4ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ 2022-24

Συμβατικά συνθετικά ανοσοτροποποιητικά φάρμακα (csDMARDs) στη θεραπεία της ΡΑ

Χρήστος Κουτσιανάς

Ρευματολόγος – Ειδικός παθολόγος

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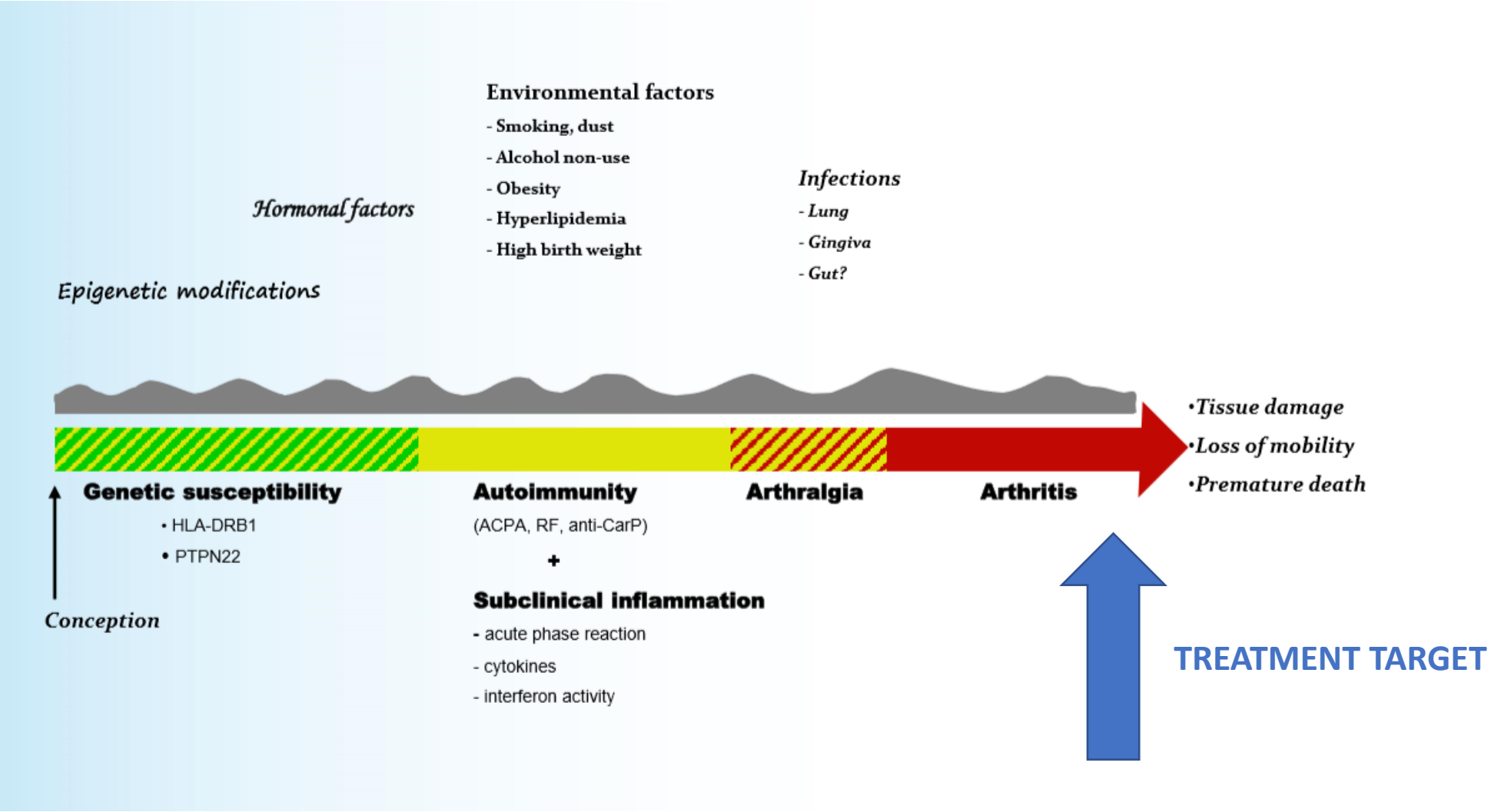
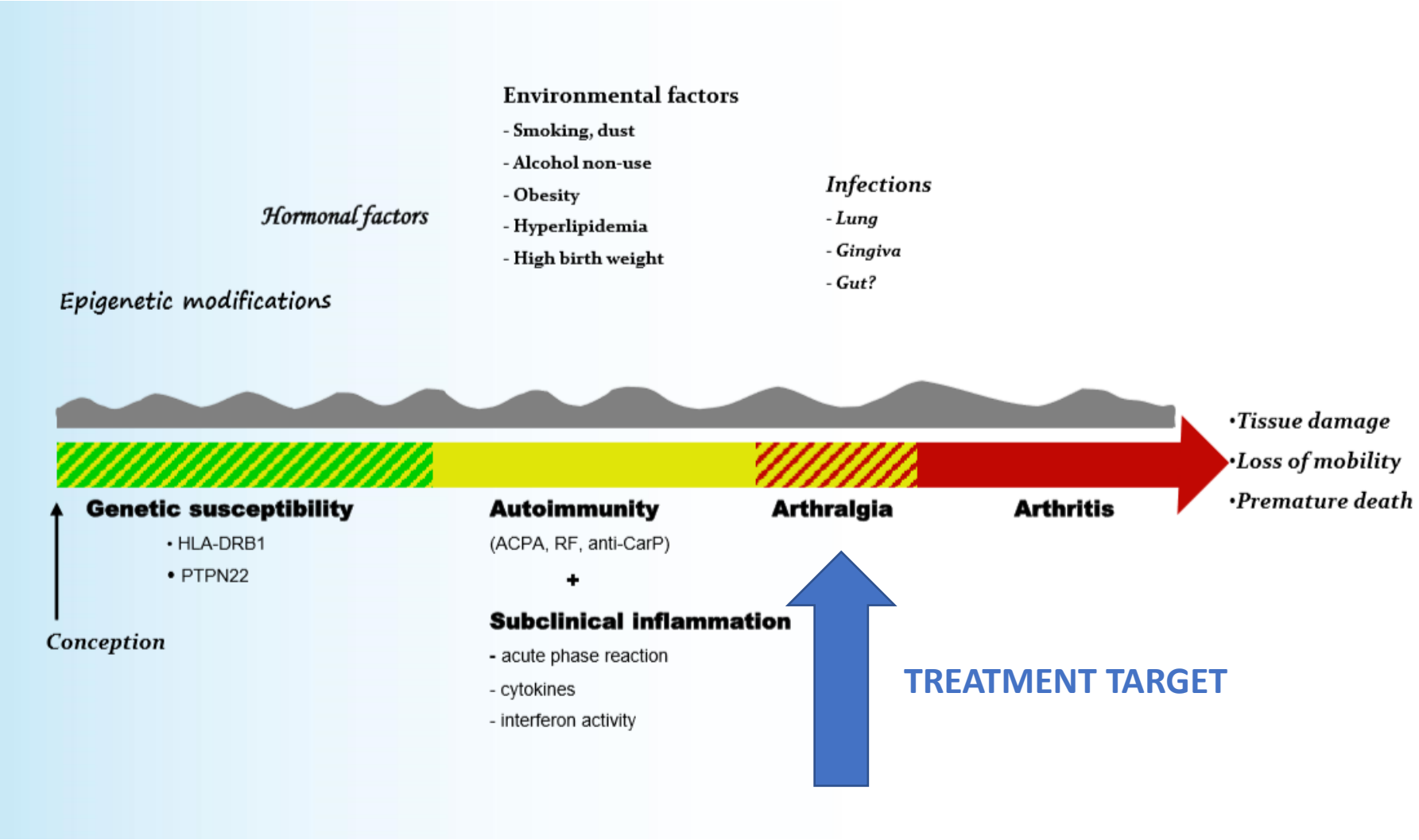
Honorary Consultant, Research & Development Department
The Dudley Group NHS Foundation Trust

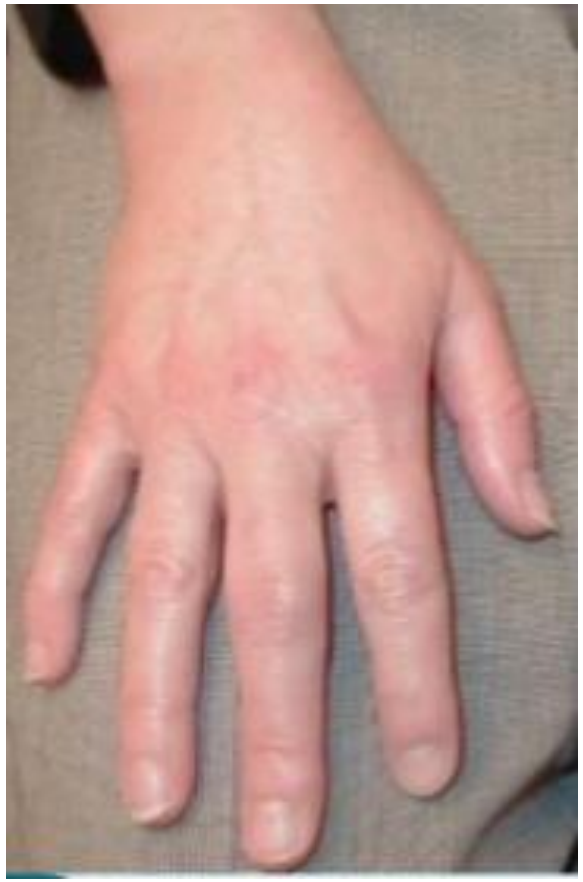
Introduction: RA natural history

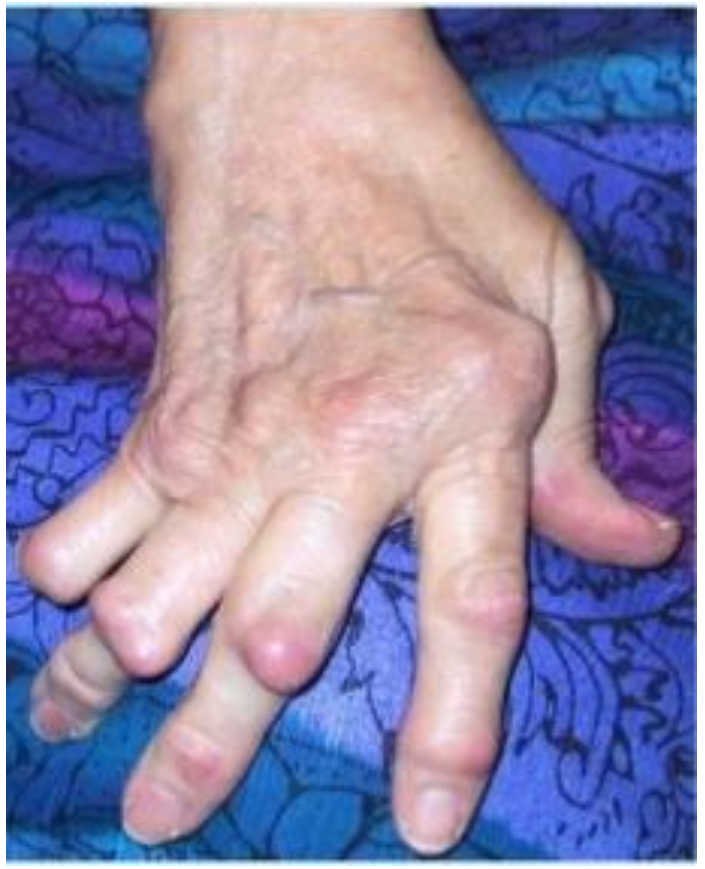


Introduction: RA natural history



Introduction: RA evolution





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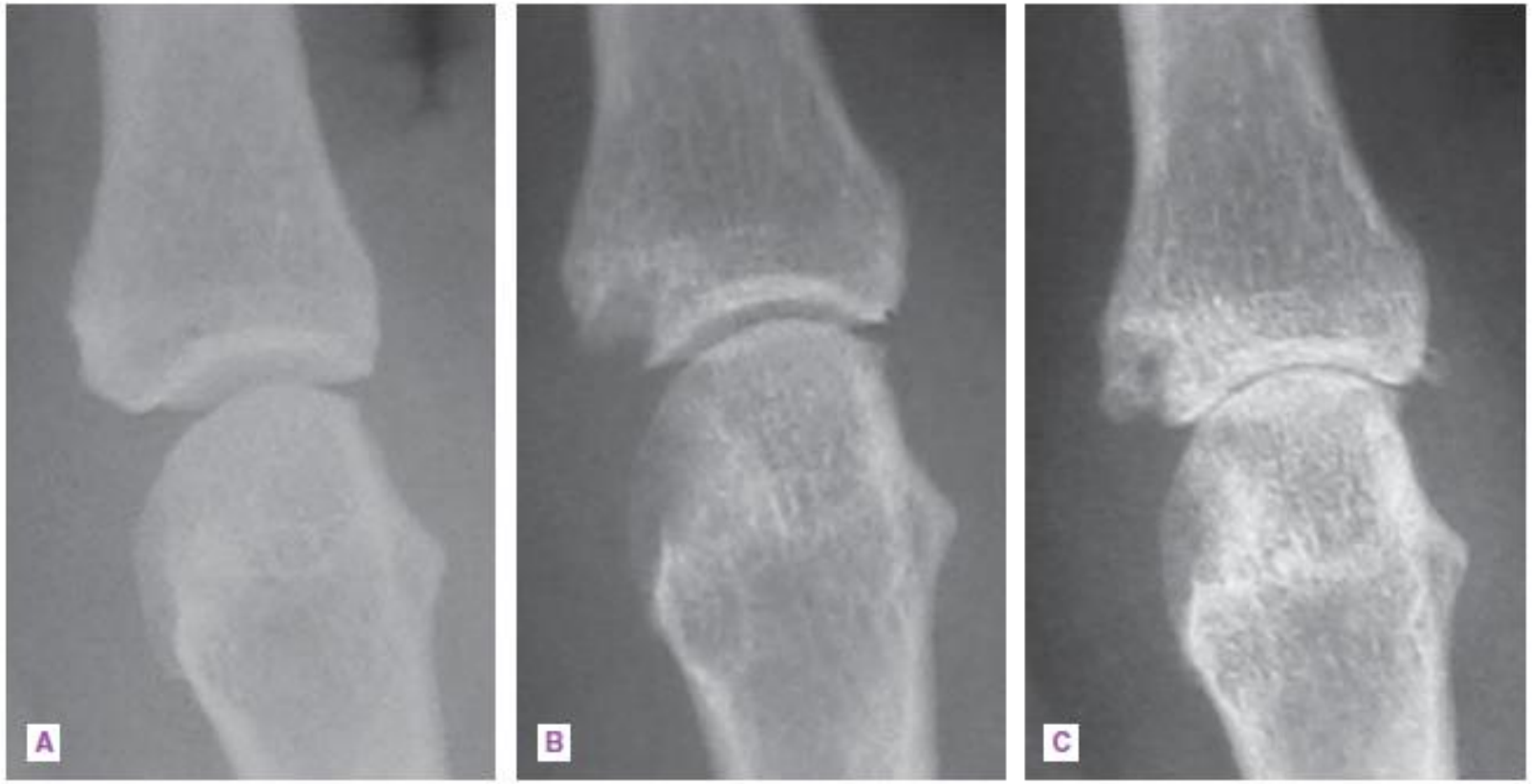

▲ **Figure 15–3.** Progressive destruction of a metacarpophalangeal joint by rheumatoid arthritis. Shown are sequential radiographs of the same second metacarpophalangeal joint. **A:** The joint is normal 1 year prior to the development of rheumatoid arthritis. **B:** Six months following the onset of rheumatoid arthritis, there is a bony erosion adjacent to the joint and joint-space narrowing. **C:** After 3 years of disease, diffuse loss of articular cartilage has led to marked joint-space narrowing.

Introduction: why DMARDs?

D isease

M odifying

A nti

R heumatic

D rug

Must change the course of disease for at least one year

Evidenced by:

- ✓ Sustained improvement in physical function
- ✓ Decreased inflammatory synovitis
- ✓ Slowing or prevention of structural damage

Introduction: why DMARDs?

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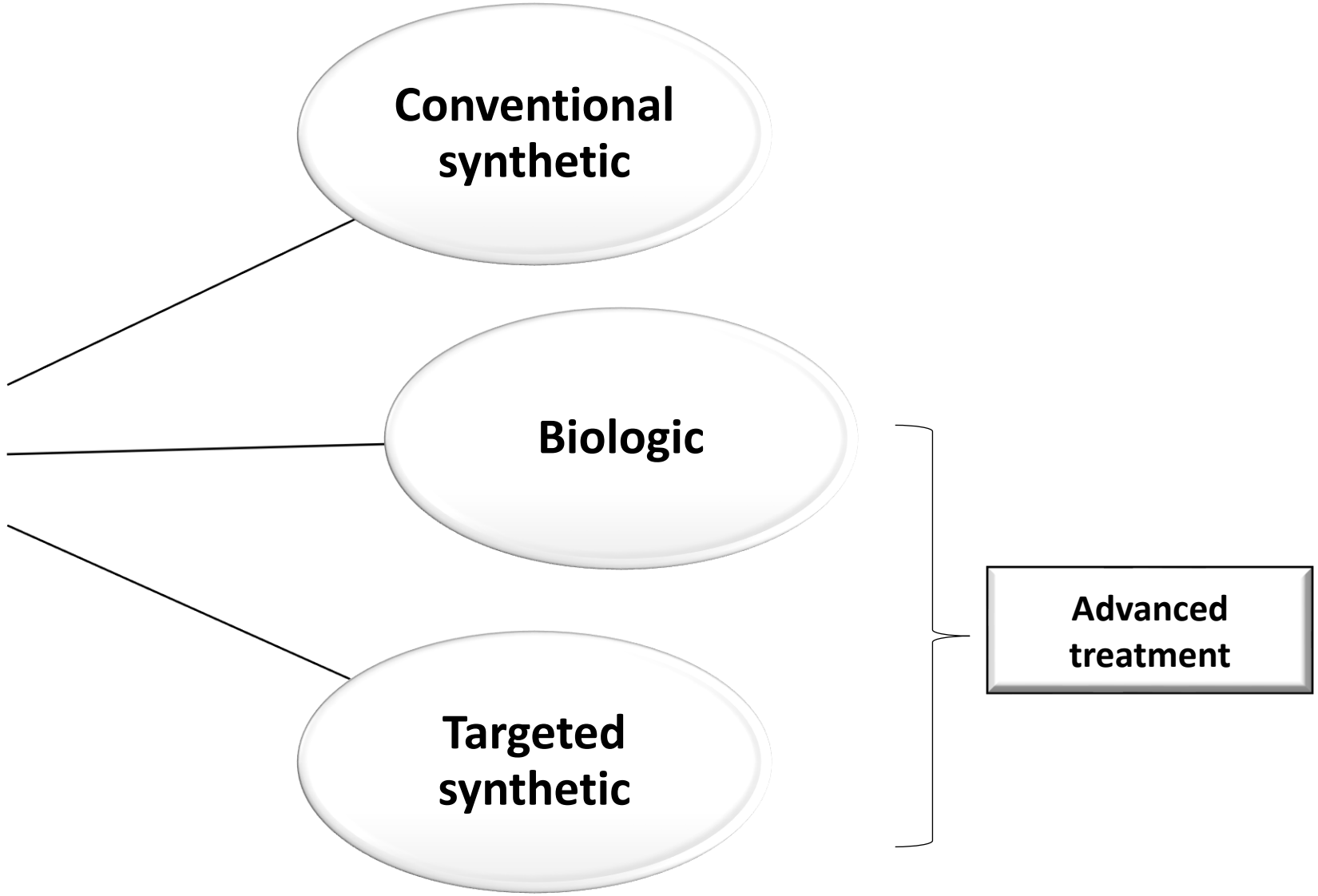

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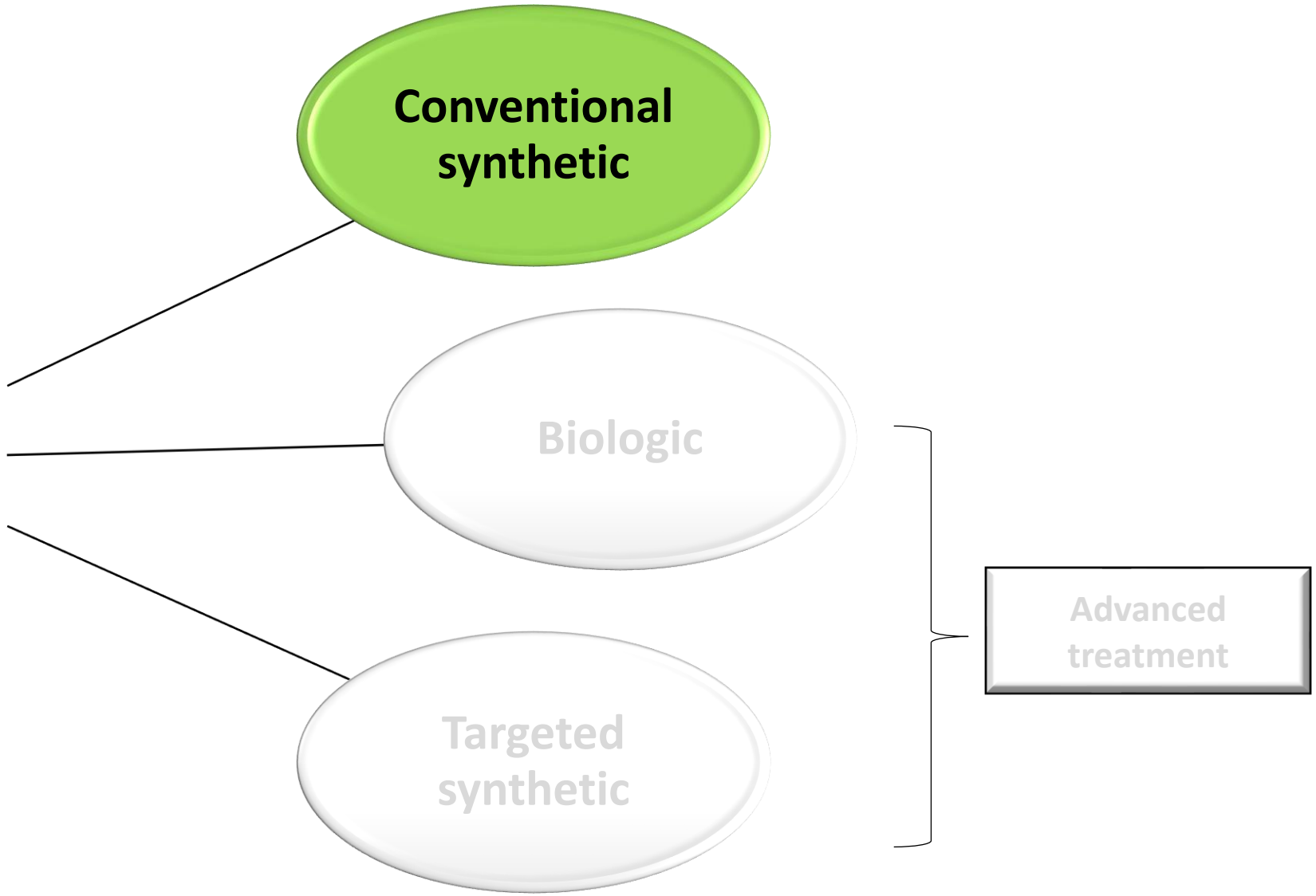
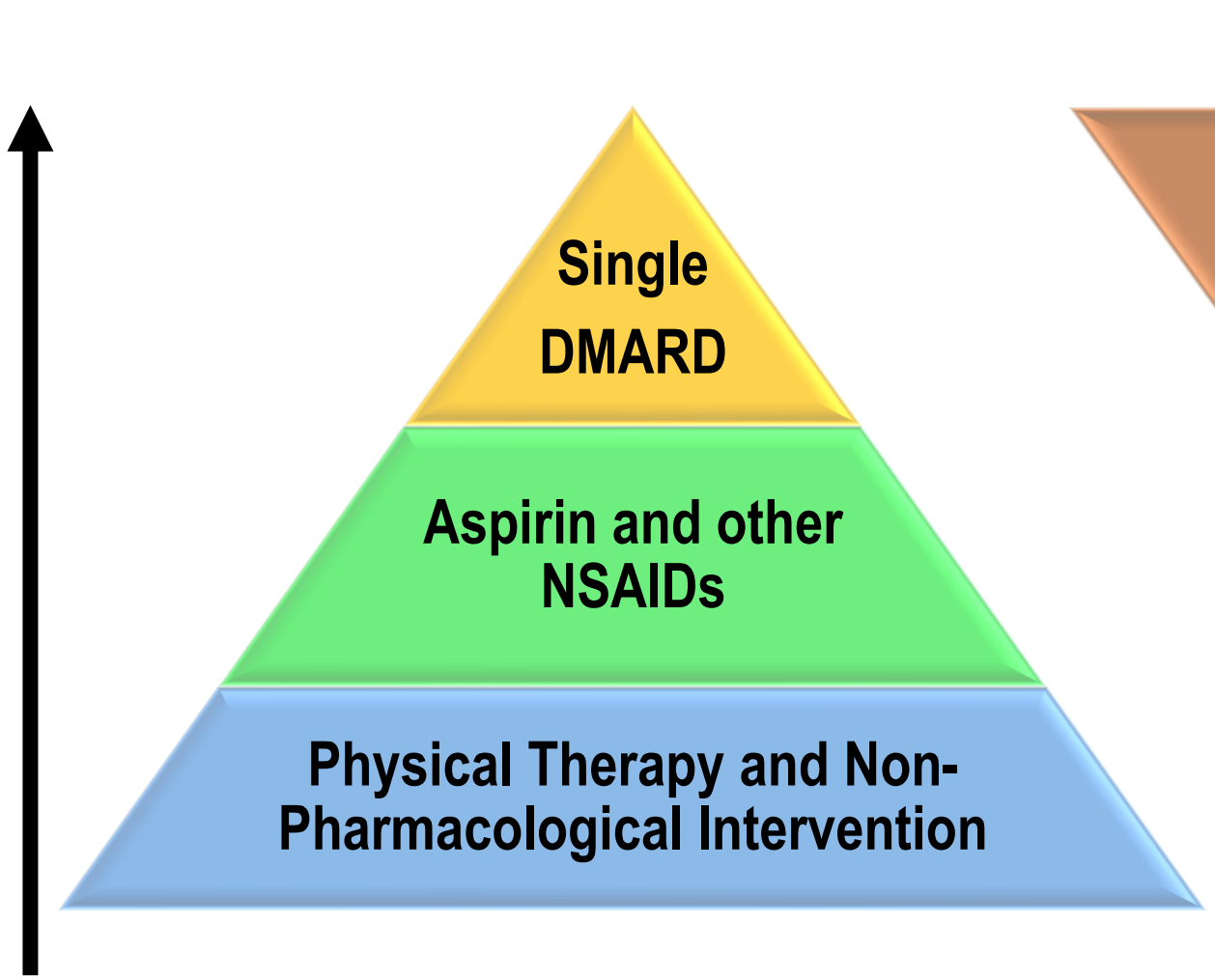
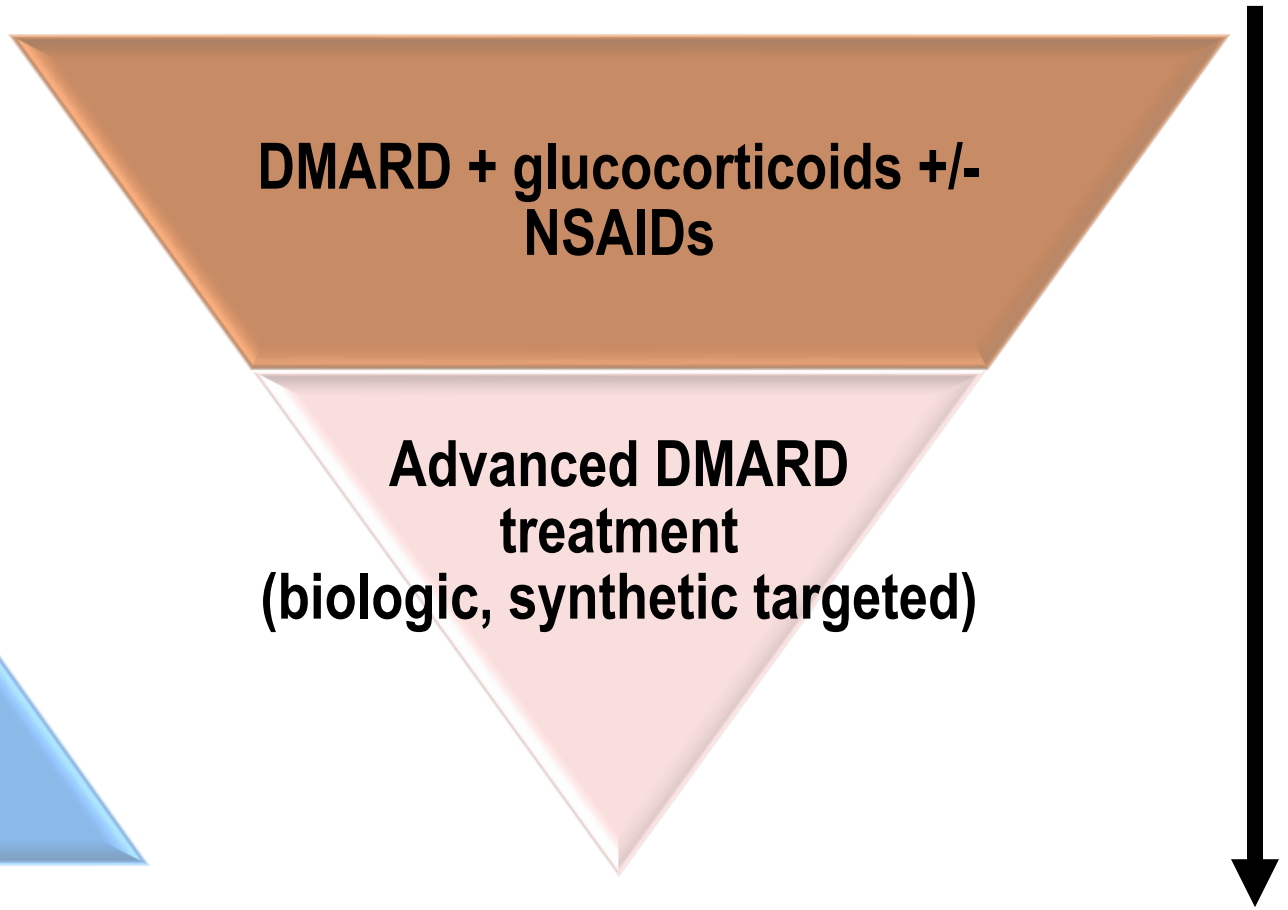


Introduction: Treatment paradigm shift in RA



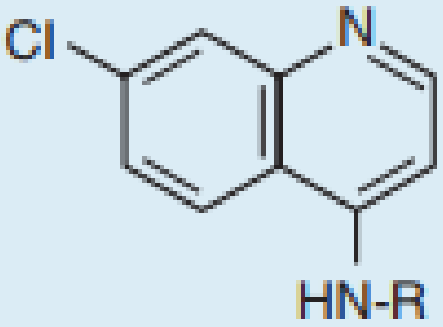
"Go Low, Go Slow"

"Inverting the pyramid"



"Treat to target"

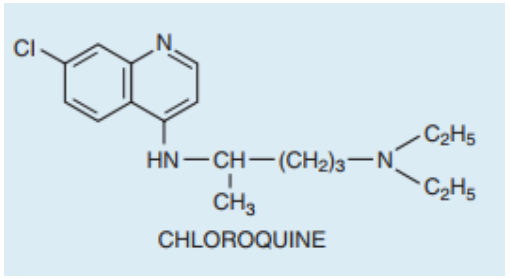
Antimalarials



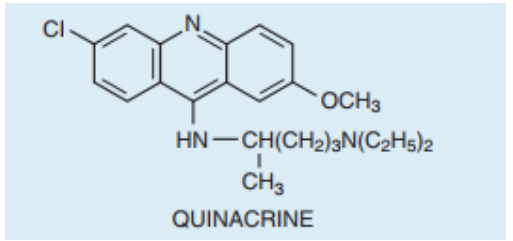
4-AMINOQUINOLINE DERIVATIVES

Antimalarials

- Chloroquine 250mg/day (<3.0 mg/kg IBW) (engineered in Germany after WWI, as alternative to quinine)



- Quinacrine 100-200mg/day



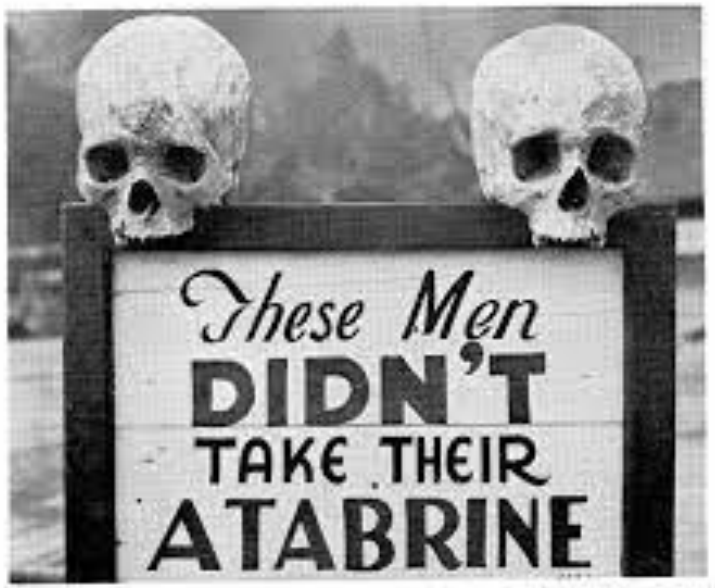


FIGURE 184.—Atabrine publicity campaign, 363d Station Hospital, March 1944.

Hydroxychloroquine

- 4-aminoquinolone derivative
  from the bark of the Peruvian cinchona tree
- 1955: Approved for medical use in the US

- Least toxic of all the DMARDs
- Particularly effective in:
  - mild arthritis
  - early treatment
  - add-on therapy

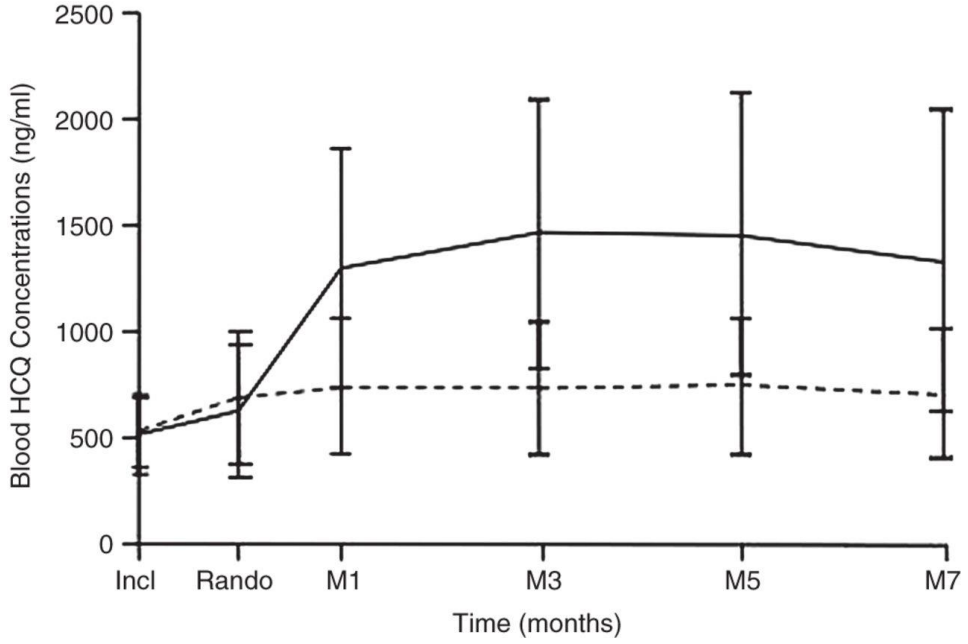
Hydroxychloroquine: pharmacology

- No effect of food on absorption (100%)
- High concentration in melatonin-rich cells (skin, retina)

- 50% renal excretion

- Half-life 40-50 days
- Steady state levels after 3 – 6 months

- No need for monitoring bloods



Costedoat-Chalumeau N et al. Ann Rheum Dis 2013;72:1786-1792.

Hydroxychloroquine: mechanism of action

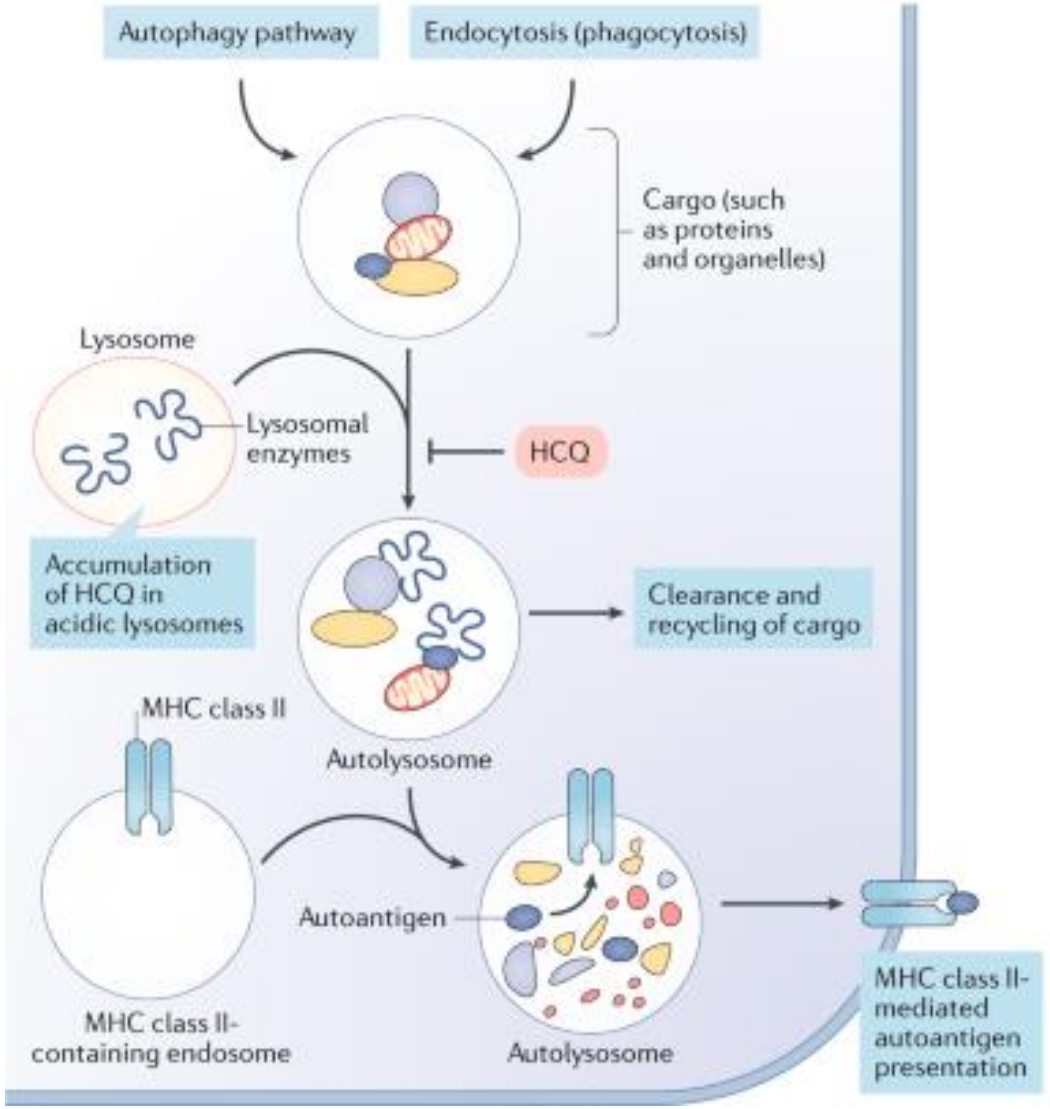
Precise MoA not known

Weak base

Accumulate in cytoplasmic vesicles (increase pH)

Theory #1: increase in pH has several immunomodulatory effects

- stabilization of lysosomal membranes
- attenuation of antigen processing
- inhibition of cell-mediated toxicity



Schrezenmeier et al *Nat Rev Rheumatol* **16**, 155–166 (2020)

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Precise MoA not known

Weak base

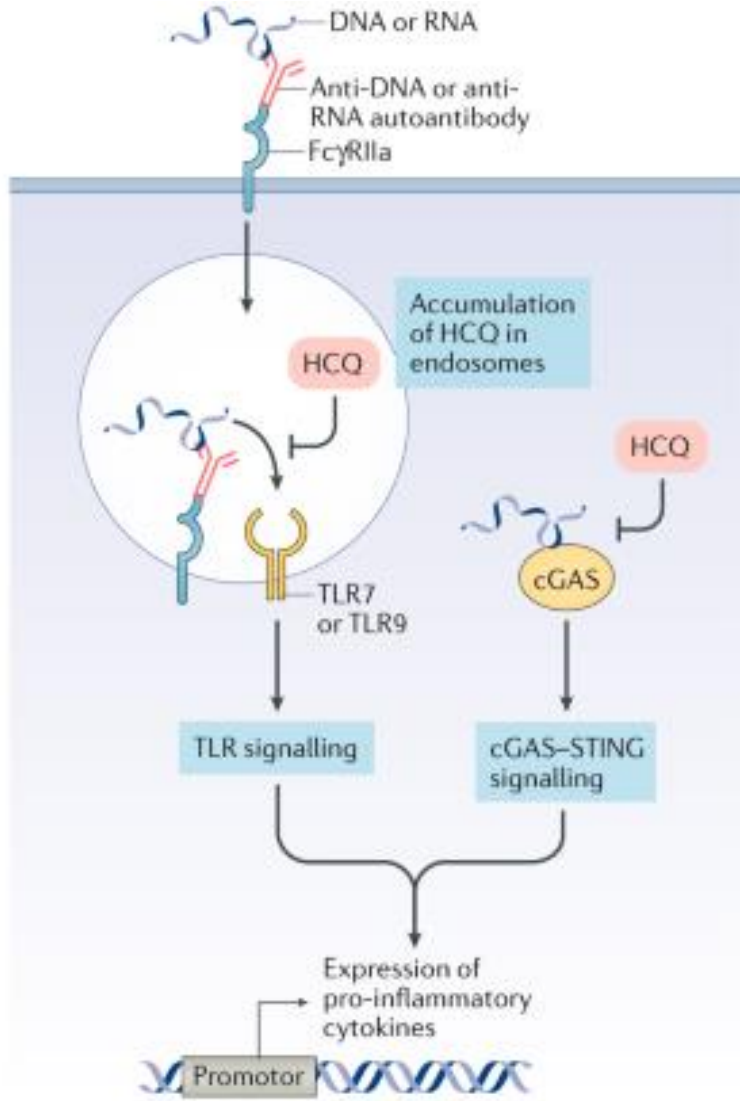
Accumulate in cytoplasmic vesicles (increase pH)

Theory #1: increase in pH has several immunomodulatory effects

- stabilization of lysosomal membranes
- attenuation of antigen processing
- inhibition of cell-mediated toxicity

Theory #2: inhibition of intracellular Toll-like receptors (esp TLR9)

- inhibitory effect on IL-1, IL-6 and IFNγ

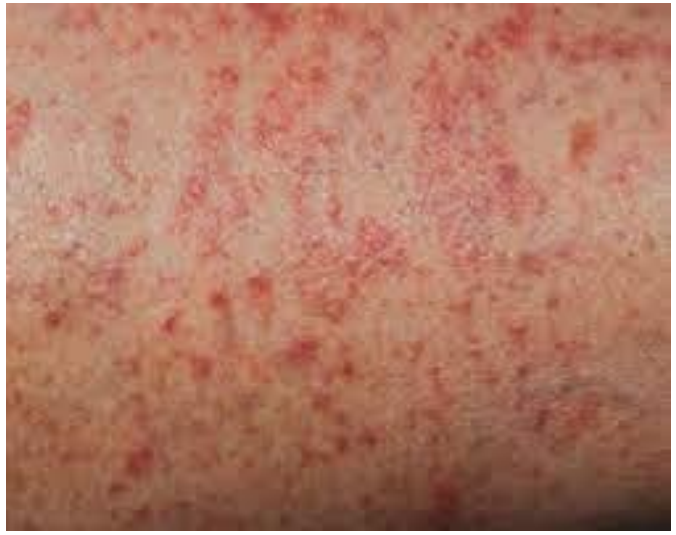


Schrezenmeier et al *Nat Rev Rheumatol* **16**, 155–166 (2020)

Hydroxychloroquine: other effects

- Photoprotective
- Anti-thrombotic effect - Inhibit PLT adhesion and aggregation
- Favorable lipid effects
- Decrease plasma glucose levels (inhibition of insulin degradation)

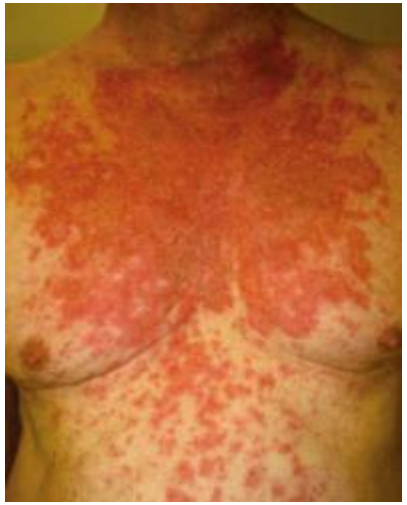
Hydroxychloroquine: side effects



- ✓ **Gastrointestinal (<10%)**:
  anorexia, nausea, vomiting, diarrhea, abdominal cramping

- ✓ **Dermatological (<5%)**:
  pruritic rash – relatively common, can lead to d/c
  photosensitivity, alopecia, depigmentation of hair
  skin pigmentation with prolonged Rx

- ✓ **Neuromuscular (<1%)**:
  Headache, insomnia, nightmares, and irritability (usually improve with treatment)
  Tinnitus, deafness
  Neuromyotoxicity (high CK, weakness) + peripheral neuropathy (rare)



- ✓ **Cardiovascular (<1%)**:
  Conduction disturbances, cardiomyopathy

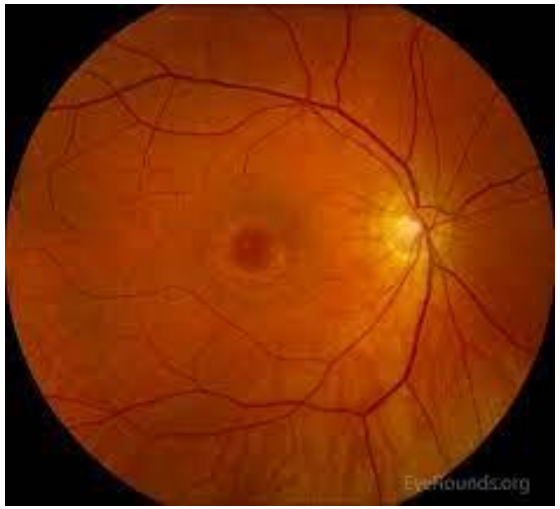
Hydroxychloroquine: fertility, pregnancy & lactation

SAFE

- ✓Not teratogenic
- ✓Safe to use throughout pregnancy
- ✓Favourable pregnancy outcomes, esp in SLE
- ✓Compatible with breastfeeding

Hydroxychloroquine: ocular toxicity

Bilateral **“bull’s eye” maculopathy**, with **retinal pigment epithelial (RPE) cell depigmentation** in the central macula and sparing of a small foveal island



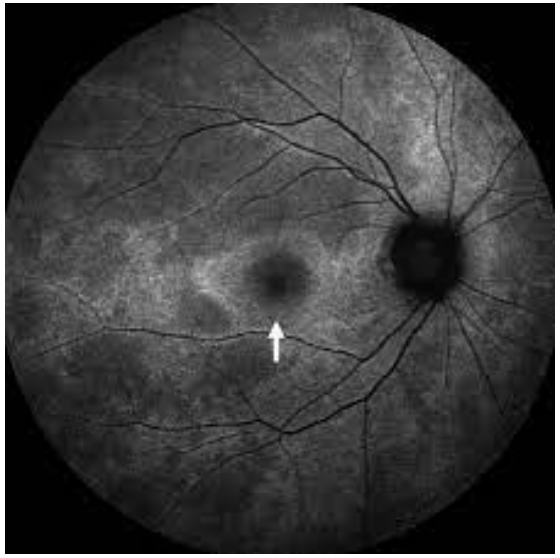
Increased risk for toxicity among patients receiving doses > 5 mg/kg/day of actual body weight.

Depends on duration of use

< 5 years: close to 0%

< 10 years: 2%

> 20 years: 20%



Mechanism: ? Genetic component
?changes in metabolism

Hydroxychloroquine: ocular toxicity

Risk factors:

- Daily HCQ dose
- Duration of therapy
- Renal failure
- Tamoxifen
- Underlying retinal or macular disease / pre-existing retinal abnormalities

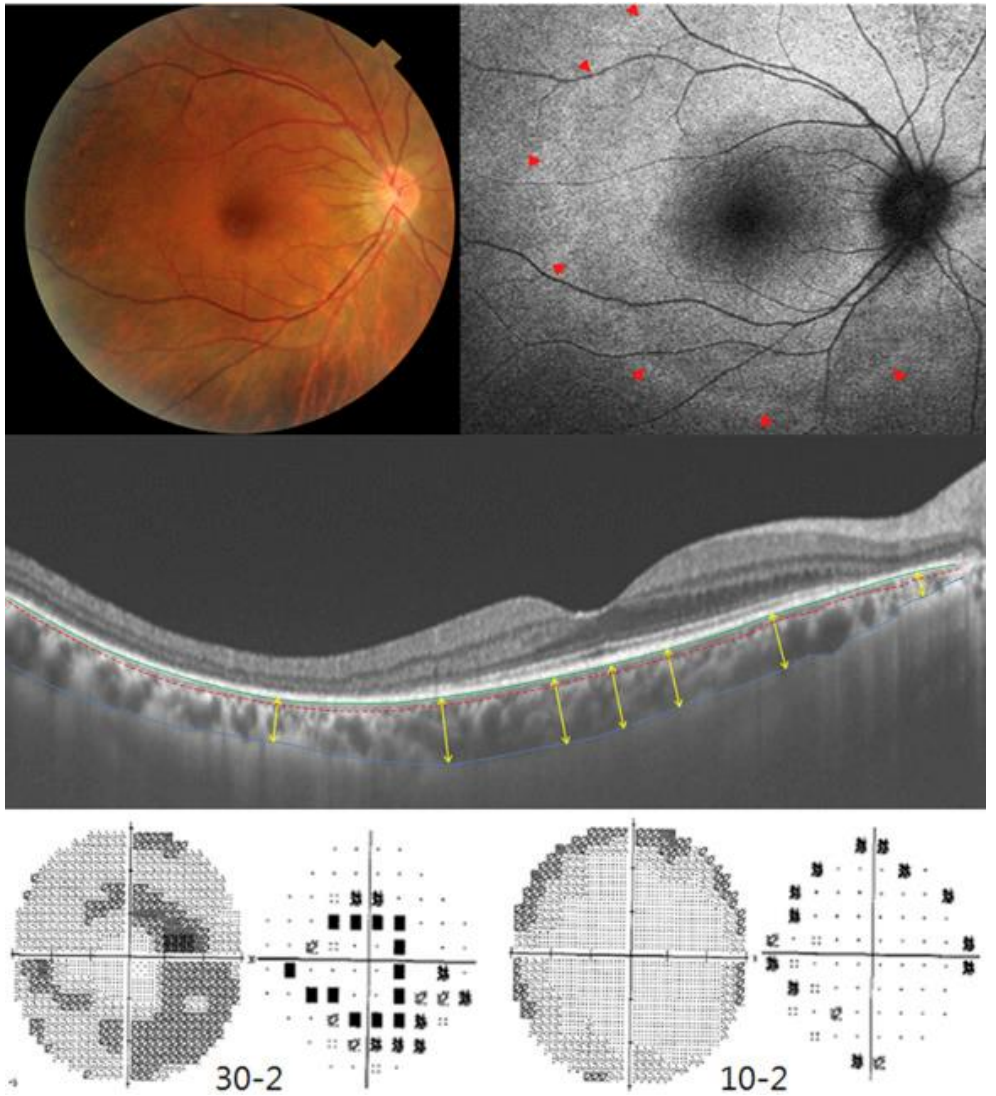
Hydroxychloroquine: ocular toxicity - monitoring

AAO: baseline eye exam within 1 year
Visual acuity, corneal / retinal exam / colour-vision testing
OCT at baseline **not** recommended

Routine **annual** eye screening for the first 5 years

Then, more detailed tests with OCT

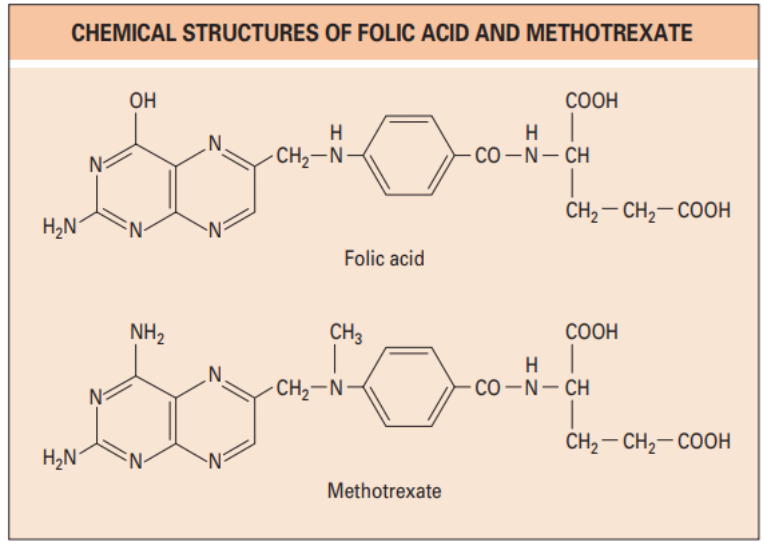
RCO: detailed exams after 5 years



Methotrexate

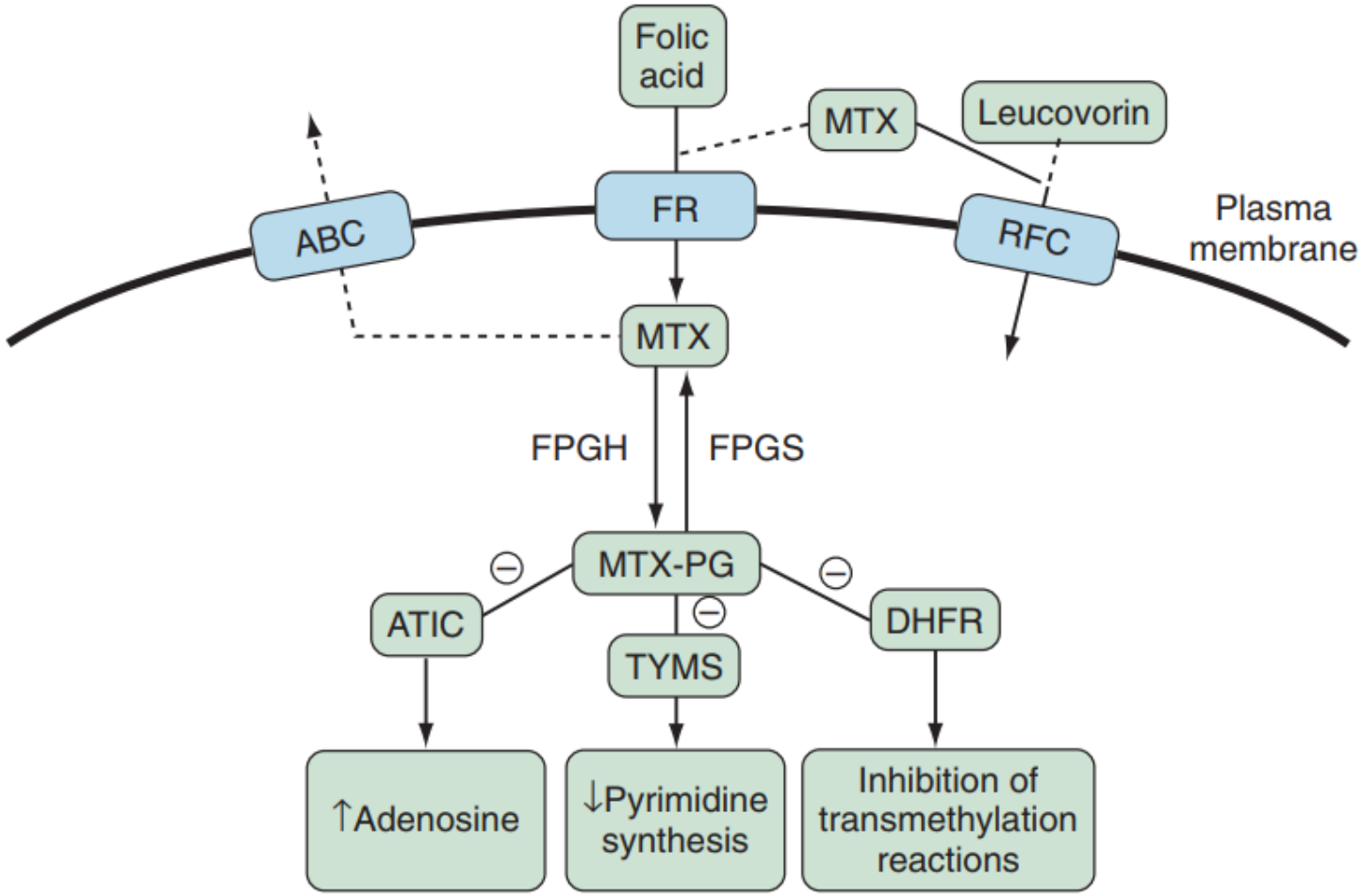
Methotrexate

- First used for malignant diseases
- Aminopterin first used for RA in 1951
- Anchor drug in RA for the last several decades
- Structurally similar to folic acid



Methotrexate: mechanism of action

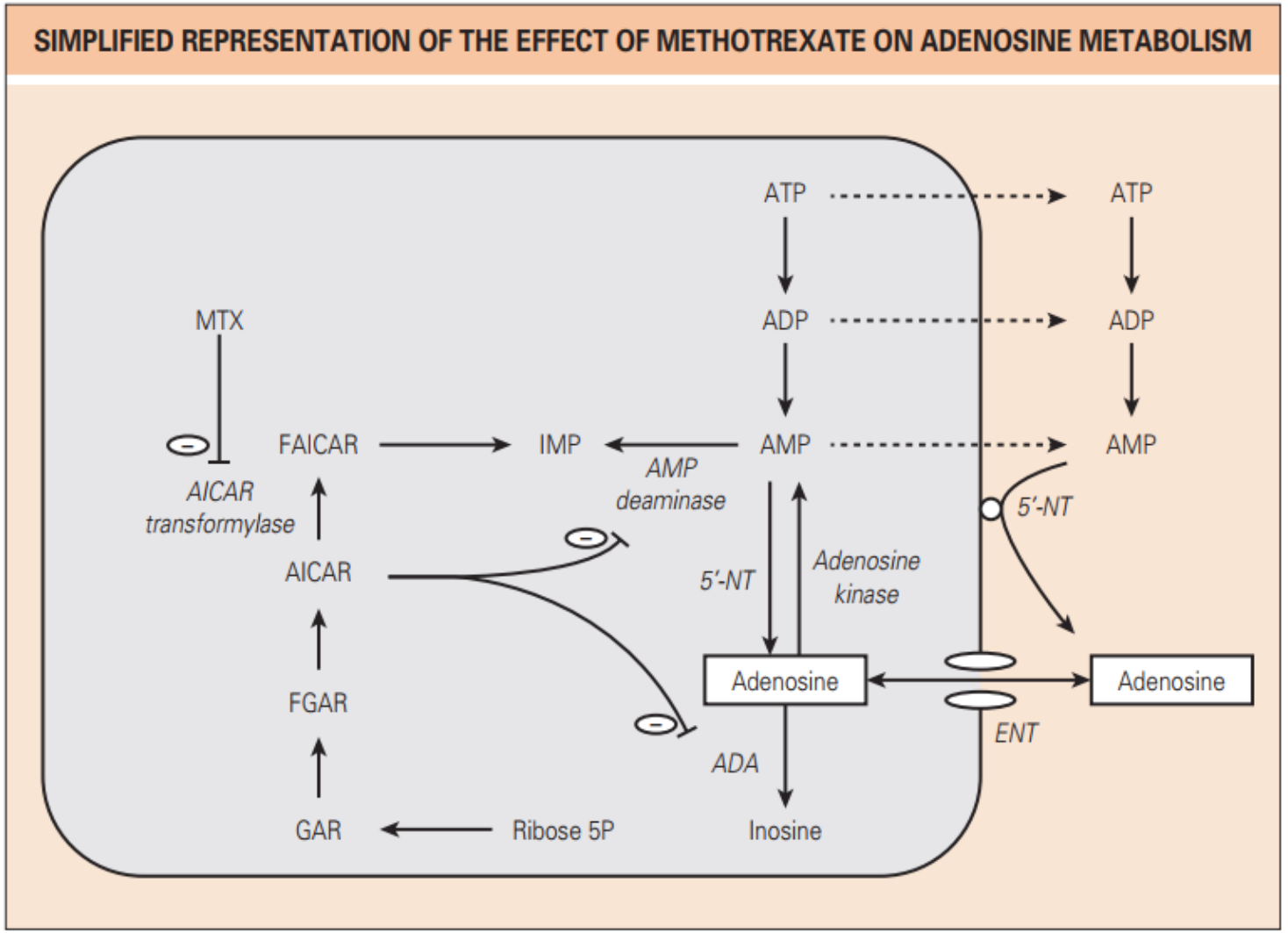
- Enters through RFC (reduced folic carrier)
- Polyglutamation by FPGS
- Increases adenosine



Methotrexate: mechanism of action

Adenosine A2A receptors are expressed on T cells, natural killer cells, monocytes, macrophages, and neutrophils

Inflammation dampened by several mechanisms:
- T-cell suppression
- inhibition of the neutrophil oxidative burst
- suppression of NF-κB



Methotrexate: pharmacology

- Available in oral and subcutaneous form
- Oral: doses > 15mg QWK may not be absorbed by 30%
- Split dose improve bioavailability
- Not reduced by food intake

- Serum half-life 6-8h
- Renal clearance

Methotrexate: oral or subcut

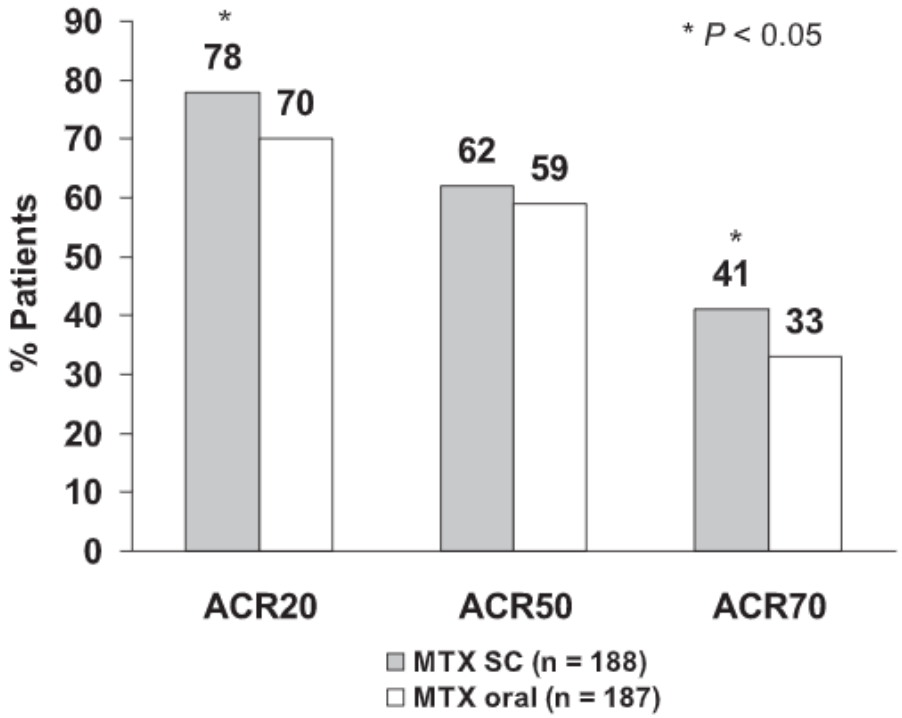


Table 2. Summary of adverse events during the study (safety analysis set)*

	No. (%) of patients receiving SC MTX (n = 193)	No. (%) of patients receiving oral MTX (n = 188)
Adverse events		
Any adverse event	128 (66)	116 (62)
At least a moderate adverse event	79 (41)	77 (41)
Adverse event possibly related to study drug	102 (53)	90 (48)
Serious adverse event	11 (5.7)	8 (4.3)
Adverse event leading to withdrawal	18 (9.3)	8 (4.3)
At least moderate adverse events reported at a ≥3% incidence		
Gastrointestinal		
Abdominal pain	17 (8.8)	20 (10.6)
Diarrhea	5 (2.6)	13 (6.9)
Dyspepsia	13 (6.7)	11 (5.9)
Loss of appetite	14 (7.3)	6 (3.2)
Nausea	32 (16.6)	23 (12.2)
Stomatitis	6 (3.1)	7 (3.7)
Vomiting	7 (3.6)	6 (3.2)
Increased alanine aminotransferase	3 (1.6)	8 (4.3)
Bronchitis	4 (2.1)	7 (3.7)
Headache	4 (2.1)	8 (4.3)
Nasopharyngitis	9 (4.7)	10 (5.3)

* Methotrexate (MTX) was administered subcutaneously (SC) or orally.

Braun et al. Arthritis Rheum 2008 Jan;58(1):73-81

Methotrexate: dosage

- Starting dose 10-15mg/wk
- Dose optimization according to tolerability & efficacy within 3 months
- Usually up to 25mg/wk

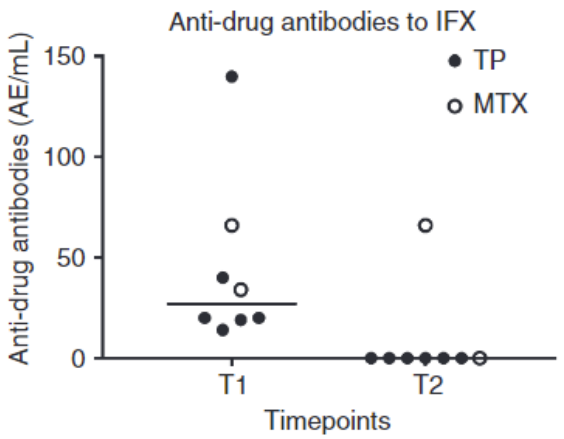
- Concomitant administration of folic acid:
  decreases several side effects (GI upset, hair thinning, stomatitis, fatigue, haematologic toxicity)
  Usually 5mg QWK (US: 1mg/day)

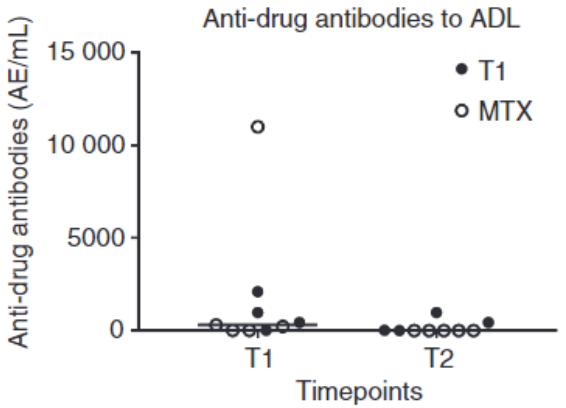
- Extra caution in geriatric population and reduced CrCl

Methotrexate: efficacy

Efficacy of methotrexate as monotherapy in studies of biologics

	TEMPO*	PREMIER†	ASPIRE‡	COMET§	AMBITION‖	Abatacept study¶
ACR20 (%)	75	63	54	67	52	Not reported
ACR50 (%)	43	46	32	49	34	43
ACR70 (%)	19	28	21	28	28	27
DAS remission (%)	13	21	15	28	12	23





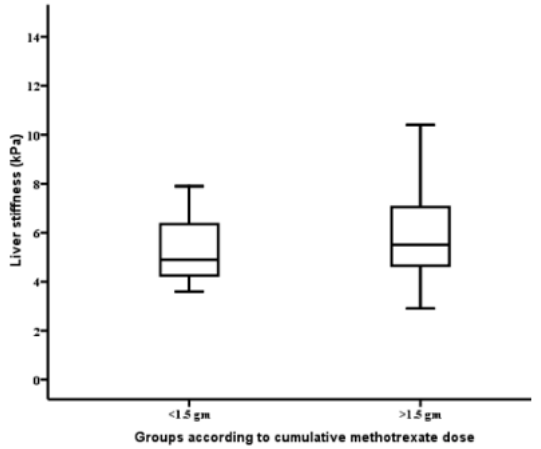
Strik et al. Aliment Pharmacol Ther. 2017 Apr;45(8):1128-1134

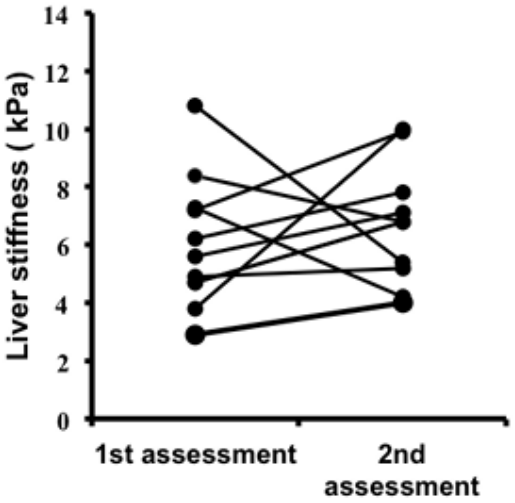
Methotrexate: side effects

- ✓ **Gastrointestinal**:
  anorexia, dyspepsia, nausea, vomiting (20-70%)
  folic acid supplementation may be of help

- ✓ **Hepatotoxicity**:
  elevated aminotransferases frequently
  risk of significant hepatotoxicity rather low
  no significant risk of liver fibrosis with the use of the drug

- ✓ **Mucocutaneous:**
  stomatitis, usually minor aphthous ulcerations





Kranidioti H et al Mediterr J Rheumatol 2016; 27(2):40-7

Methotrexate: side effects

- ✓ **Haematologic**:
  Bone marrow toxicity (dose dependent) < 1-2%
  responds to folic acid supplementation – in severe case, leucovorin iv + GM-CSF
  Risk factors: renal failure, hypoalbuminaemia, dosing errors, concomitant use of other drugs (e.g. probenecid, SMX/TMP)

- ✓ **Pulmonary**:
  - acute interstitial pneumonitis: rare, hypersensitivity reaction
  - pleuritis & pleural effusions
  - interstitial fibrosis: ?does it really exist
  - pulmonary nodules
  - non-cardiogenic pulmonary oedema

- ✓ **Other:**
  "methotrexate flu"
  nodulosis

Kranidioti H et al Mediterr J Rheumatol 2016; 27(2):40-7

Methotrexate: treatment considerations

- ✓ **Perioperative management**:
  2022 ACR/AAKHS guidelines[1] – no need to stop for arthroplasty surgery

- ✓ **Vaccination**:
  discontinuation 1-2 weeks after the flu vaccine had increased rated of immunogenicity[2]

1. Goodman et al. Arthritis Care Res 2022 2. Park et alArthritis Rheumatol 2022 Aug 05

Methotrexate: fertility, pregnancy & lactation

Teratogenic

"aminopterin syndrome": craniofacial, limb & CNS abnormalities

WOMEN:

✓Discontinue at least 3 mo prior to conception efforts

✓Folic acid supplementation

✓Contraindicated during lactation

MEN:

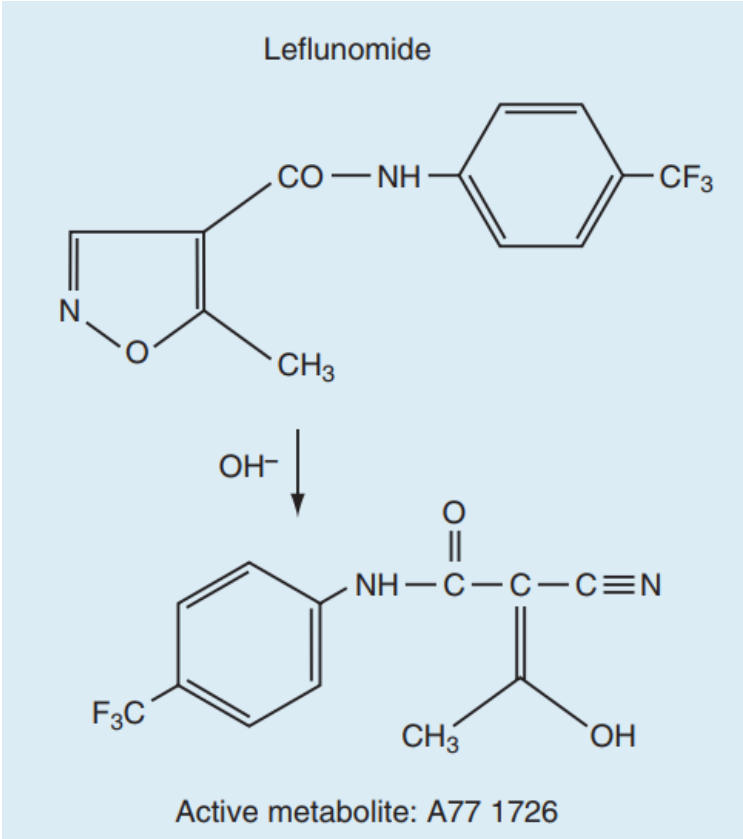
Although the drug label suggests d/c of MTX before attempting pregnancy, data show no evidence for mutagenesis or teratogenicity – ACR guidelines: conditionally continue

Sammaritano et al Arthritis Rheumatol 2020

Leflunomide

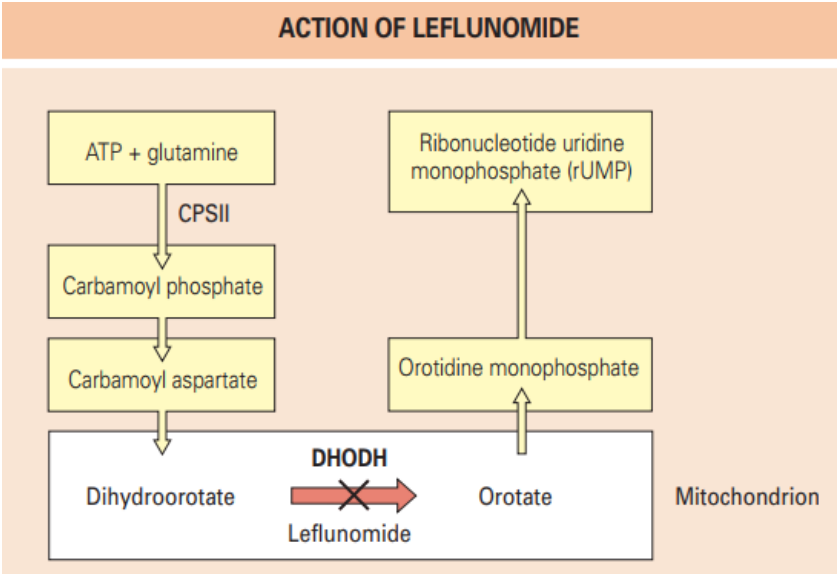
Leflunomide

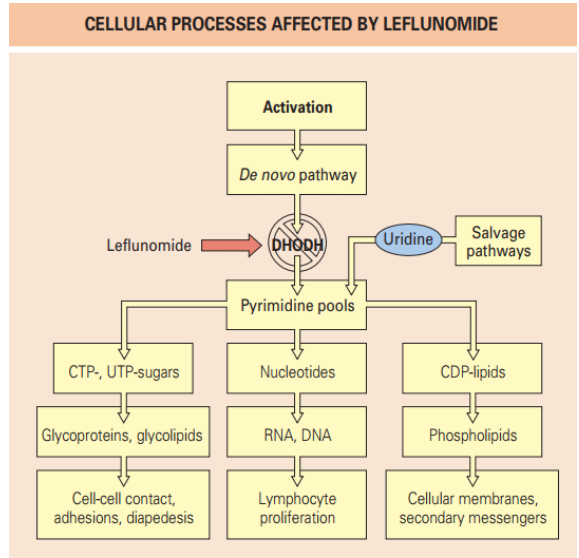
- Isoxazole derivative
- Converted to active metabolite, teriflunomide
- Immunomodulatory effect
- Orally administered



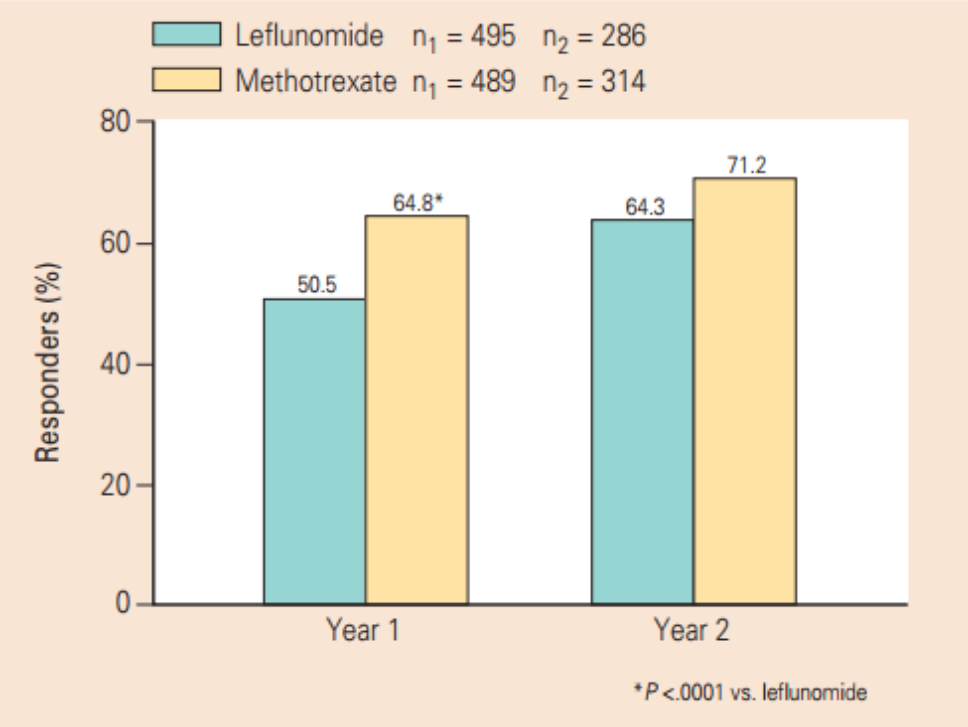
Leflunomide: mechanism of action

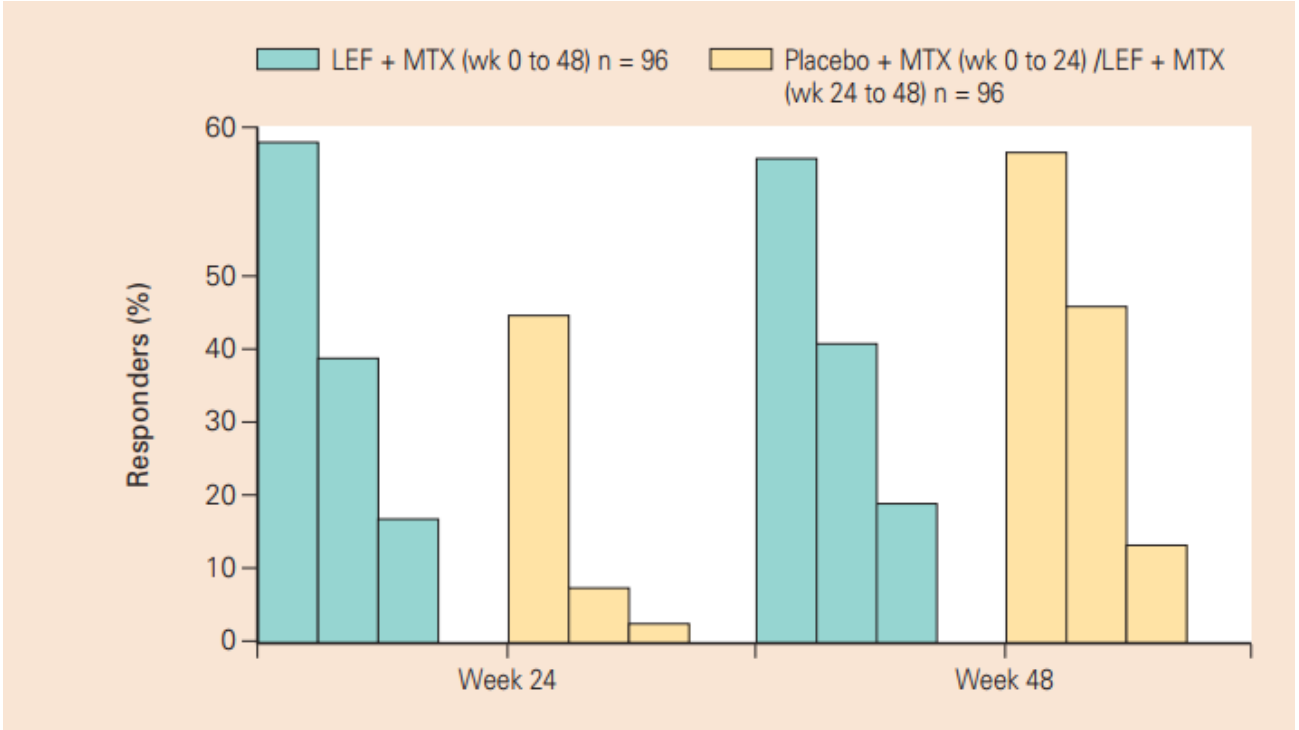
- Inhibitor of DHODH
- Stops pyrimidine synthesis
  - ✓ Blocks proliferation of lymphocytes
  - ✓ Inhibits NF-Kβ activation & gene expression
  - ✓ Suppresses IL-17 and IL-1 pathways
  - ✓ Inhibits chemotaxia of neutrophils





Leflunomide: efficacy





Leflunomide: side effects

- ✓ **Cardiovascular**:
  Arterial hypertension.

- ✓ **Gastrointestinal**:
  anorexia, dyspepsia, diarrhea, abdominal pain
  abnormal aminotransferases

- ✓ **Cutaneous**:

  Skin reactions (~10%). Most between 2nd – 5th month
  Alopecia

- ✓ **Infection**

- ✓ **Neurologic**:
  headache, dizziness, parasthesia (usually mild)

LEF WASH OUT

1. **Cholestyramine 8g TDS for 11 days**
2. **Activated charcoal 50gr QDS for 11 days**

Leflunomide: treatment considerations

- ✓ **Perioperative management**:
  2022 ACR/AAKHS guidelines[1] – no need to stop for arthroplasty surgery

- ✓ **Vaccination**:
  no need to discontinued treatment

1. Goodman et al. Arthritis Care Res 2022

Leflunomide: fertility, pregnancy & lactation

Teratogenic

WOMEN:

- ✓ Discontinue at least 24 mo prior to conception efforts
- ✓ Cholestyramine wash out
- ✓ Measurement of drug levels?

MEN:

ACR 2020 guidelines – conditionally continue

Sammaritano et al Arthritis Rheumatol 2020

Sulfasalazine

Sulfasalazine

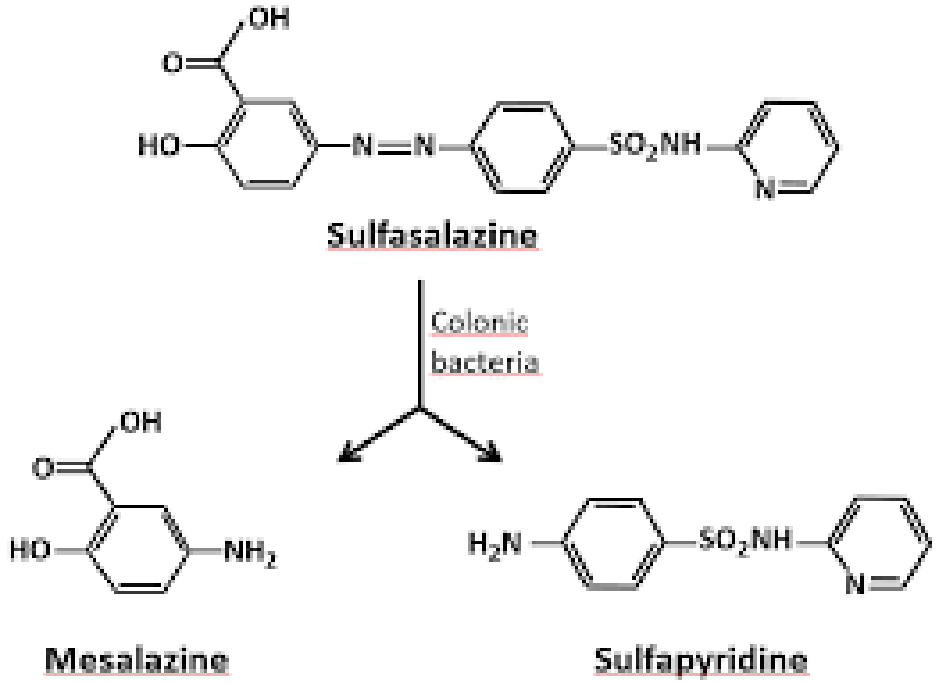
- 1938: produced in the lab by Dr Svartz
- Drug for RA in mid 70s
- Not very commonly used today, due to lack of convincing efficacy
- Mainly used in combined regimens
- Maybe better in SpA and peripheral arthritis/enthesitis

- Dosage 2g/d (up to 3g/day)

Sulfasalazine

Metabolised in the liver and gut into:

- sulfapyridine (absorbed systematically)
- 5-ASA (mainly active in the bowel)



Excreted unchanged in urine

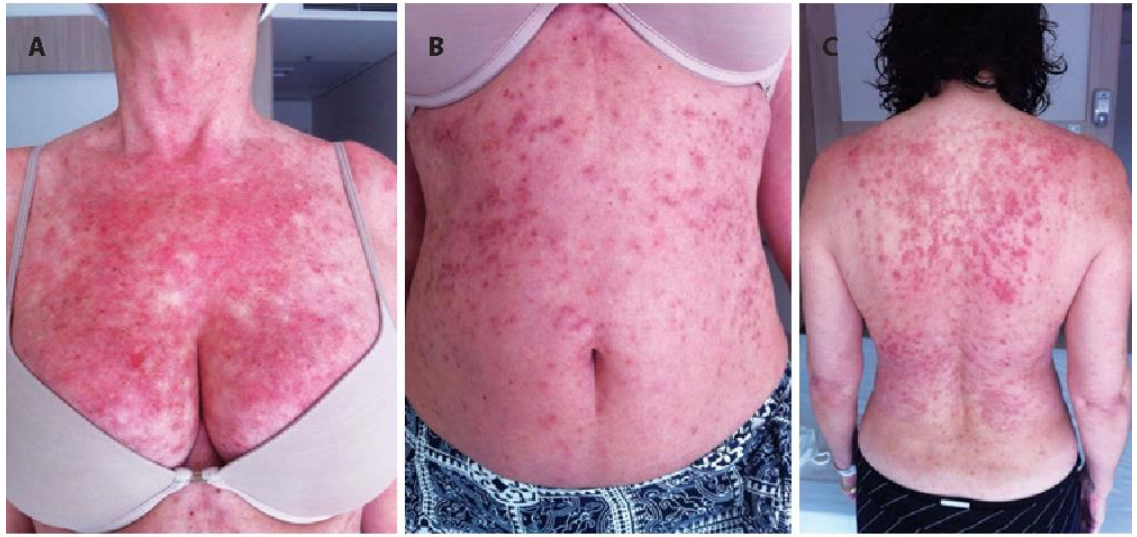
Elimination half-life ~5 hrs

MECHANISM OF ACTION

- Inhibits pro-inflammatory effects of the **arachidonic acid cascade**
- inhibits **neutrophil activation** by decreasing the flux of second messengers involved in intra-cellular signalling
- Inhibits **enzymes of phosphorylation** activity like MTX does

Sulfasalazine: side effects

- ✓ **Gastrointestinal**:
  anorexia, dyspepsia, nausea, diarhhea
  withdrawal rate 25%



- ✓ **Cutaneous**:
  pruritic rash
  DRESS syndrome

- ✓ **Haematologic:**
  Leukopenia<3% usually transient
  rarely severe agranulocytosis
  G6PD deficiency →haemolsis
  decrease in Igs, megaloblastic anaemia

- ✓ **other:**
  hepatotoxicity (usually mild), eosinophilic pneumonia, and anaphylactic reactions.

Sulfasalazine: treatment considerations

- ✓ **Perioperative management**:
  2022 ACR/AAKHS guidelines[1] – no need to stop for arthroplasty surgery

- ✓ **Vaccination**:
  discontinuation 1-2 weeks after the flu vaccine[2]

1. Goodman et al. Arthritis Care Res 2022 2. ACR guidelines for COVID vaccination 2022

Sulfasalazine: fertility, pregnancy & lactation

<u>WOMEN</u>:

✓Continue with added folic acid supplementation

✓Can be used throughout pregnancy and lactation

<u>MEN</u>:

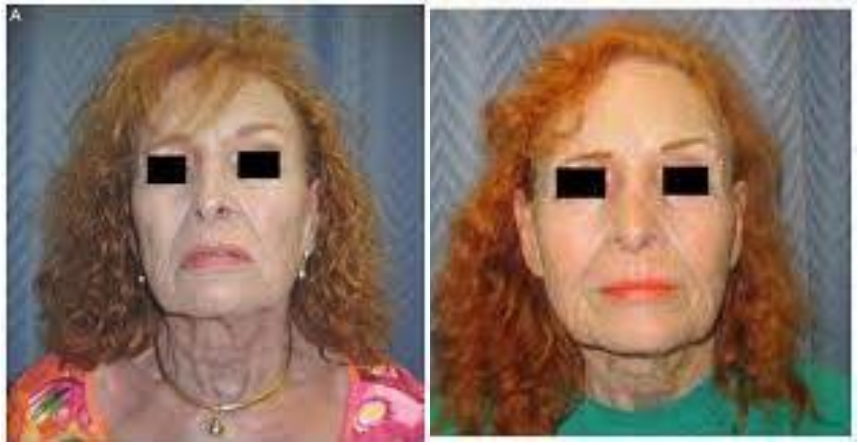
Reversible oligospermia

Sammaritano et al Arthritis Rheumatol 2020

Honourable mentions…

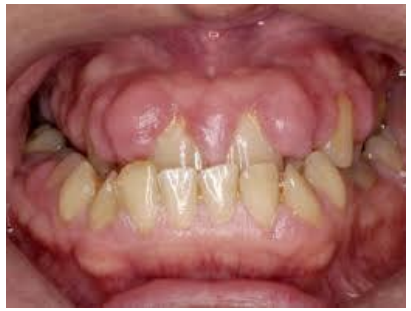
Honourable mentions

- **Gold salts:**
  injectable and per os (auranofin). MoA not understood - ?reduce oxidative stress
  transient symptoms of flushing, sweating, dizziness, nausea, hypotension, and malaise that occur within minutes of drug administration
  Cutaneous reactions (chrysiasis)

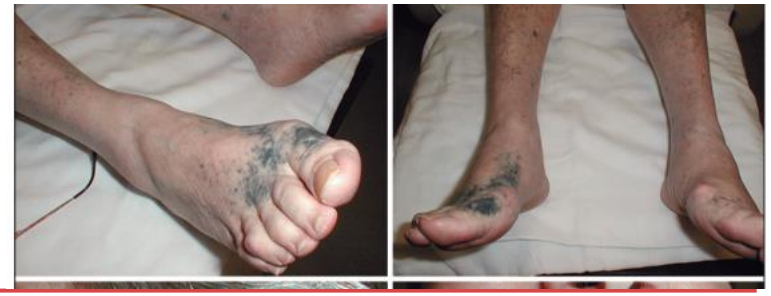


- **Cyclosporin:**

  calcineurin inhibitor – regulates gene coding for IL2 (T-cell inhibition)
  drug interactions
  dose related decrease in eGFR, arterial hypertension
  hirsuitism, gingival hyperplasia



- **Tetracyclines:**
  antibiotics with modest clinical benefit in RA
  Hyperpigmentation and drug induced lupus



Thank you for your attention

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