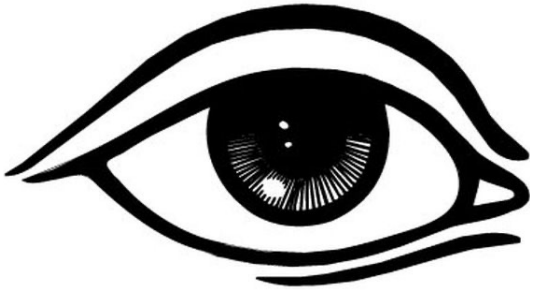
Hydroxychloroquine: Retinal Toxicity

- 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.)

What is “Triple Therapy” for RA?

A. Methotrexate + Leflunomide + Hydroxychloroquine

B. Methotrexate + Hydroxychloroquine + Sulfasalazine

C. Methotrexate + Sulfasalazine + Prednisone

D. Methotrexate + Hydroxychloroquine + Prednisone

What is “Triple Therapy” for RA?

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D. Methotrexate + Hydroxychloroquine + Prednisone

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 **up to 2 years** 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

References

Crofford, LJ. Use of NSAIDs in treating patients with rheumatoid arthritis. Arth Res Ther, 2013; 15 (Suppl 3)

Colebatch AN. Safety of NSAIDs in people receiving methotrexate for inflammatory arthritis. J Rheum Suppl 2012; 15: 62-73

Hua C. Glucocorticoids in rheumatoid arthritis: current status and future studies. RMD Open 2020; 6:e000536

Corras R. RA Improvement after exposure to ITIS diet. ACR 2020 Abstract

Khanna S. Managing Rheumatoid Arthritis with Dietary Interventions.
Front Nutr 2017; 4: 52

https://www.uptodate.com/contents/nsaids-therapeutic-use-and-variability-of-response-in-adults

https://www.uptodate.com/contents/nsaids-therapeutic-use-and-variability-of-response-in-adults?search=nsaids&sectionRank=1&usage_type=default&anchor=H8&source=machineLearning&selectedTitle=2~147&display_rank=1#H8

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