
# Welcome!

## Initial Therapy: Methotrexate

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INDIAN + COUNTRY ECHO

AMERICAN COLLEGE of RHEUMATOLOGY
*Empowering Rheumatology Professionals*

UCSF Health

# DISCLOSURES

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## Disclosure Statement

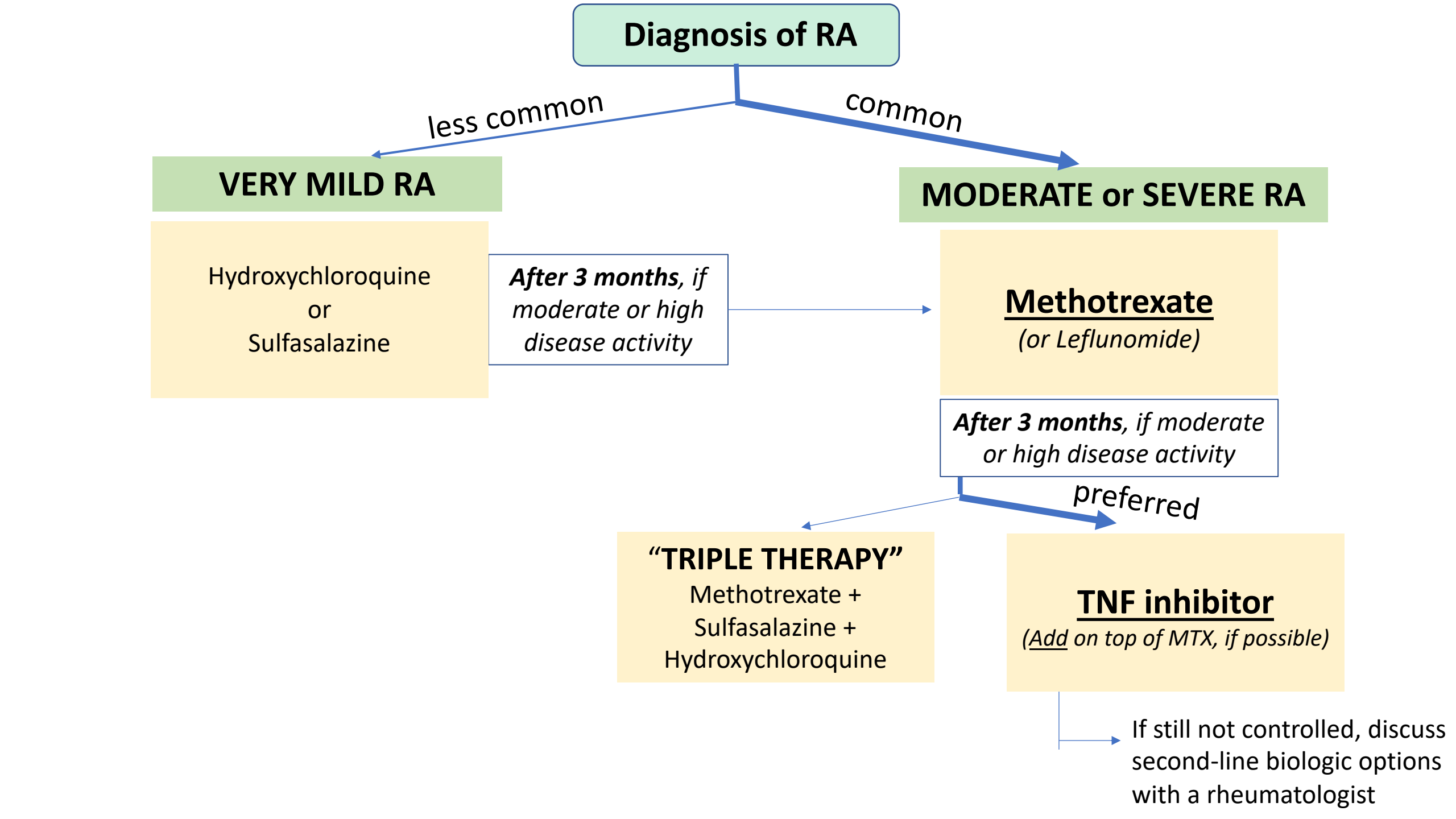
Planners Jennifer Mandal, MD, Leslie Dexheimer Gleason, RN, and Tabitha Carroway, MPH have stated they have no relationships to disclose. Speaker Jennifer Mandal, MD has stated she has no relationships to disclose.

# Terminology: DMARDs

*Disease Modifying Anti-Rheumatic Drugs*

- “Conventional DMARDs”:
  - Methotrexate, Hydroxychloroquine, Sulfasalazine, Leflunomide

- “Biologic DMARDs”:
  - TNF inhibitors: etanercept/Enbrel (SQ), adalimumab/Humira (SQ), infliximab/Remicade (IV)
  - Others: abatacept (T cell costimulatory inhibitor), rituximab (anti-CD20), tocilizumab (IL-6 inhibitor), tofacitinib (JAK inhibitor)


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

# Methotrexate

- MTX is the preferred first-line DMARD in patients with moderate-severe RA
- First used to treat RA in the 1950s, but didn't see widespread use until the 1980s
- MTX is a structural analogue of folic acid – it competitively inhibits folic acid metabolism (disrupting B and T cell proliferation) and increases extracellular concentrations of adenosine (anti-inflammatory effects)

# Methotrexate

## FDA-approved indications:

- RA
- Psoriasis

## Off-label use:

- Inflammatory arthritis in SLE, MCTD
- Spondyloarthritis w/ peripheral joint involvement: Psoriatic arthritis, Reactive arthritis
- ANCA vasculitis, PAN, Takayasu arteritis
- Sarcoidosis
- Dermatomyositis/Polymyositis
- Scleroderma (skin/joints)
- Scleritis, Uveitis

# Poll Question #1:

Which of the following is FALSE?

A. The liquid formulation of MTX (for SQ injections) can be mixed with juice and taken orally
B. Patients who don’t have adequate disease response to 25mg of PO MTX should switch to 25mg of SQ MTX
C. Typical starting dose of MTX is 7.5-10mg weekly
D. Patients on MTX should take folic acid 1mg daily, except on the day of the week that they take their MTX

# Poll Question #1: Answer

Which of the following is FALSE?

A. The liquid formulation of MTX (for SQ injections) can be mixed with juice and taken orally
B. Patients who don't have adequate disease response to 25mg of PO MTX should switch to 25mg of SQ MTX
C. Typical starting dose of MTX is 7.5-10mg weekly
D. **Patients on MTX should take folic acid 1mg daily, except on the day of the week that they take their MTX**

# Methotrexate Dosing

ONCE A WEEK (not daily)

Pills, oral liquid, or SQ

Starting dose for RA:

- Moderate disease: **7.5mg weekly** for 1 month → check labs → **15mg weekly**
- Severe disease: **10mg weekly** for 1 month → check labs →**20mg weekly**
- Max dose = 25mg weekly

Oral bioavailability varies greatly (20-95%).

If 20-25mg PO is not getting adequate response, try splitting the PO dose AM/PM, or switch to SQ.

Everyone on MTX should also take **folic acid 1mg daily** (can increase to 2-5mg daily if needed)

# Poll Question #2:

Which of the following is TRUE?

- Methotrexate typically achieves full effect within 1-2 months
- Methotrexate should not be combined with NSAIDs due to decreased MTX metabolism
- Methotrexate can be used in combination with sulfasalazine
- Methotrexate should not be combined with TNF inhibitors (infliximab, adalimumab) due to increased risk of serious infections

# Poll Question #2: Answer

Which of the following is TRUE?

- Methotrexate typically achieves full effect within 1-2 months
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- **Methotrexate can be used in combination with sulfasalazine**
- Methotrexate should not be combined with TNF inhibitors (infliximab, adalimumab) due to increased risk of serious infections

# Expectations

- Can take 2-3 months to start seeing improvement. ~6 months for full effect.
- May need to combine with other medications (ex: sulfasalazine, hydroxychloroquine, or biologic DMARDs) to achieve adequate disease control
- When possible, MTX should be continued when adding a TNFi (especially adalimumab/Humira or infliximab/Remicade)
  - Decreases the risk of forming anti-TNFi antibodies

# Poll Question #3:

Which of the following is TRUE?

- Non-alcoholic fatty liver disease (NAFLD) is an absolute contraindication to MTX
- MTX is contraindicated in pregnancy, but safe during breastfeeding
- Patients taking MTX should be counseled to limit alcohol consumption to 2 drinks/week
- Men who are planning to father a child should stop MTX 3 months prior to trying to conceive

# Poll Question #3: Answer

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# Avoid methotrexate if:

- Person of childbearing age considering pregnancy or not using birth control. (Pregnancy Category X)
- Breastfeeding
- Pre-existing liver disease, hepatitis B or C
  - Mild NAFLD with normal liver enzymes is ok
- Heavy alcohol use
  - US guideline is ≤2 drinks/week, European guideline more lenient…
- CKD stage 4 or 5 (caution w/ stage 3)
- Consider alternatives if they also have lung disease

# Potential side effects

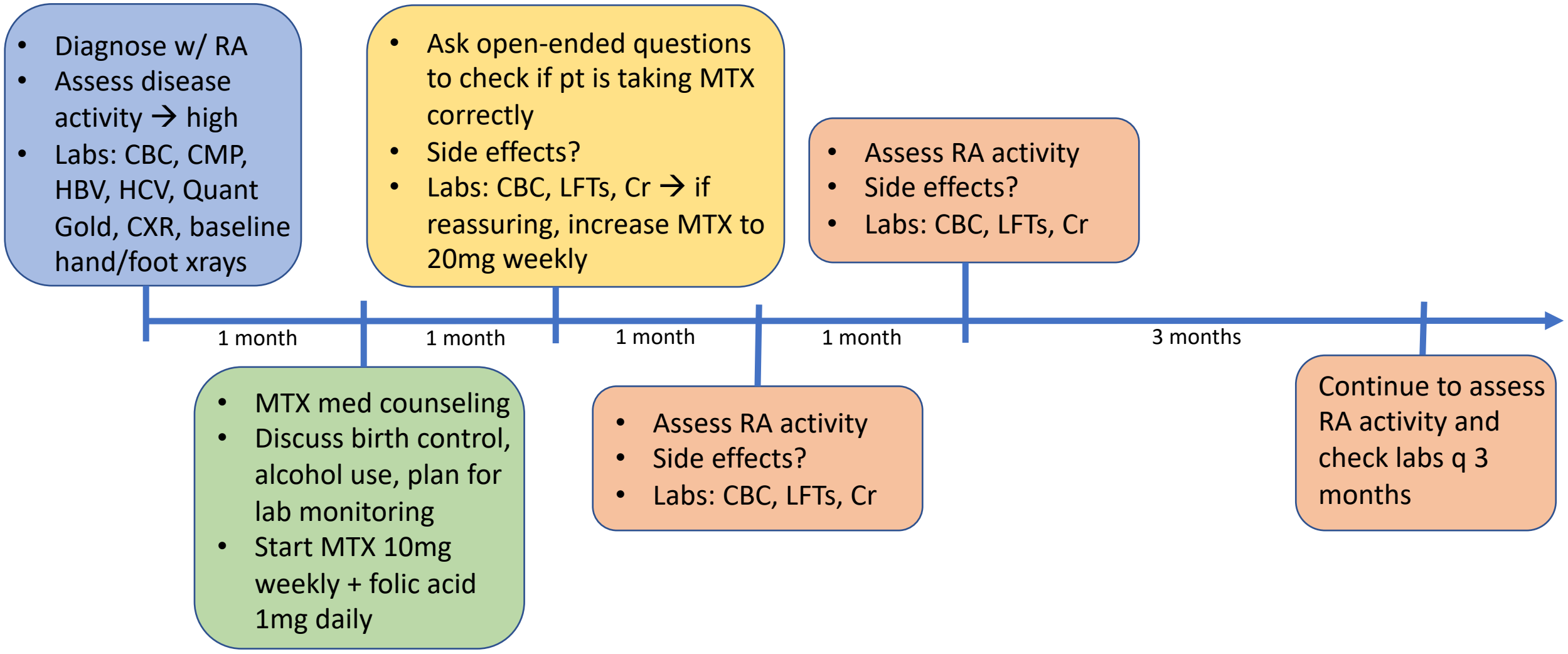
- GI upset (splitting the dose AM/PM can help)
- Oral ulcers
- Hepatotoxicity (transaminitis, cirrhosis)
- Infections
- Bone marrow suppression (cytopenias)
- Macrocytosis
- Brain fog
- Pneumonitis (very rare)

***Safety Pearl:***
*MTX is renally cleared, thus any impairment of GFR will result in ↑ serum levels of MTX and higher risk of toxicities*

# Medication Monitoring

- Before starting MTX:
  - CBC
  - CMP
  - Pre-immunosuppression labs: HBV Surface Ag/Surface Ab/Core Ab, HCV, Quant Gold/PPD
  - CXR
- Once on MTX:
  - CBC, LFTs, Cr every month for the first 3 months, then q3 months if stable dose

# Typical MTX Timeline



# Poll Question #4:

A 78F with h/o diabetes and mild dementia was newly diagnosed with RA and prescribed 15mg (6x 2.5mg tablets) once weekly. The pharmacy dispensed a 3-month supply of pills. 7 days later, she presents to the ER with severe nausea, diarrhea, bleeding oral ulcers, leukopenia (WBC 1.9), thrombocytopenia (platelets 70K), and transaminitis (AST 510, ALT 720). She is admitted to the hospital. What therapeutic intervention is most appropriate?

- A. Empiric broad-spectrum antibiotics
- B. IV leucovorin
- C. IV methylprednisolone
- D. IVIG

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- C. IV methylprednisolone
- D. IVIG

# MTX overdose

- Causes:
  - Misunderstanding of med instructions (i.e. taking dose daily instead of weekly)
  - Decreased GFR leading to increased serum levels of MTX
- Treatment:
  - Admit to hospital
  - Stop MTX
  - IV leucovorin (folinic acid) 5-10mg every 12 hours until recovery (improvement in cytopenias to safe range, improvement in transaminitis to <2x ULN, resolution of GI symptoms)

# Prevention is better than cure

- Dispense only a 1-month supply of MTX, especially for new starts
- Provide easy-to-read instructions w/ a specific day of the week, e.g. “Take 4 pills every Sunday for rheumatoid arthritis”
- Emphasize that MTX should not be taken as-needed for symptom control
- At first follow-up appointment, ask open-ended questions (“How are you taking your methotrexate?”)
- Monitor Cr: If GFR <50, downtitrate or consider stopping MTX, if GFR<30, stop MTX

# CME Credit Link