PHARMACOTHERAPY OF RHEUMATOID ARTHRITIS

DR SHAMS SULEMAN

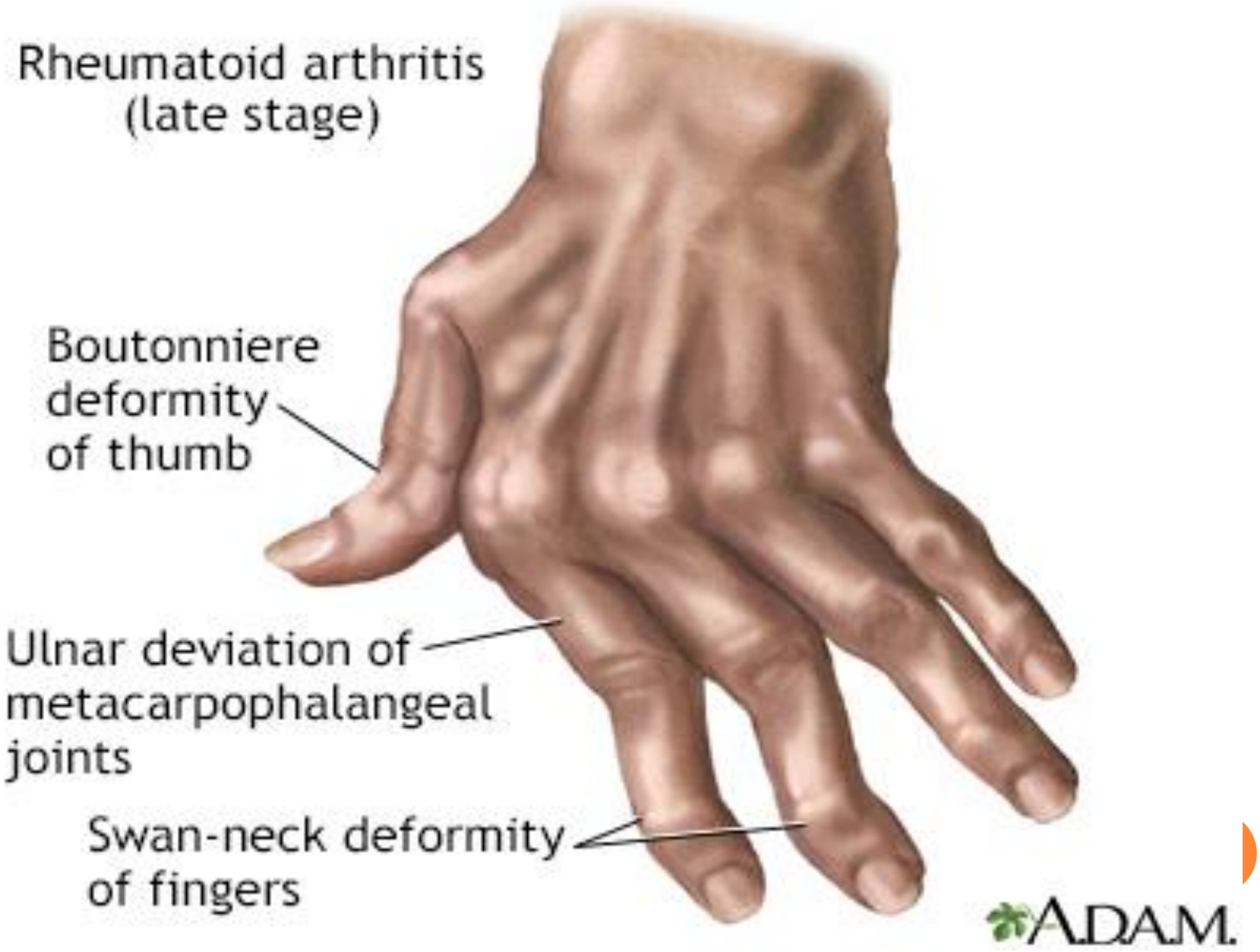
LEARNING OBJECTIVES

- Classify drugs used in Rheumatoid arthritis
- Discuss the role of NSAIDs in Rheumatoid Arthritis
- Discuss the role of Glucocorticoids in Rheumatoid Arthritis
- Define and classify DMARDs
- Enlist biological and non-biological agents used to treat rheumatoid arthritis

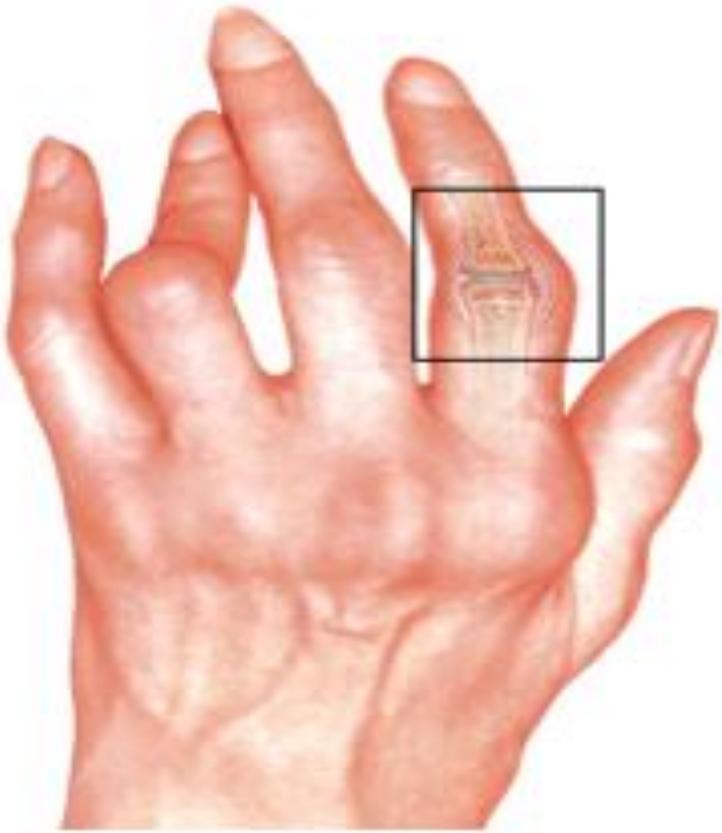
LEARNING OBJECTIVES

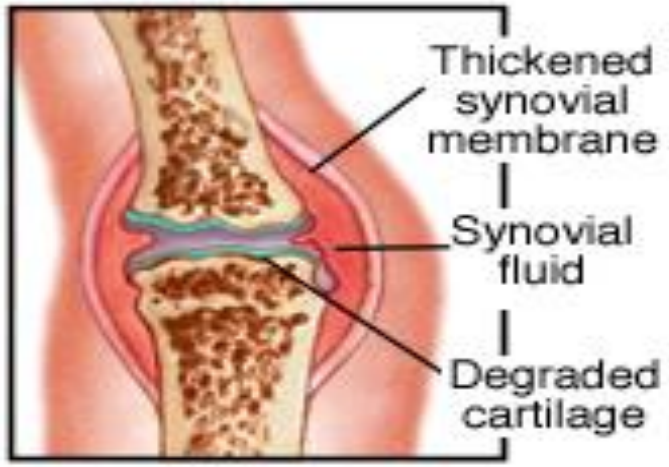
- Describe pharmacokinetics mechanism of action, clinical uses and adverse effects of methotrexate.

- Enlist adverse effects and therapeutic uses of DMARDs


Rheumatoid arthritis
(late stage)
Boutonniere
deformity
of thumb
Ulnar deviation of
metacarpophalangeal
joints
Swan-neck deformity
of fingers
A.D.A.M.

- **Common chronic systemic disease producing**
  - A symmetrical inflammatory polyarthritis
  - Extra articular involvements
  - Progressive joint damage





PHARMACOTHERAPY IN RHEUMATOID ARTHRITIS

National Institute of Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse
The Arthritis Foundationwww.arthritis.org

COMMON RA TREATMENTS

NSAIDS

A.K.A. non-steroidal anti-inflammatory drugs (think ibuprofen). Often need high doses.

DMARDS

Short for disease-modifying anti-rheumatic drugs. Usually your first line of treatment.

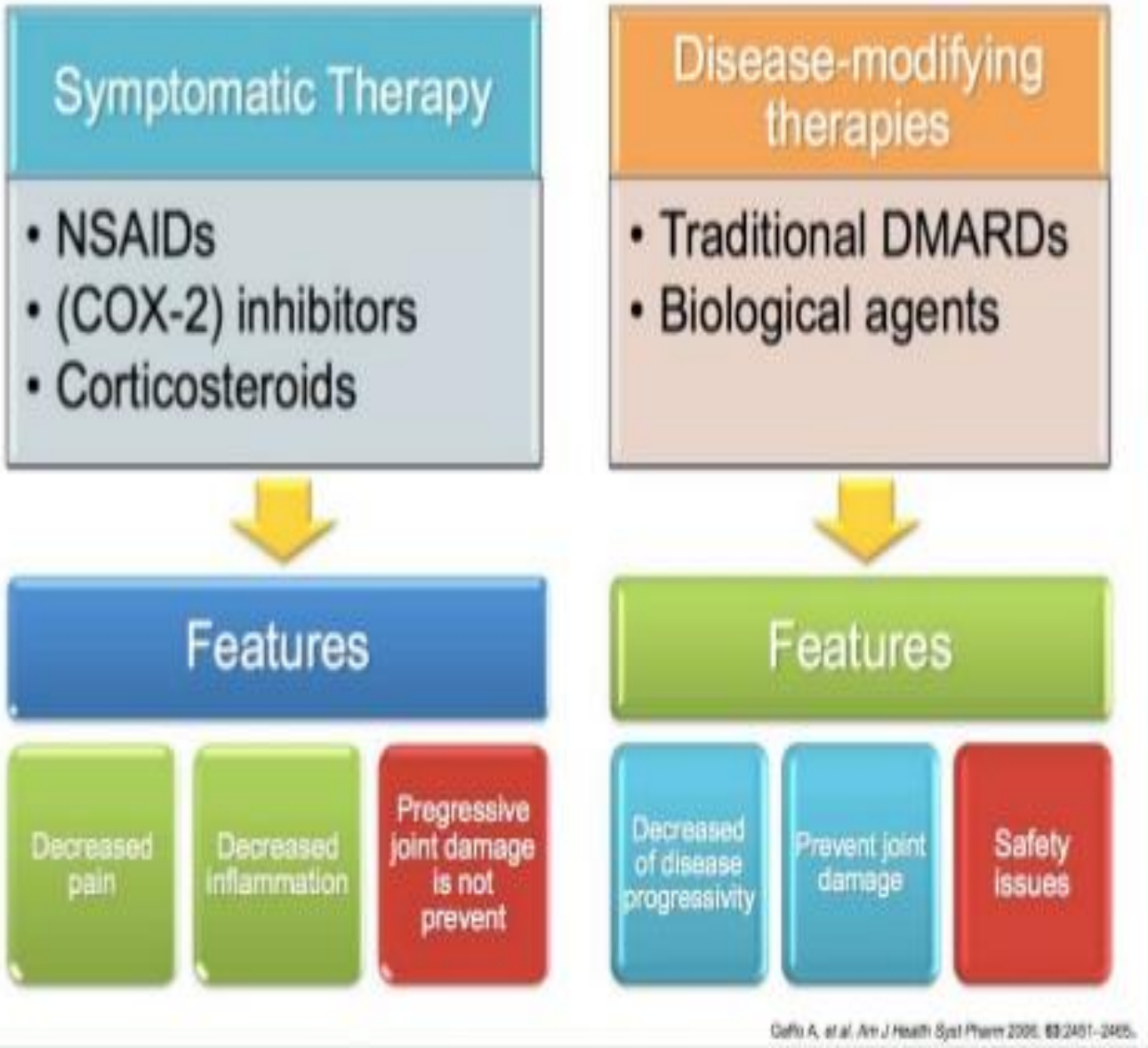
BIOLOGICS

Newest kids on the Rx block. Offer powerful and highly targeted treatment to slow RA progression.

STEROIDS

Helpful for calming flares. Can be injected into joints for quick relief. Best for short-term use only.

Types of RA therapy currently available



Rheumatoid arthritis

Mild

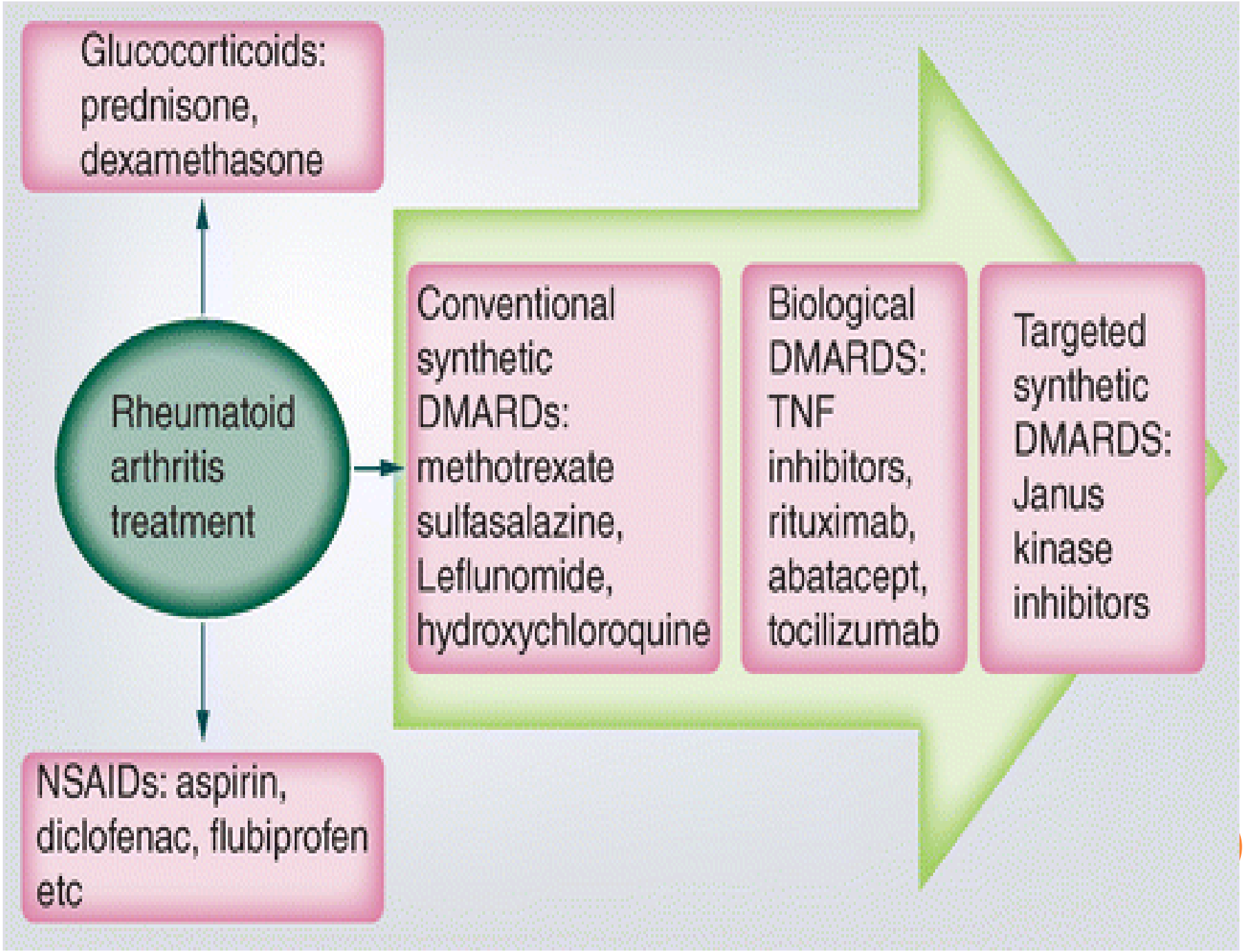
NSAIDs or hydrochloroquine

Moderate/severe

Non-biologic DMARDs
methotrexate, hydroxychloroquine, sulfasalazine
(combinations with MTX recommended)

TNF α-blockers
etanercept, adalimumab or infliximab

B-cell depleting therapy
rituximab


Glucocorticoids: prednisone, dexamethasone
Rheumatoid arthritis treatment
NSAIDs: aspirin, diclofenac, flubiprofen etc
Conventional synthetic DMARDs: methotrexate sulfasalazine, Leflunomide, hydroxychloroquine
Biological DMARDS: TNF inhibitors, rituximab, abatacept, tocilizumab
Targeted synthetic DMARDS: Janus kinase inhibitors

Conventional Pharmacotherapy in Rheumatoid Arthritis

Rheumatoid Arthritis: Drug Treatment Options

- NSAIDs
  - Symptomatic relief, improved function
  - No change in disease progression
- Low-dose prednisone (□10 mg qd)
  - May substitute for NSAID
  - Used as bridge therapy
  - ~~If used long term, consider prophylactic treatment for osteoporosis~~
- Intra-articular steroids (Abscess approach)
  - Useful for flares

Paget. *Primer on Rheum Dis.* 11th edition. 1997:168.

Pharmacotherapy in rheumatoid arthritis

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Traditional NSAIDs

- Aspirin
- Ibuprofen
- Ketoprofen
- Naproxen

COX-2 Inhibitors

- Celecoxib
- Rofecoxib

CORTICOSTEROIDS IN RA

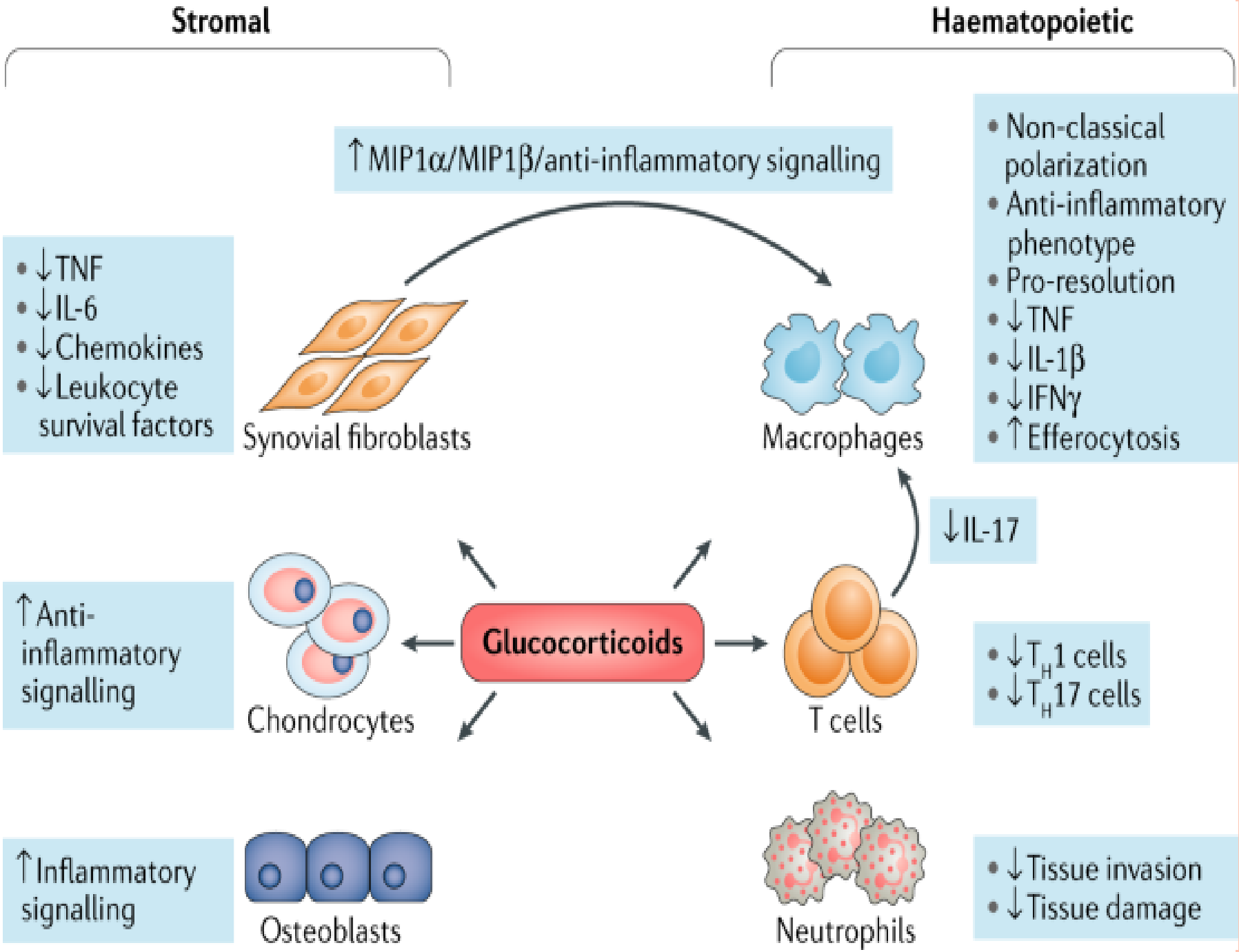
- Corticosteroids , both systemic and intra-articular are important adjuncts in management of RA.
- Indications for systemic steroids are:-
  - For treatment of rheumatoid flares.
  - For extra-articular RA like rheumatoid vasculitis and interstitial lung disease.
  - As ***bridge therapy*** for 6-8 weeks before the action of DMARDs begin.
  - Maintainence dose of 10mg or less of predinisolone daily in patients with active RA.
  - Sometimes in pregnancy when other DMARDs cannot be used.

Corticosteroids therapy is most effective and appropriate in three scenarios of early inflammatory arthritis.

1/ New onset early (<12 weeks) undifferentiated inflammatory arthritis in which oral, IM or IA steroids can be given in very early patients with the hope of inducing remission.

2/ New – onset RA for which prednisolone can be used as symptomatic therapy (usually in doses of 5-20 mg/day) in the first few weeks while the workup & symptoms evolve.

3/ Early – aggressive RA for which prednisone can be used as adjuvant therapy (usually part of DMARD combination regimen) where in high – dose prednisone (60 mg/day) acutely is followed chronically by 5-10mg daily


Stromal
Haematopoietic
↑MIP1α/MIP1β/anti-inflammatory signalling
• ↓TNF
• ↓IL-6
• ↓Chemokines
• ↓Leukocyte survival factors
Synovial fibroblasts
Macrophages
• Non-classical polarization
• Anti-inflammatory phenotype
• Pro-resolution
• ↓TNF
• ↓IL-1β
• ↓IFNγ
• ↑Efferocytosis
↓IL-17
↑Anti-inflammatory signalling
Chondrocytes
Glucocorticoids
T cells
• ↓T_H1 cells
• ↓T_H17 cells
↑Inflammatory signalling
Osteoblasts
Neutrophils
• ↓Tissue invasion
• ↓Tissue damage

Corticosteroid Therapy

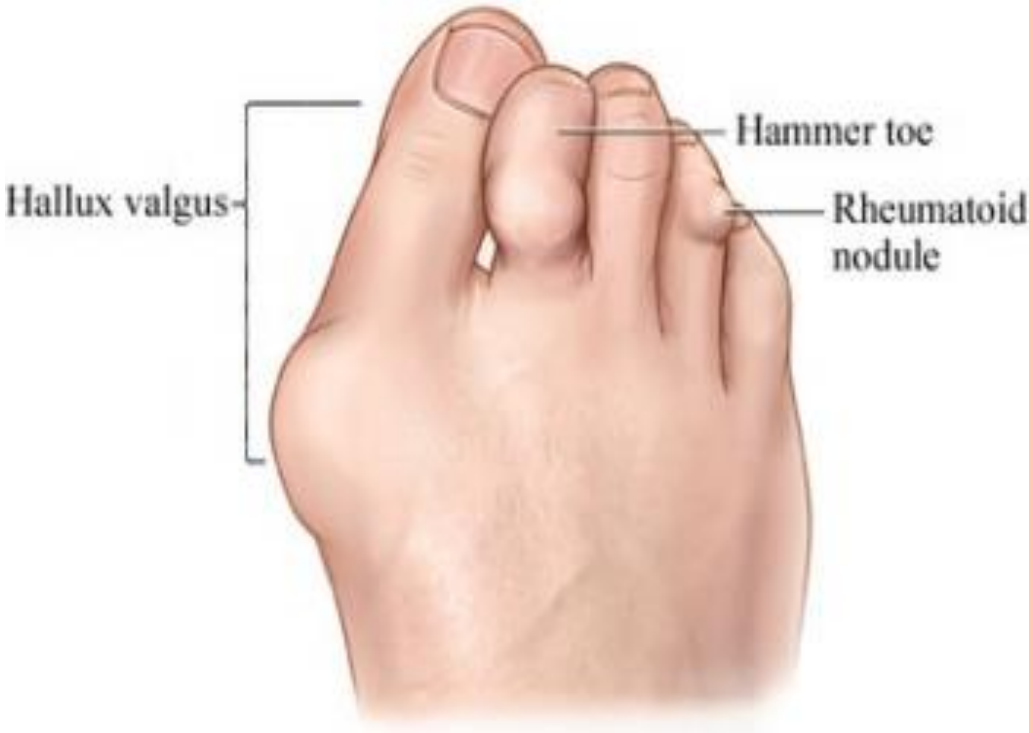
Advantages

- Anti-inflammatory and immunosuppressive effects
- Can be used to bridge gap between initiation of DMARD therapy and onset of action.
- Intra-articular injections can be used for individual joint flares

Disadvantages

- Does not conclusively affect disease progression
- Tapering and discontinuation of use often unsuccessful
- Low doses result in skin thinning, ecchymoses, and Cushingoid appearance
- Significant cause of steroid-induced osteopenia

DISEASE MODIFYING ANTI – RHEUMATIC DRUGS



DISEASE MODIFYING ANTI-RHEUMATOID DRUGS (DMARDS)

- Slow course of disease
- Induce remission
- Prevent further destruction of joint / soft tissues
- Delayed onset of action – 3 – 4 months

Rationale for DMARDs

- NSAIDS – offer symptomatic relief.
- No effect on cartilage or bone destruction.
- Inflammation is maximal at an early stage.
- If given early, DMARDs can stabilise joint function at a level which is near to normal, rather than preserving the joint in a state of disability

DMARDs CLASSIFICATION

- **NON-BIOLOGIC DMARDS**
  - Methotrexate
  - Azathioprine
  - Chloroquine & hydroxychloroquine
  - Cyclophosphamide
  - Cyclosporine
  - Sulfasalazine
  - Leflunomide
  - Mycophenolate mofetil
  - Minocycline
- Gold Compounds
  - a. Sodium Aurothiomalate (deep IM injection)
  - b. Auranofin (oral preparation)
- Penicillamine

DMARDS CLASSIFICATION

Biologic DMARDs

1. T- cell modulating drugs
   - (co stimulation inhibitors)
     - Abatacept
     - Belatacept
2. B- cell cytotoxic (depleting) agent
   - Rituximab
3. Anti-IL-6 receptor antibody
   - Tocilizumab

Biologic DMARDs

4. TNF-α-blocking drugs

- **Etanercept**
- **Infliximab**
- **Adalimumab**
- **Certolizumab**
- **Golimumab**

Biologic DMARDs

- 5. JANUS KINASE inhibitors
  - **Tofacitinib**
  - **Baricitinib**
  - **Upadacitinib**

Table 34–3 Disease-Modifying Anti-Rheumatic Drugs

DRUG	CLASS OR ACTION
Small molecules	
Methotrexate	Anti-folate
Leflunomide	Pyrimidine synthase inhibitor
Hydroxychloroquine	Anti-malarial
Minocycline	5-lipoxygenase inhibitor, tetracycline antibiotic
Sulfasalazine	Salicylate
Azathioprine	Purine synthase inhibitor
Cyclosporine	Calcineurin inhibitor
Cyclophosphamide	Alkylating agent
Biologicals	
Adalimumab	Ab, TNF-α antagonist
Golimumab	Ab, TNF-α antagonist
Infliximab	IgG-TNF receptor fusion protein (anti-TNF)
Certolizumab	Fab fragment toward TNF-α
Abatacept	T-cell co-stimulation inhibitor (binds B7 protein on antigen-presenting cell)
Rituximab	Ab toward CD20 (cytotoxic toward B cells)
Anakinra	IL-1-receptor antagonist

METHOTREXATE

- ✓ Immunosuppressant
- ✓ Mainstay of therapy
- ✓ Slows appearance of new erosions
- ✓ Onset of action: 3 – 6 weeks
- ✓ Low doses – required
  7.5 mg / week – 20 mg / week (oral)
- ✓ Minimal adverse effects

Pharmacokinetics

- Routes Of Administration:
  - Oral
  - IM & IV
  - Intra thecal
- Metabolized to less active metabolite
- Renal & biliary excretion

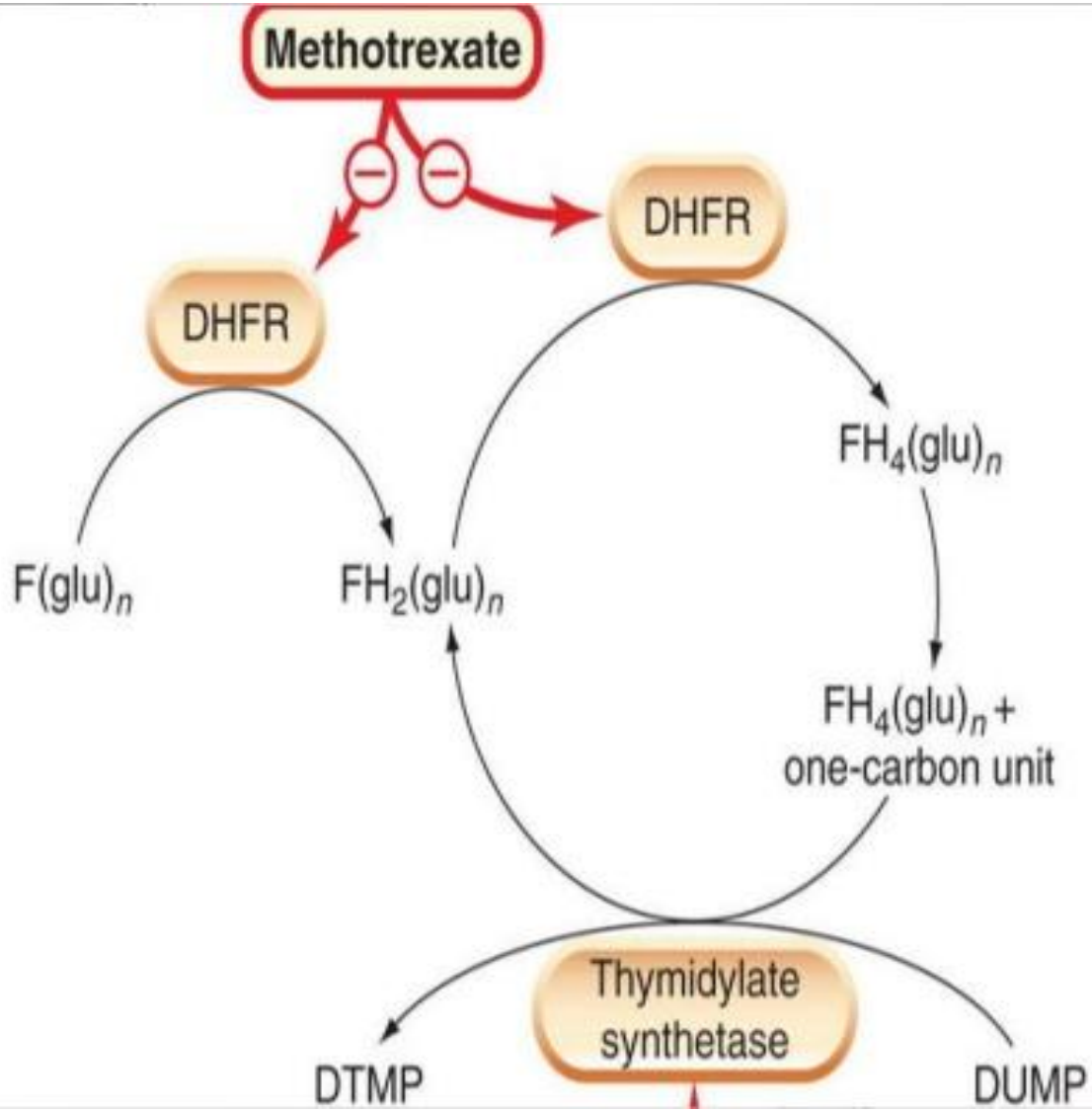
METHOTREXATE

- Drug of choice.
- Required in much lower doses as compared to cancer therapy.

M.O.A:

- It inhibits amino-imidazole carboxamide ribonucleotide(AICAR) transformylase & thymidylate synthetase
- Secondary effects on inflammatory function of polymorph nuclear cells.
- It also inhibits polymorph nuclear chemotaxis.

MOA: METHOTREXATE



METHOTREXATE

- Also affects lymphocyte & macrophage function through its inhibition of Dihydrofolate reductase.
- Induces apoptosis in immune inflammatory cells
- Inhibits proinflammatory cytokines

THERAPEUTIC USES

- Juvenile chronic arthritis
- Rheumatoid arthritis
- Psoriatic arthritis

ADVERSE EFFECTS

✓ Common:

- Nausea
- Mucosal ulceration

✓ Chronic use:

- Myelosuppression
- GI ulcerations
- Alopecia
- Hepatotoxicity
- Hypersensitivity-like lung reactions
- Teratogenic

SULFASALAZINE

- ✓ Local intestinal flora split sulfasalazine → sulfapyridine & 5-amino salicylic acid
  - o Sulfapyridine absorbed
  - o Suppression of T cells,
  - o IgA & IgM rheumatic factor production is decreased
  - o Decreased IL-1,-6 & -12; & TNF-α.
  - o Inhibit cytokines.
- ✓ **Dose:**

2g / day in 4 divided doses

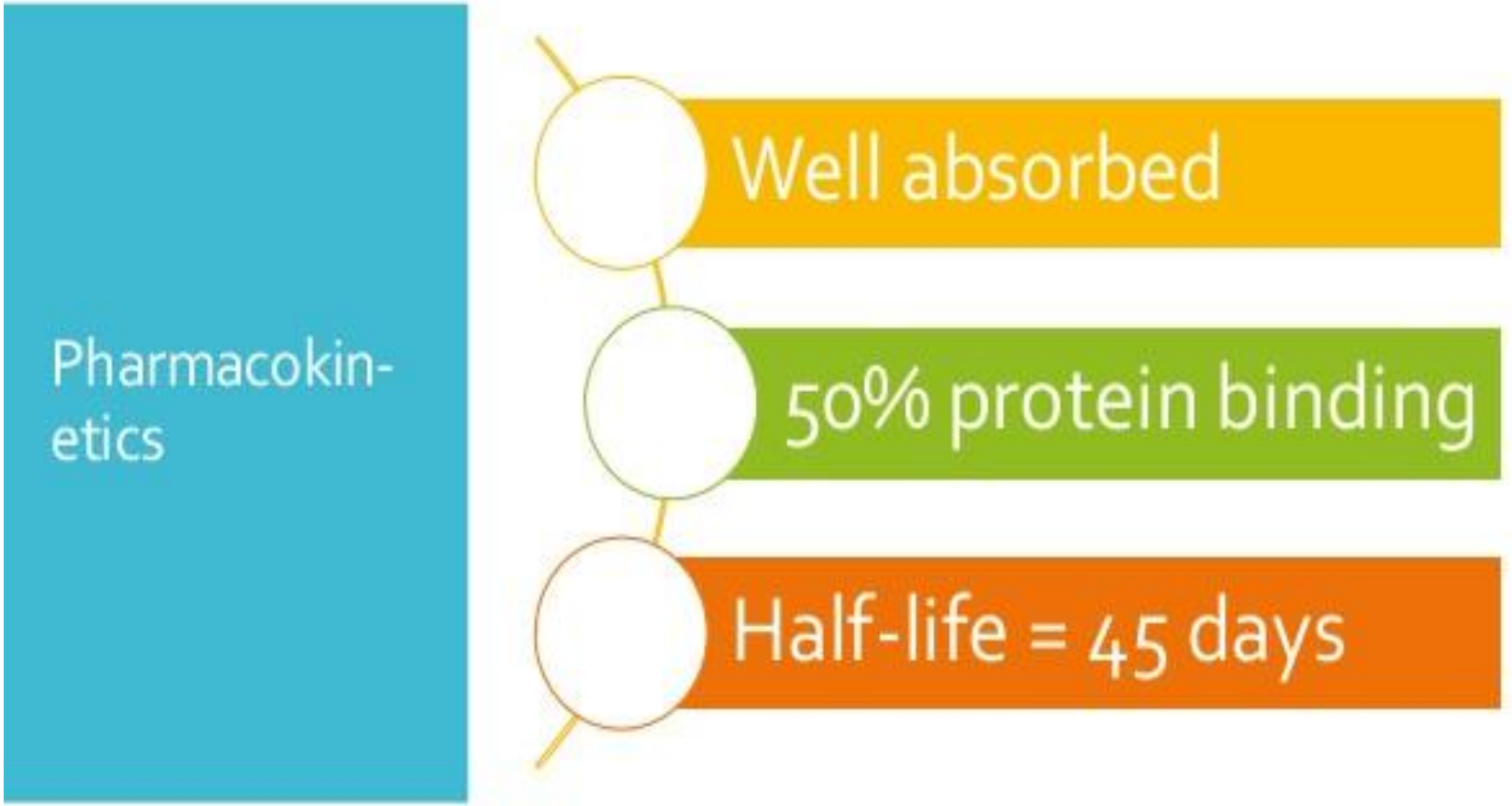
ADVERSE EFFECTS

1) GI upsets
2) Hypersensitivity reactions
3) Haemolytic anaemia, Neutropaenia, Thrombocytopenia
4) Pulmonary toxicity
5) Reversible infertility in men

CHLOROQUINE & HYDROXY CHLOROQUINE

- ✓ 4 – aminoquinoline derivative
- ✓ Anti-inflammatory activity: through the inhibition of the production of Interleukin (IL) -6 and Tumor Necrosis Factor (TNF)-α
- ✓ Good safety profile.
- ✓ Compared to chloroquine, hydroxy chloroquine is a drug more readily available and with a higher safety profile
- ✓ Response – delayed (3 – 6 months)
- ✓ Hydroxy chloroquine tablets 200 mg.

Hydroxy Chloroquine



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Chloroquine & hydroxychloroquine- MOA

- Unclear
- Depression of T-lymphocytes
- Inhibition of DNA/RNA synthesis
- Trapping of free radicals

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CYCLOSPORINE

- A peptide antibiotic and a non biological DMARD
- Inhibits IL-1 &-2 receptor production and inhibits macrophage- T-cell interaction through regulation of gene transcription
- Also affects T-cell dependent B-cell function
- Oral use
- A/E: leukopenia, thrombocytopenia, anemia
- Cardiotoxic and sterility in women

CYCLOSPORIN

- Fungal peptide-impairs the function of B and T lymphocytes by suppressing the synthesis and release of IL-1 & IL-2
- Started at a dose of 2.5mg/kg daily in two divided doses.
- Increased gradually after six weeks to a maximum of 4mg/kg daily
- Full response will take 12 wks.

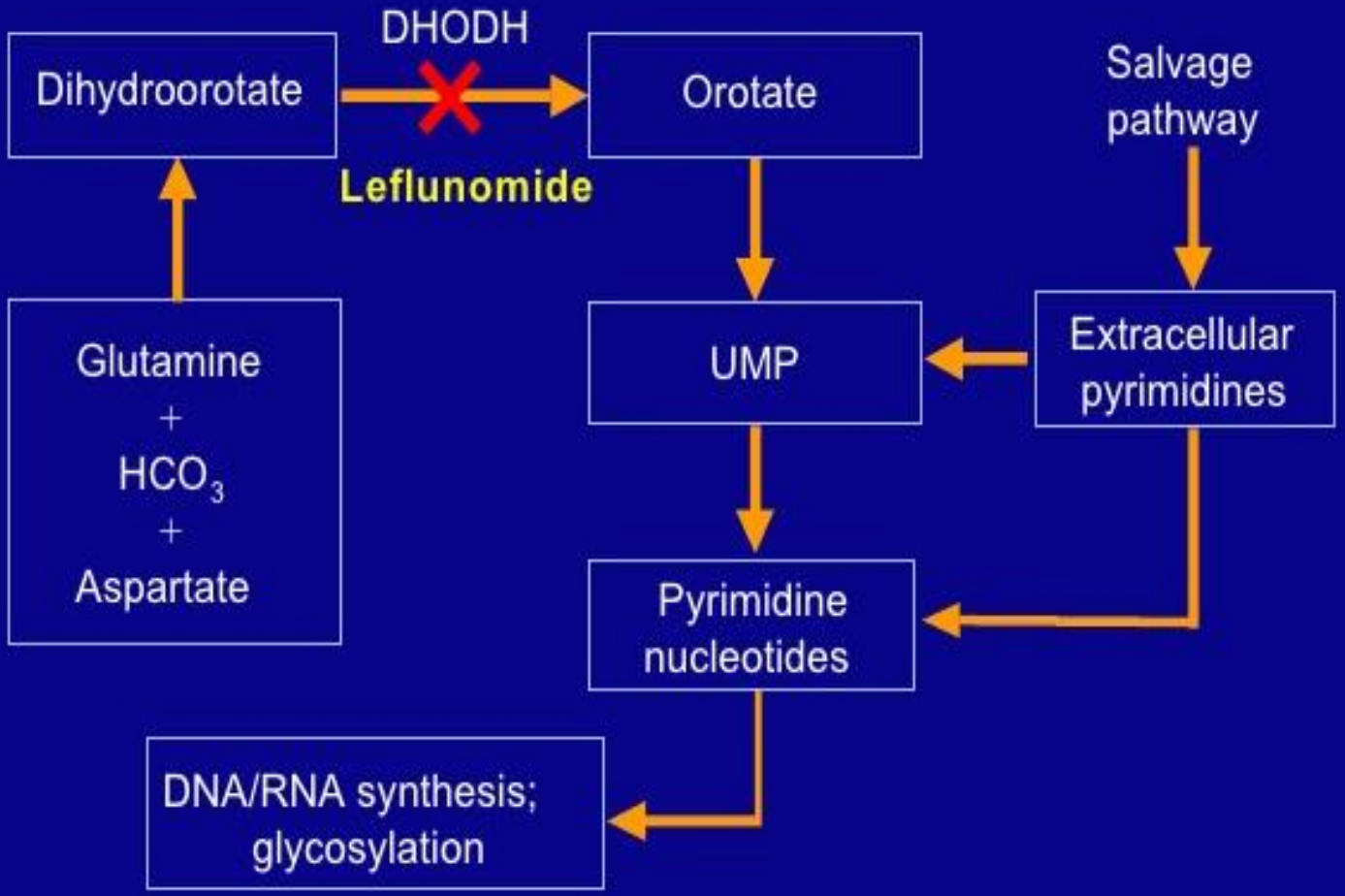
CYLOSPORIN IN R.A

- Good efficiency
- Less well tolerated because of hypertension and nephrotoxicity which are common and dose related.
- used in patients with severe disease who failed on other treatments or unsuitable for other DMARDs
- valuable when used together with methotrexate in patients with very active early disease.

LEFLUNOMIDE

- ✓ Rapid conversion to active metabolite A77-1726
- ✓ Inhibits T cell proliferation by inhibiting dihydroorotate dehydrogenase
- ✓ Arrests stimulated cells in G1 phase
- ✓ Inhibits T cell and B cells proliferation and production of antibodies

Leflunomide/A77 1726
Primary Mechanism of Action



PHARMACOKINETICS

- Good oral absorption
- $t_{1/2}$ – 19 days
- Active metabolite
- Enterohepatic recirculation

INDICATIONS

- As effective as methotrexate in RA
- Inhibits bony damage

LEFLUNAMIDE

- Increases IL-10 receptor m RNA
- Decreases IL-8 receptor type A m RNA
- P.Kinetics: completely absorbed.
- Enterohepatic circulation.
- Indicated in RA for inhibition of bone damage.

LEFLUNAMIDE: ADVERSE EFFECTS

- diarrhoea
- reversible alopecia, hypertension, dizziness
- teratogenic in mammals and is therefore not recommended in women of childbearing age in the absence of reliable contraception
- Liver function should be monitored

LEFLUNAMIDE

Dosage

- Daily dose of 10-20 mg
- Loading dose of 100 mg once weekly for 3 wks in addition to daily dose.
- Complete effect takes 6-12 wks.

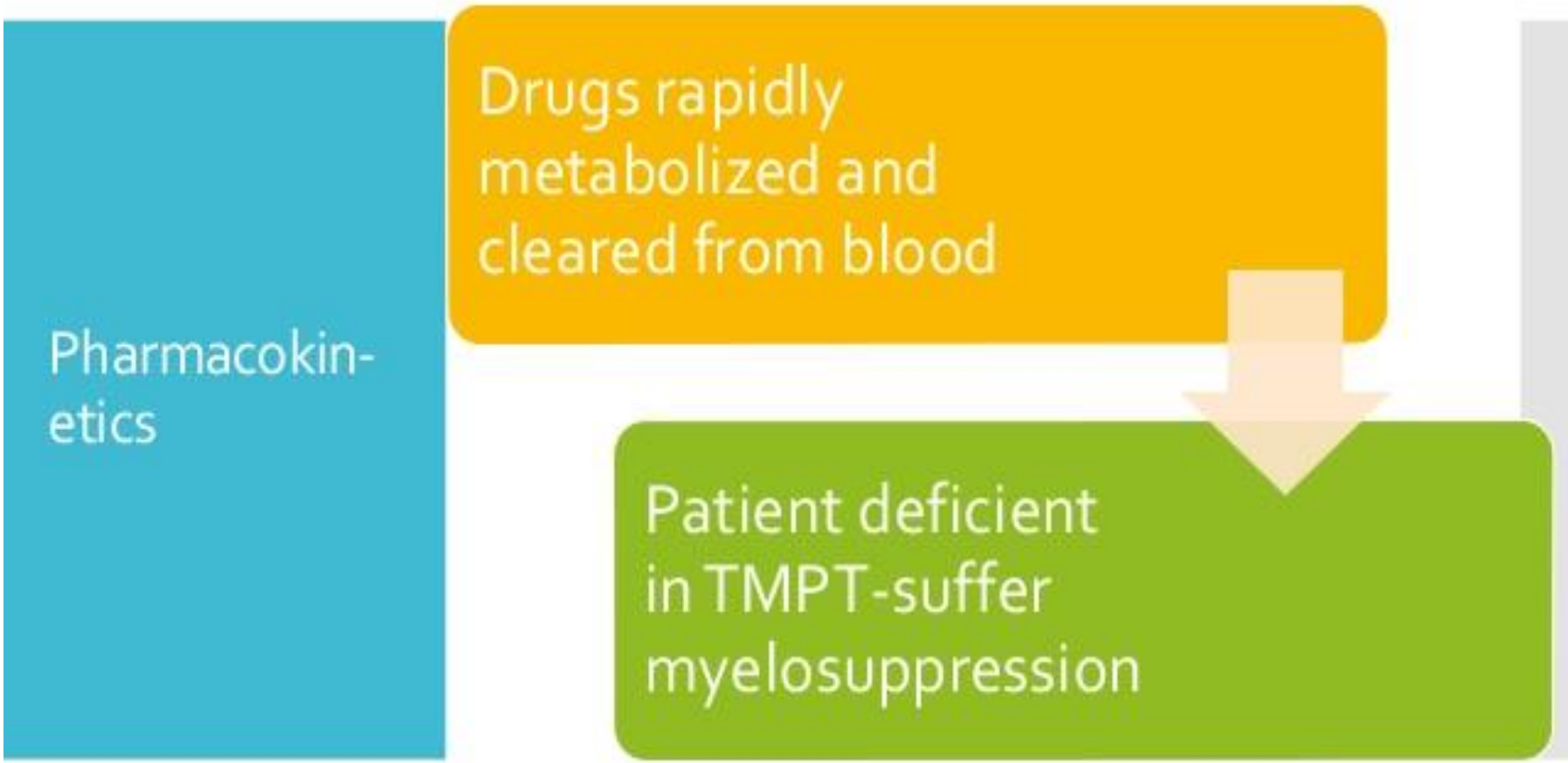
AZATHIOPRINE

- Synthetic non biological DMARD
- Acts through its metabolite 6 thioguanine by the action of the enzyme Thio Puurine Methyl Transferase (TPMT)
- 6-thioguanine suppresses inosinic acid, B and T cell function.
- Metabolism is bimodal (slow and rapid metabolizers)
- Slow metabolizers have low activity of TPMT thus myelosuppression can occur

MECHANISM OF ACTION

- ↓ responsiveness of T lymphocytes to mitogens
- Stabilize lysosomal membrane
- ↓ leukocyte responsiveness or chemotaxis
- Inhibit DNA & RNA synthesis
- Trapping of free radicals

AZATHIOPRINE



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Azithioprine MOA

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AZATHIOPRINE

- dose of 1.5 to 2.5mg/kg daily in divided doses
- efficacy comparable to that of gold but greater toxicity.
- potential for lymphoproliferative cancers
- Used for progressive disease which is refractory to other DMARDs of comparable potency or as a steroid-sparing agent

CYCLOPHOSPHAMIDE

- Synthetic non biological DMARD
- Active metabolite is Phosphoramide mustard
- DNA crosslinks prevent replication
- T-cell suppression produces anti-rheumatic effect
- Oral administration

PENCILLAMINE

- chelator of divalent cations structurally similar to cysteine
- impair antigen presentation, diminish globulin synthesis, to inhibit PMN leucocyte myeloperoxidase,
- Rarely used today because of toxicity.

GOLD COMPOUNDS

- Gold is administered in the form of organic complexes; **sodium aurothiomalate** and **auranofin** are the two most common preparations.
- The effect of gold compounds develops slowly over 3-4 months.
- Pain and joint swelling subside, and the progression of bone and joint damage diminishes.

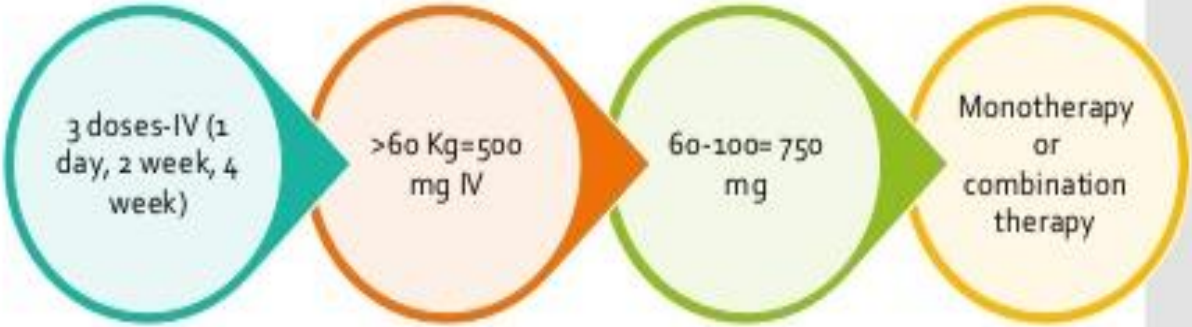
- The mechanism of action is not clear, but auranofin, although not aurothiomalate, inhibits the induction of IL-1 and TNF-alpha.

ABATACEPT

- Biologic
- Inhibits T-cell activation
- IV administration
- $T_{1/2}$ 13-16 days
- Both as monotherapy or in combination
- Increase risk of infection
- Infusion related and hypersensitivity reactions

ABATACEPT

Pharmacokin-etics



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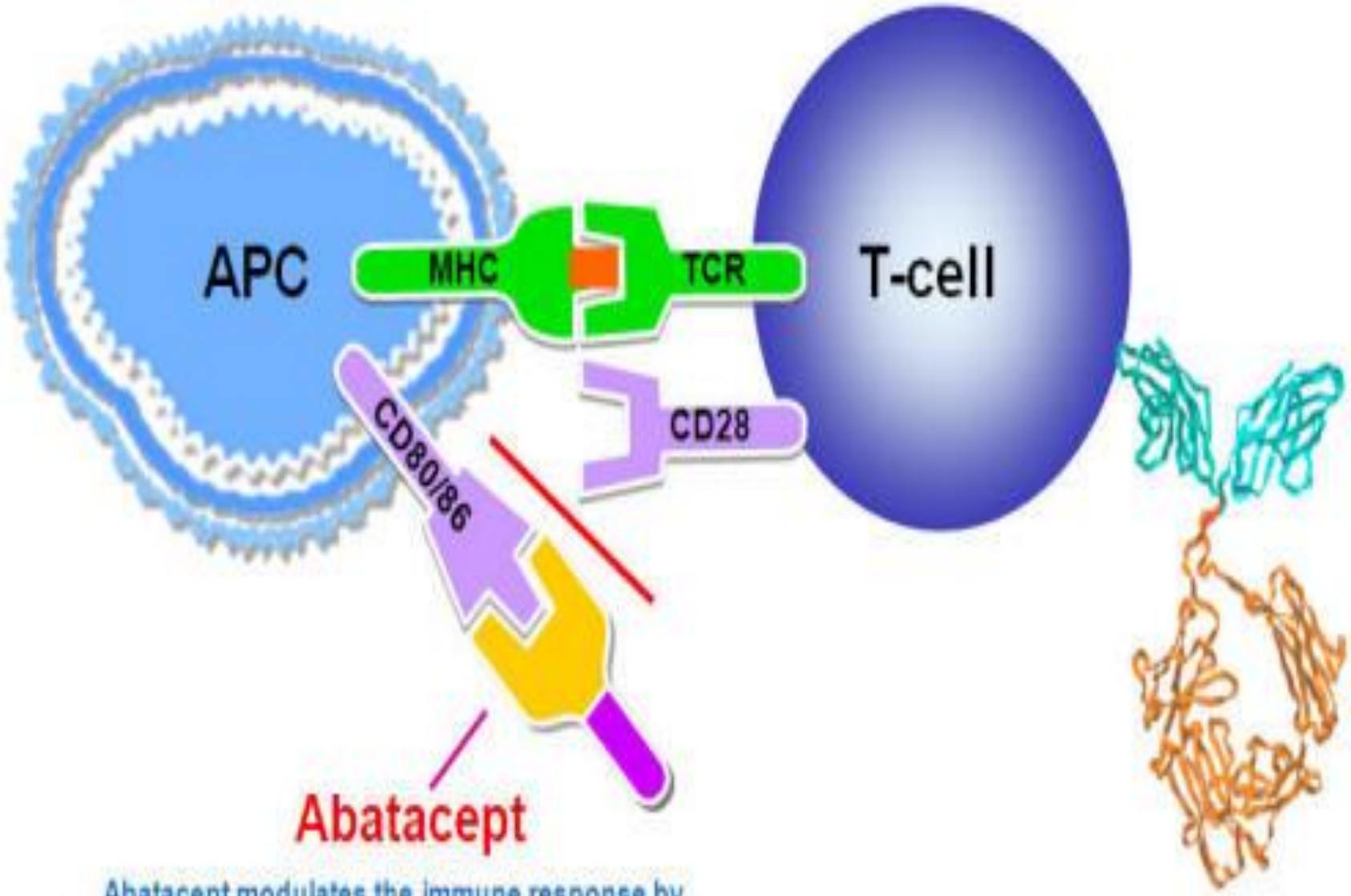

Abatacept modulates the immune response by binding to CD80/CD86 on an antigen-presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding of CD28 on naive T cells and attenuating T-cell activation.

ABATACEPT

Adverse Effects

Hypersensitivity

Lymphomas

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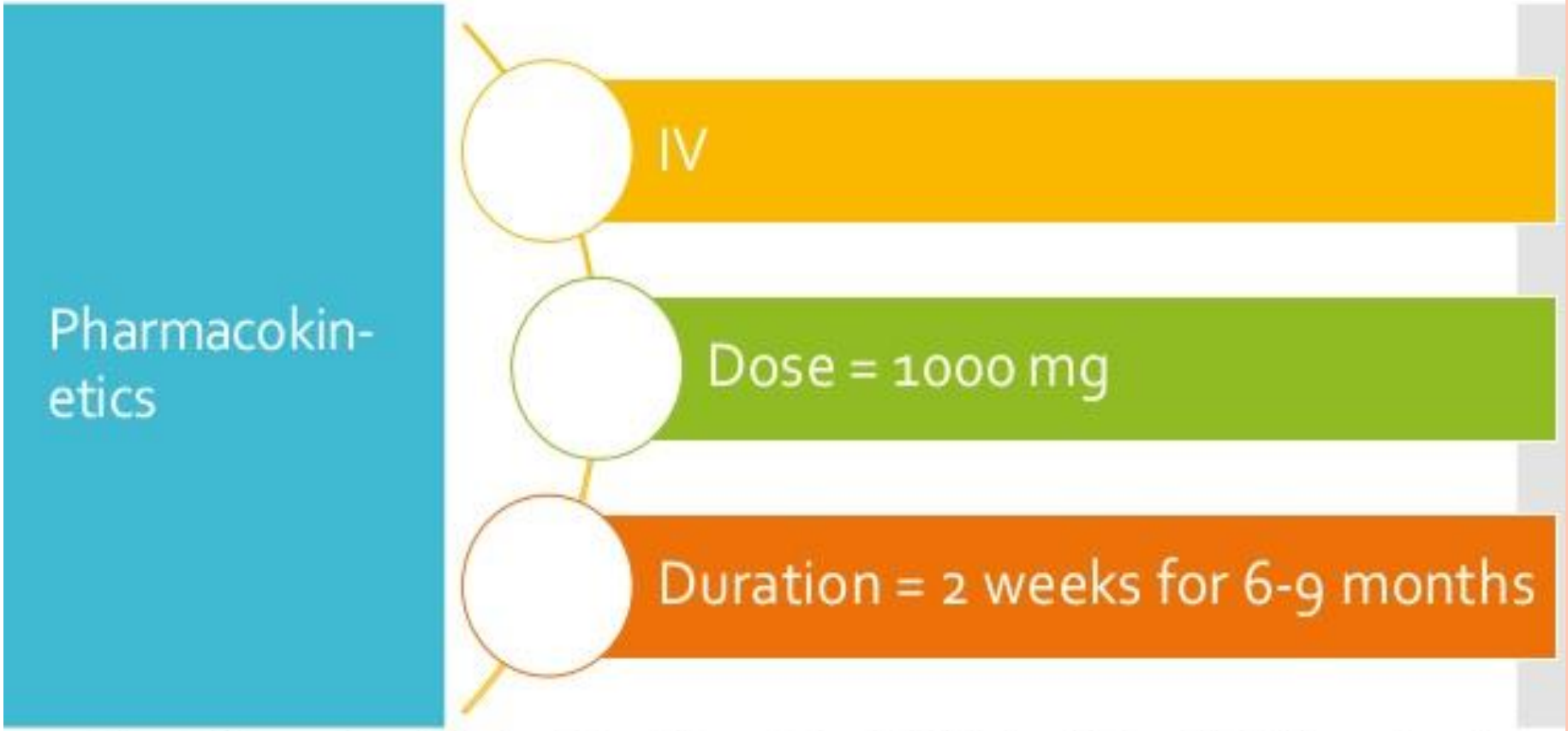
RITUXIMAB

- Chimeric monoclonal antibody
- Targets CD20 B lymphocytes
- Decrease presentation of antigens to T-lymphocytes
- Inhibit secretion of proinflammatory cytokines
- Administered I/V
- Infusion related toxicity can be decreased by pretreatment
- Rash , infections, reactivation of HBV

RITUXIMAB



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TOCILIZUMAB

- Biologic Humanized antibody
- Binds to soluble and membrane bound IL-6 receptors
- Inhibits IL-6 mediated signaling
- IV administration
- Both as monotherapy or in combination with non biological DMARDS
- Increase risk of serious infections like TB, fungal, viral, opportunistic

TNF A-BLOCKING DRUGS

ETANERCEPT

- Genetically engineered fusion protein – 2 TNF receptor moieties linked to human IgG

- Inhibits TNFα
- Inhibits lymphotoxin-**α**
- Etanercept + MTX → more effective in
  - Retarding disease process
  - Achieving remission

ETANERCEPT

Pharmacokin-
etics

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- S/C administration

ADVERSE EFFECTS:

- ✓ Bacterial infections
- ✓ Activation of latent TB
- ✓ Local inflammation at injection site

INFLIXIMAB

- Chimeric monoclonal IgG antibody
- Binds to & inhibits TNFα
- Given in combination with MTX
- I / V administration

ADVERSE EFFECTS:

1) Anti-infliximab antibodies

2) Infusion reactions:
   - o Fever
   - o Chill
   - o Urticaria

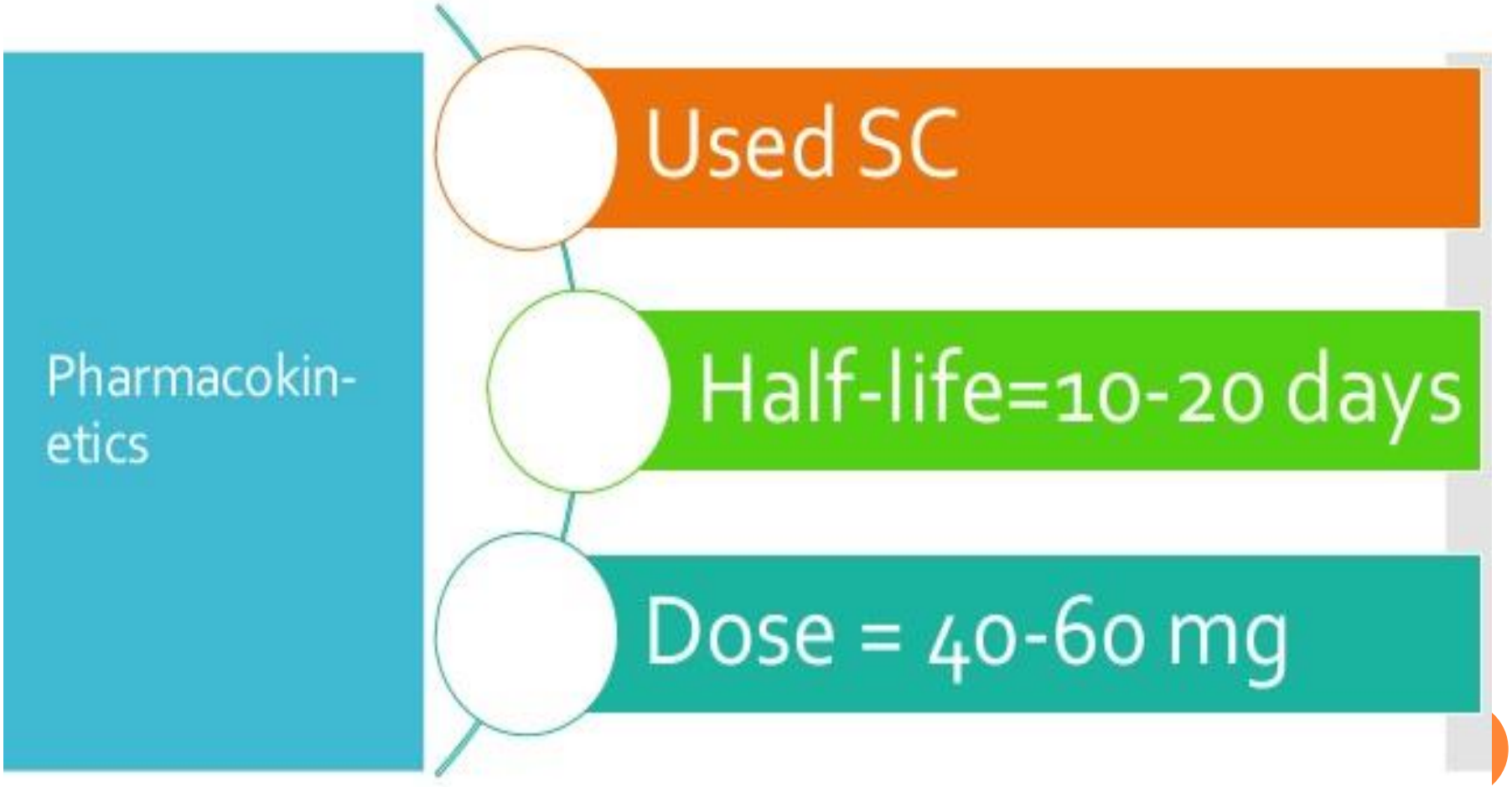
3) Infections:
   - o Pneumonia
   - o Cellulitis

4) Myelosuppression

ADALIMUMAB

- Fully human monoclonal IgG antibody
- Binds to & inhibits TNFα by preventing interaction with p55 and p75
- Useful in treatment of active RA
- Administered – S / C
- May cause:
  - Headache
  - Nausea
  - Reaction at injection site

ADALIMUMAB



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ADALIMUMAB

Adverse Effects

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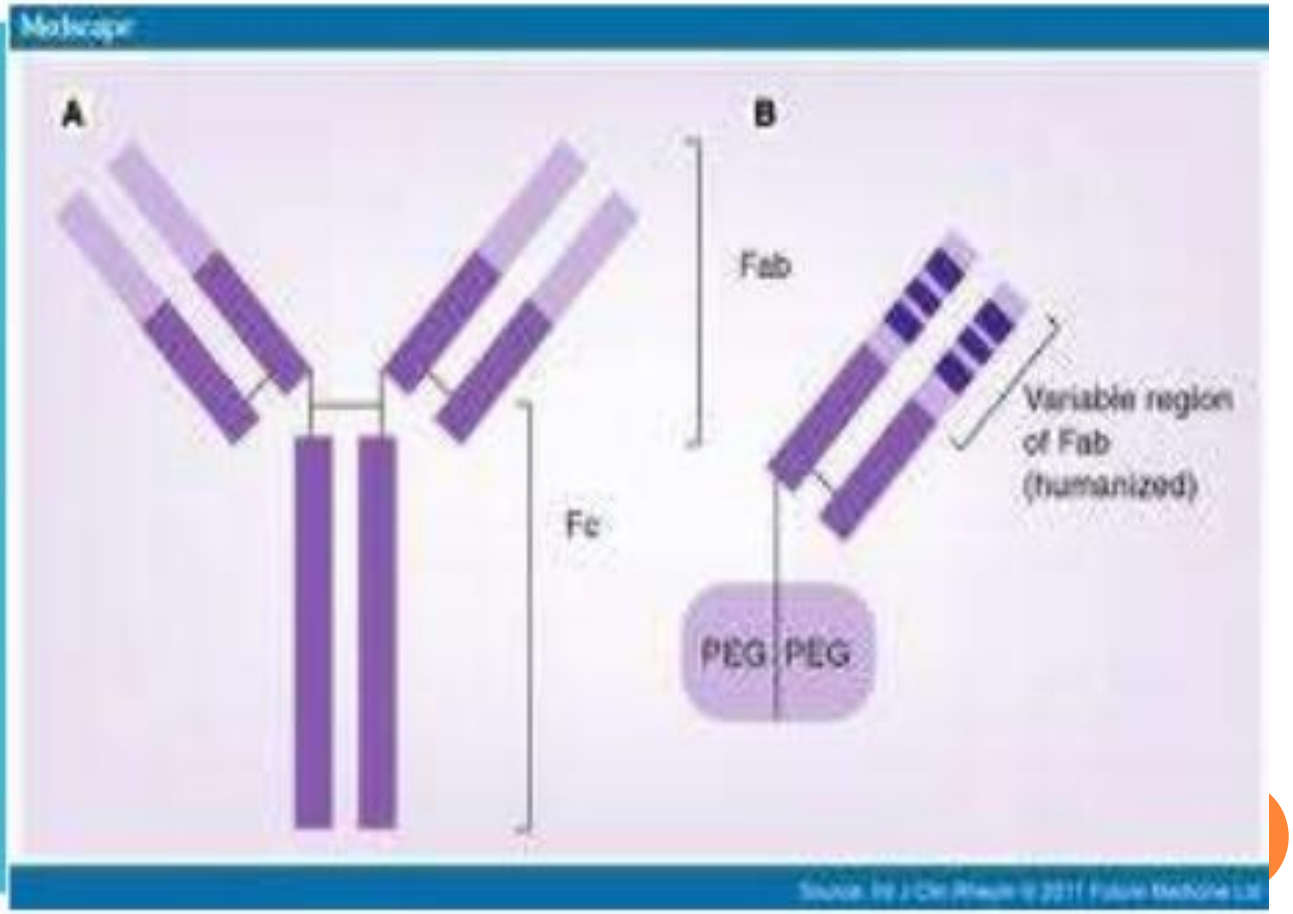
CERTOLIZUMAB

Certolizumab-MOA



CERTOLIZUMAB

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COMBINATION THERAPY WITH DMARDS

Combination therapy

- Complementry MOA
- Non-overlapping pharmacokinetics
- Non-overlapping toxicity.
- With MTx back ground therapy, cyclosporin, HCQ, LFN, infliximab adalimumab, etanercept shows improves efficiency.
- With auronofin, azothioprine, SS- no additional benefit.

Combination DMARD therapy

- MTX + SSZ
- MTX + Hydroxychloroquine
- MTX + cyclosporine
- MTX + Leflunomide

Excellent safety & improved efficacy over MTX alone

CLINICAL PHARMACOLOGY

Perioperative medication recommendations

- NSAIDS: Discontinue 5 half-lives before surgery.
- Aspirin: discontinue 7-10 days before surgery.
- Corticosteroids:Perioperative use depends on level of potential surgical stress
- MTx:Continue perioperatively for all procedures.

CLINICAL PHARMACOLOGY

- withholding 1 to 2 doses of MTx for patients with poorly controlled diabetes; the elderly; and those with liver, kidney, or lung disease
- Leflunomide: Continue for minor procedures. Withhold 1-2 days before moderate and intensive procedures and restart 1-2 weeks later.
- Sulfasalazine, HCQ - Continue for all procedures

CLINICAL PHARMACOLOGY

- TNF antagonists:Continue for minor procedures. For moderate to intensive procedures, withhold etanercept for1 week, and plan surgery for the end of the dosing interval for adalumimab and infliximab.
- Restart 10-14 days Postoperatively.
- IL-1 antagonist:Continue for minor procedures. Withhold 1-2 days before surgery and restart 10 days postoperatively for moderate to intensive procedures

Q2

- Although the patient's disease was adequately controlled with an NSAID and methotrexate for some time, her symptoms began to worsen and radiologic studies of her hands indicated progressive destruction in the joints of several fingers. Treatment with a new second-line agent for rheumatoid arthritis was considered. This drug is available only in a parenteral formulation; its mechanism of anti-inflammatory action is antagonism of tumor necrosis factor. The drug being considered is:-
- (A) hydroxychloroquine
- (B) infliximab
- (C) methotrexate
- (D) chloroquine
- (E) Sulfasalazine

REFERENCES

- **Basic and Clinical Pharmacology: Katzung BG, Masters SB, Trevor AJ. 14th Edition.**
- **Katzung & Trevor's Pharmacology: Examination & Board Review. 12th Edition**
- **Lippincott's Illustrated Reviews: Pharmacology, Clark MA, Finkel R, Rey JA, Whalen K. 7th Edition**
- **Goodman & Gilman's The Pharmacological Basis of Therapeutics: Brunton LL. 12th Edition**

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