Disease Modifying Antirheumatic Drugs (DMARDs)

Nehal M. Ramadan. M.B.B.CH, MSc, PhD, MD

Associate professor of Clinical Pharmacology

Clinical Pharmacology department, Faculty of Medicine, Mansoura University, Egypt

Learning objectives:

By the end of this lecture, the student will be able to:

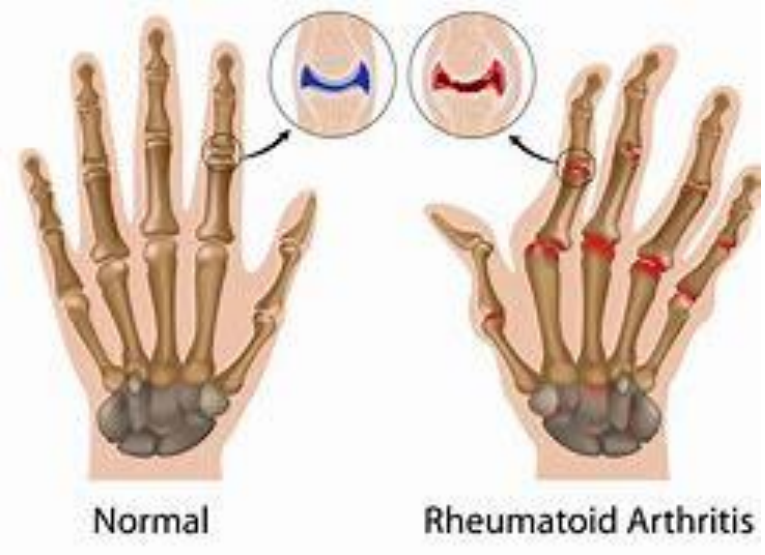
- List the DMARDs and Describe their **mech. Of action, side effects and Cis.**
- List different **biologic DMARDs** used in treating RA and Describe their major **side effects & CIs**.

Lecture outline:

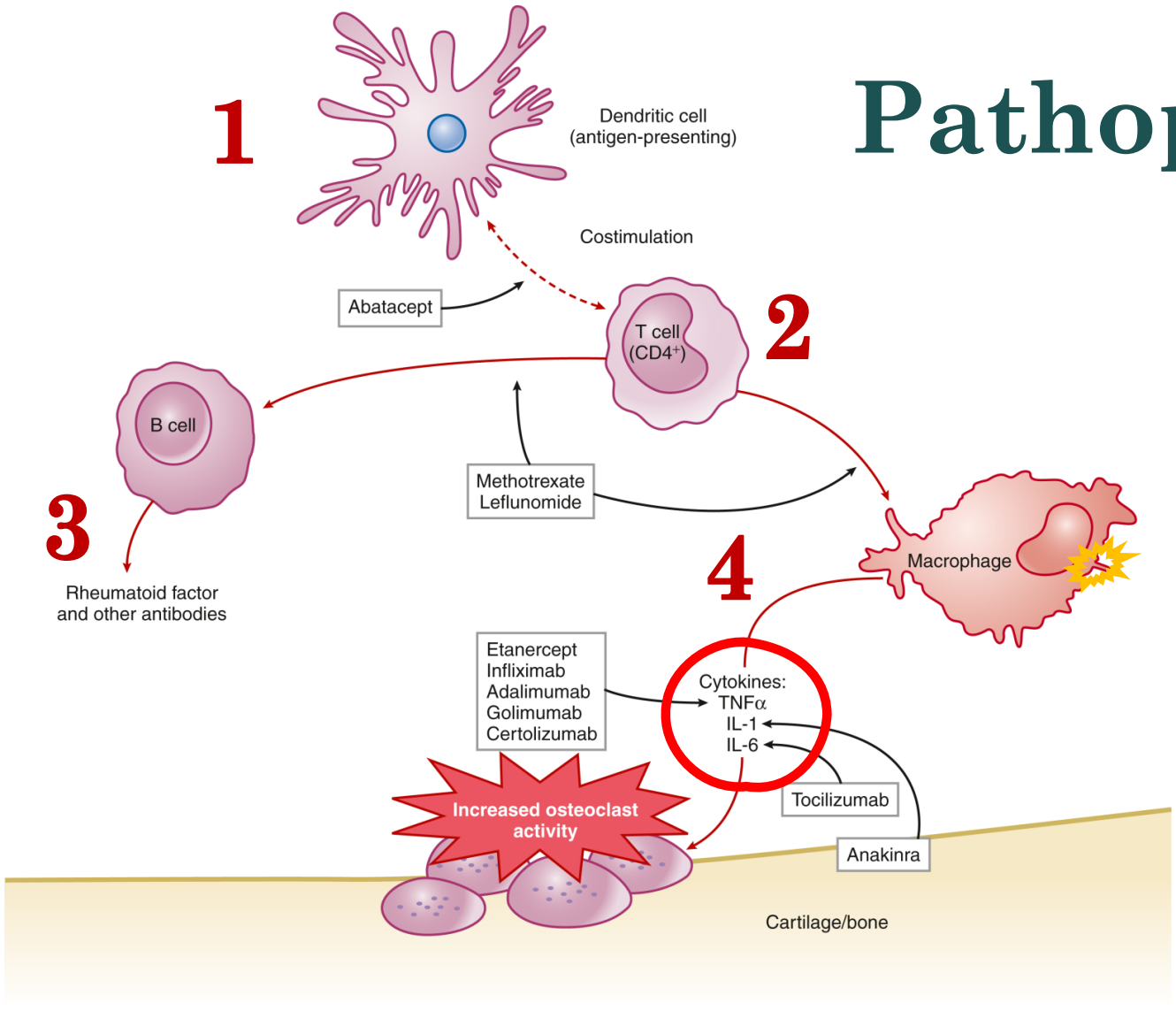
- Rheumatoid arthritis (definition, pathophysiology, C/P, diagnosis)
- Symptomatic treatment of RA
- Non biologic DMARDs (Methotrexate, leflunomide, HCQ, sulphasalazine, cyclosporine)
- Biologic DMARDs (MOA & side effects)

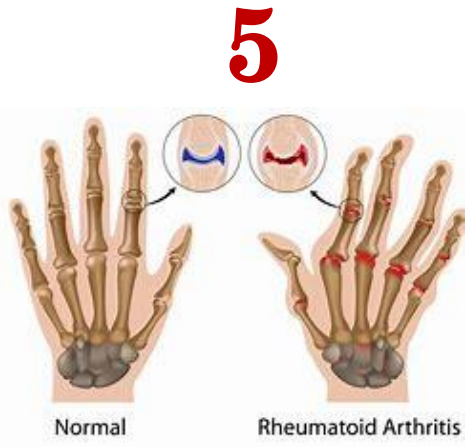
Rheumatoid arthritis (RA)

RA is an **autoimmune**, **chronic**, **progressive** **inflammatory** disease; characterized by **symmetric** **small** joint inflammation, swelling, and deformity and systemic manifestations.



Pathophysiology





Clinical manifestations

Articular manifestations:

- Affects mainly **small joints** of the hands and feet.
- Joint involvement is usually **symmetric**
- Symptoms → painful joints and prolonged **morning joint stiffness.**
- Signs → warm, tender, swollen, red joints, **with limited mobility.**

Extra-articular manifestations:

- The clinical manifestations of RA can extend to include systemic organs e.g., pleural effusion, conjunctivitis, anemia, vasculitis, etc.

Diagnosis

- **Serological:**

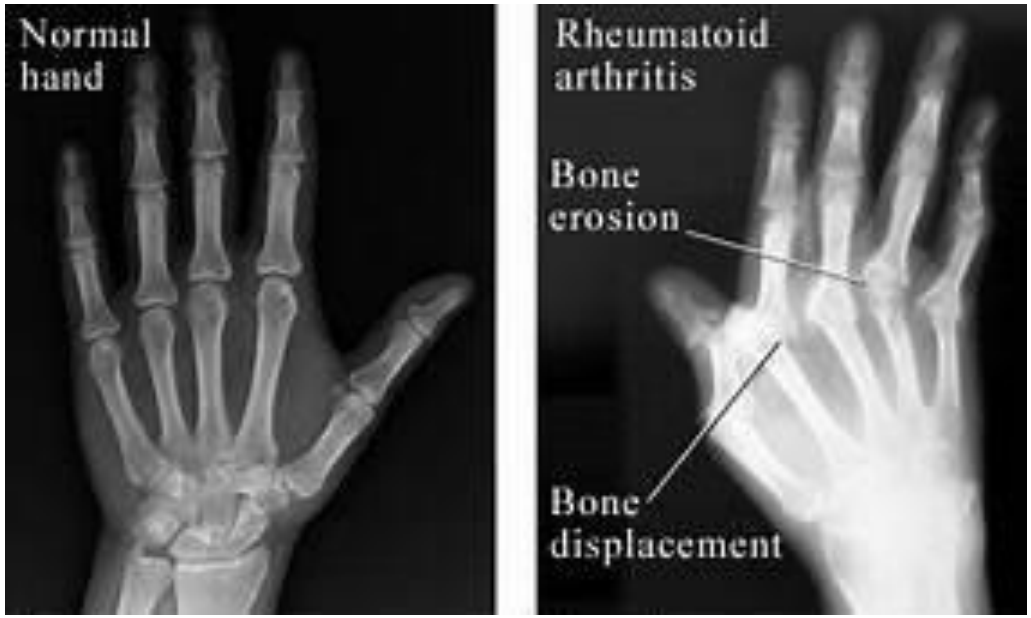
Abnormal antibodies **"rheumatoid factor“** → in 80% of RA patients.

Elevated CRP & ESR

Positive **anti-CCP antibodies.**

- **Joint X-ray:**

Show joint swelling and bony erosions typical of RA.

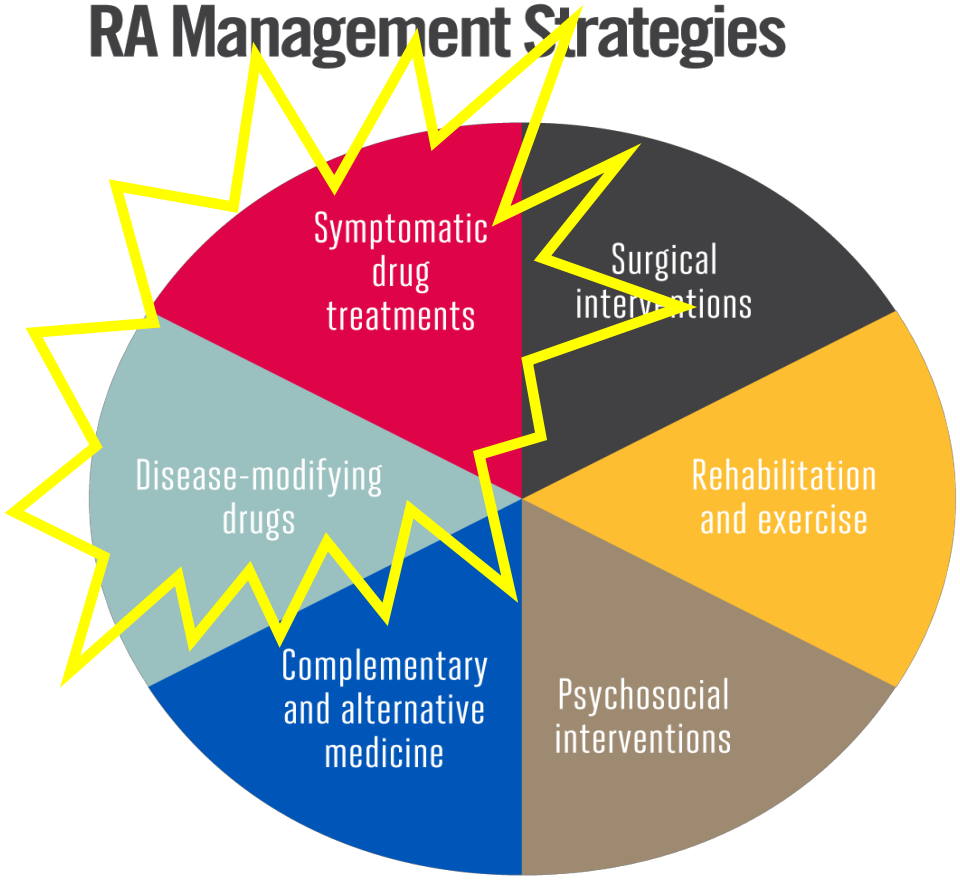


Drug treatment of RA

Aims of drug treatment are:

1. To reduce pain, stiffness and improve joint mobility (**symptomatic** drug treatment).

2. To prevent chronic deformity by stopping the inflammation that results in joint destruction (**DMARDs**).



Symptomatic treatment

1. **NSAIDs**: analgesic/anti-inflammatory drugs may be used to relief pain.
   - They are relatively ineffective when used alone in RA → They **do not prevent joint damage.**

2. **Corticosteroids**: anti-inflammatory/immunosuppressive .

NSAIDs and/or corticosteroids are used as **a 'bridge therapy'** → provide **symptomatic** relief till the therapeutic effect of DMARDs is observed.

DMARDs

Act by various mechanisms to **suppress the proliferation & activity of lymphocytes and macrophages.**

DMARDs
(non-biologic & biologic)

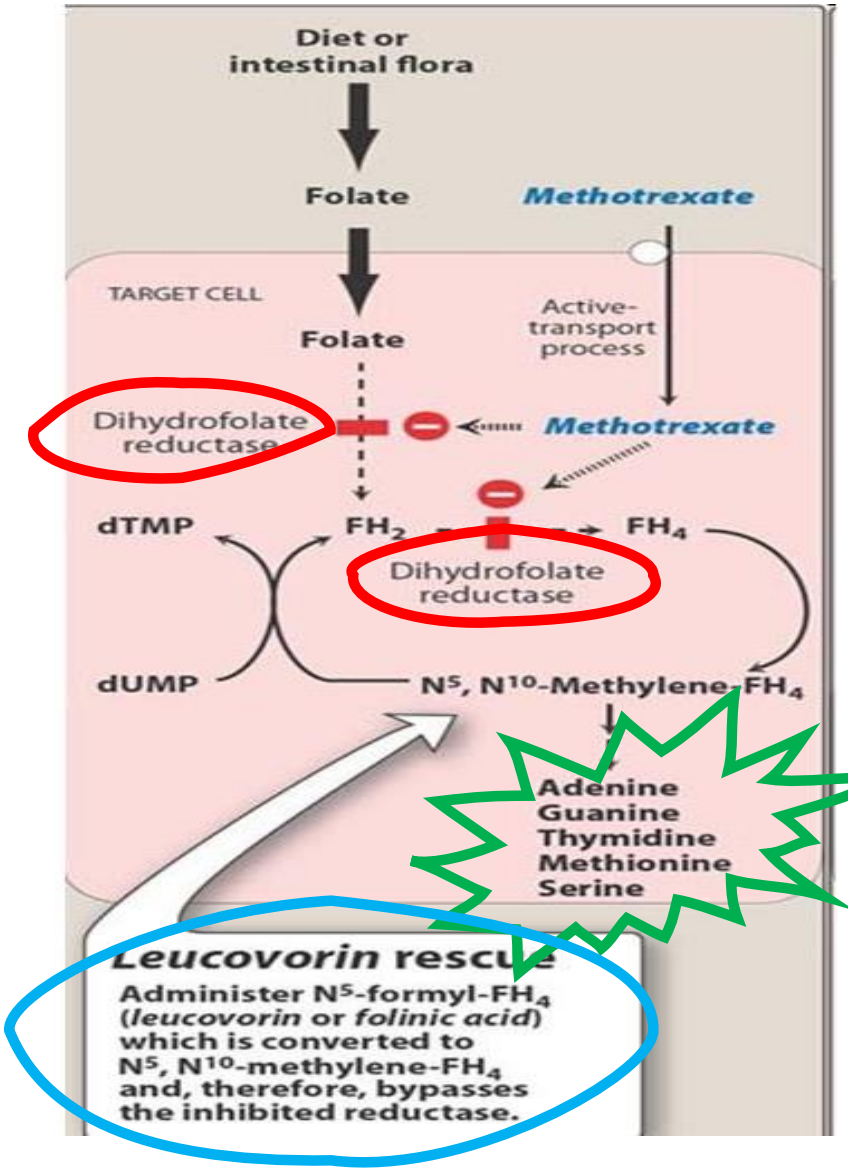
- They **prevent disease progression** and **slow joint destruction** by modifying the immune reactions.
- They should be **started as early as possible** (within 3 months of symptom onset) → more favorable outcome.
- **1 or more DMARDs** are used depending on disease severity.
- There is **a lag between starting therapy and observing an effect** (3 weeks to 3 months).
- It is usual to **continue NSAIDs/corticosteroids with DMARDs.**

I. Methotrexate

MOA:

An **antineoplastic** and **immuno-suppressant** drug

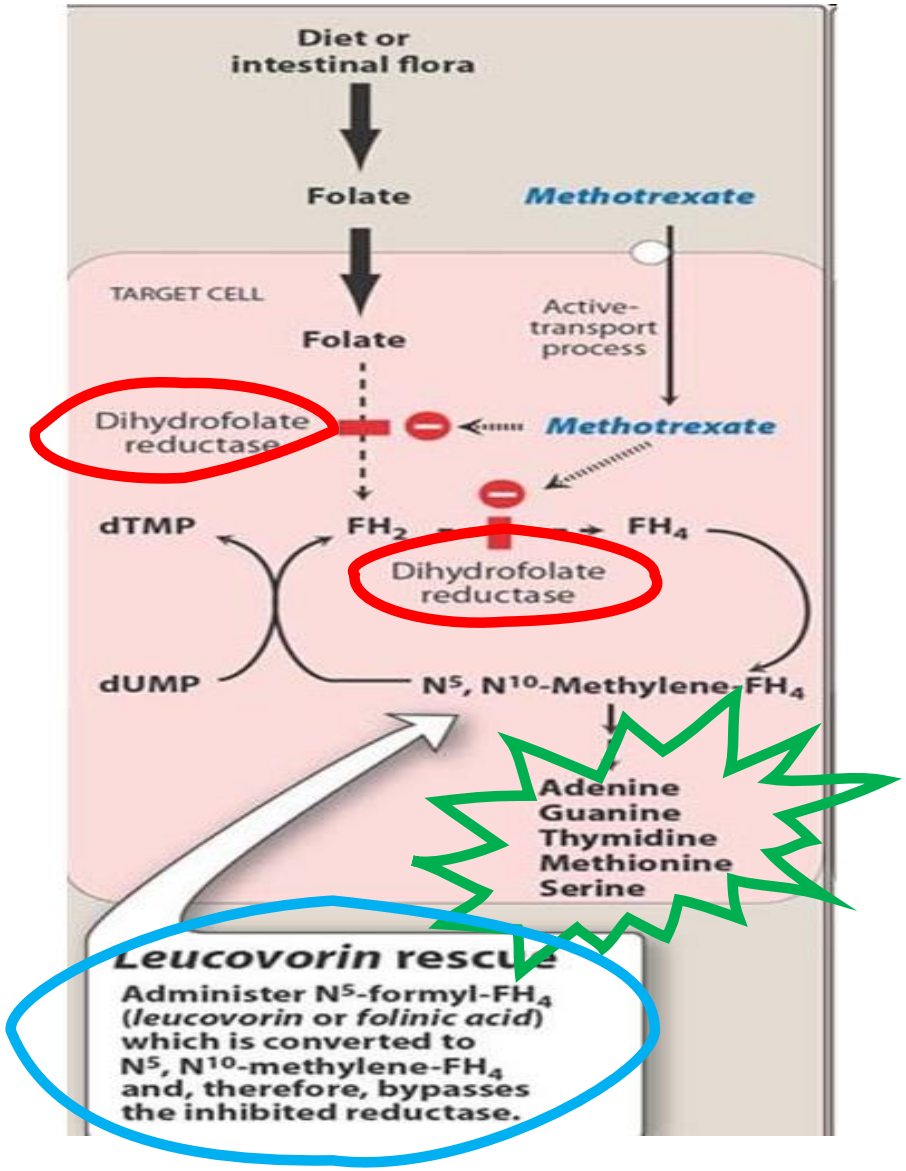
- It is **a folic acid antagonist** → inhibits **dihydrofolate reductase enzyme** → ↓ activation of folate to tetrahydrofolate (FH4) → ↓ synthesis of purine and pyrimidine bases of DNA and RNA.
- **Immuno-suppressant properties** → ↓ **cytokine production and inhibits activation & proliferation of T cells and macrophages.**



I. Methotrexate

Use in RA:

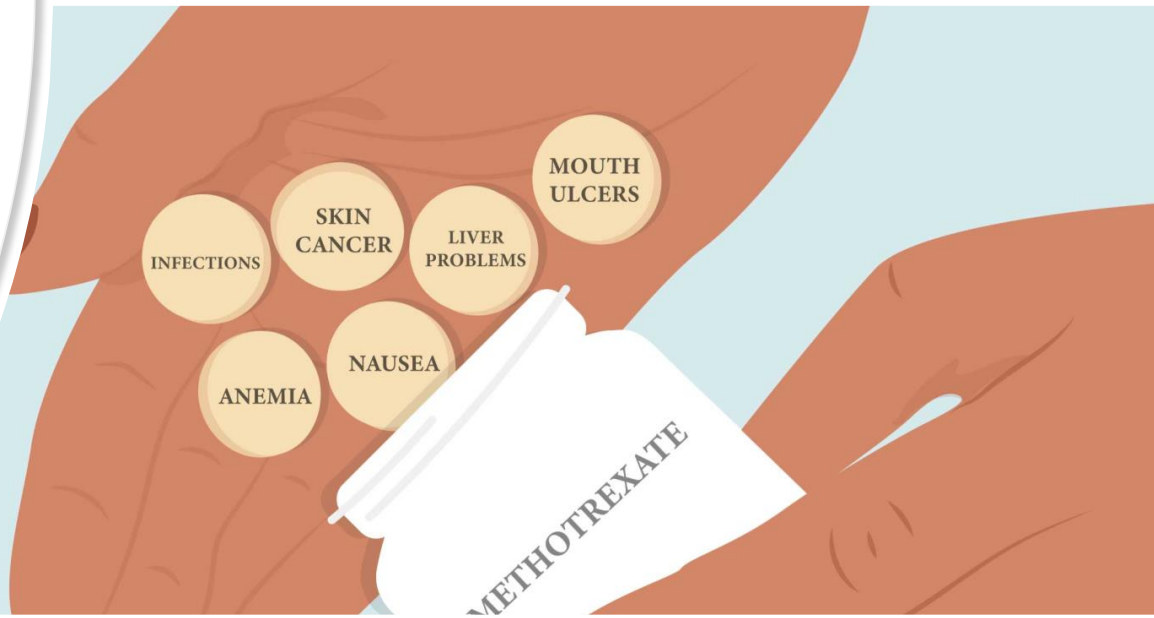
- **1st line DMARD** → it is used in **more than 60% of RA cases.**
- It is given **once weekly** orally or IM.
- The toxic effects of methotrexate can be reversed by the subsequent administration of **folinic acid (leucovorin)**



Methotrexate

Common adverse effects:

1. **GIT: nausea and mucosal ulceration.**
2. **Myelosuppression,** esp. leucopenia → ↑ infections (periodic CBC)
3. **Hepatotoxicity** is common (monitoring liver functions is essential).
4. Acute pneumonia-like syndrome.
5. **CI in pregnancy.**

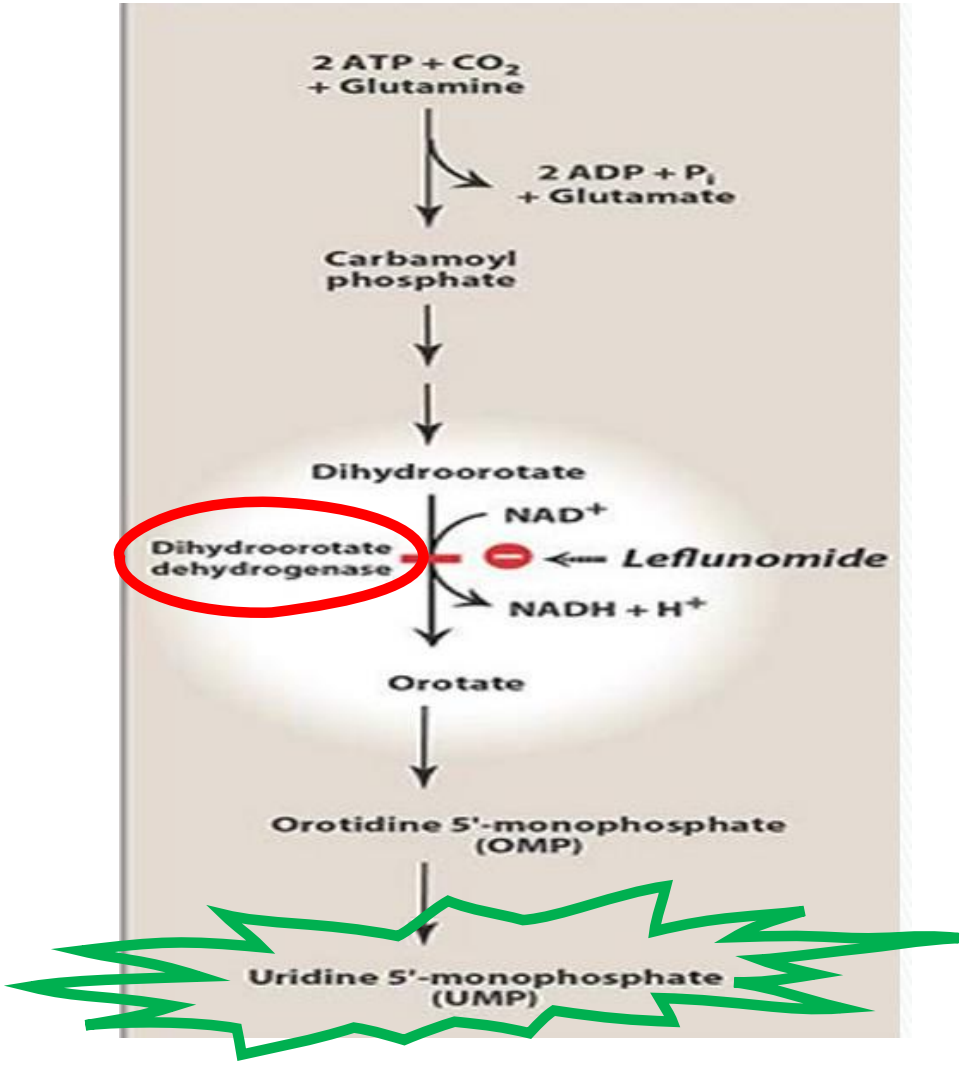


II. Leflunomide

MOA:

1. It inhibits the mitochondrial enzyme, **dihydroorotate dehydrogenase (DHODH)** → inhibits pyrimidine base synthesis → suppresses T cell and B cell proliferation & activation.

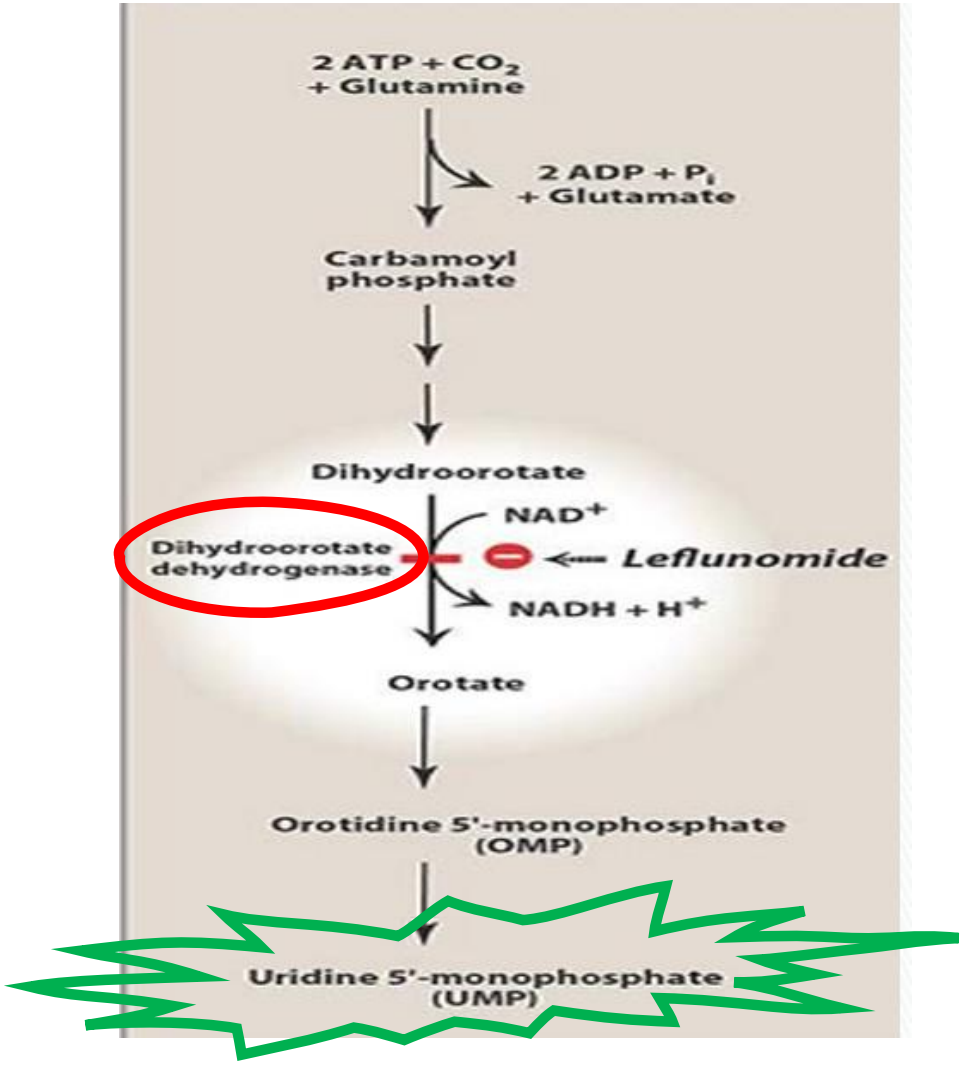
2. Leflunomide → **an alternative to methotrexate** for the first-line management of RA



II. Leflunomide

Adverse effects:

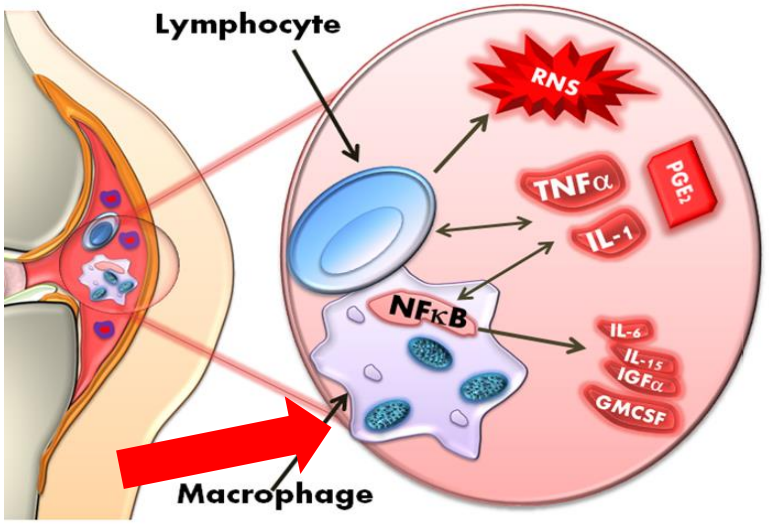
1. GIT: nausea & diarrhea
2. **Hepatotoxicity**
3. Reversible alopecia & rash
4. **CI in pregnancy.**



III. Hydroxychloroquine (anti-malarial drug)

MOA: unknown, but might be:

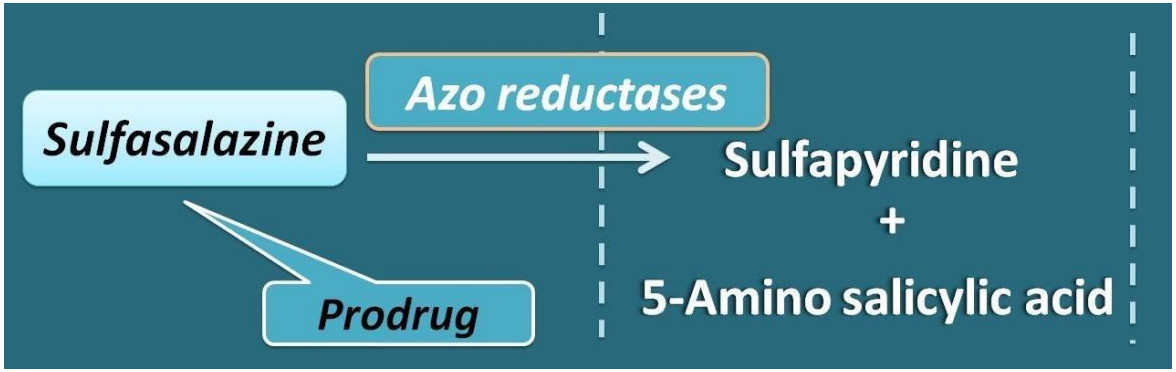
- Inhibition of phagocytic functions.
- Stabilization of lysosomal membranes



Side effects:

1. **GIT:** diarrhea
2. **Corneal deposits & Retinopathy:** the most disturbing toxic effect, rare, is a result of gradual accumulation of the drug in the retina → **irreversible retinal damage** with permanent blindness
3. Skin discoloration & rash
4. **Hemolysis** in **G6PD deficiency.**

IV. Sulphasalazine



MOA:

A prodrug → cleaved by gut bacteria → 5-aminosalicylic acid & sulphapyridine.

Sulphapyridine is thought to be the principal anti-rheumatic agent.

Adverse reactions:

1. **GIT:** nausea, vomiting, diarrhea
2. **Myelosuppression:** Occasional leucopenia and thrombocytopenia.
3. **Hemolysis** in **G6PD deficiency.**

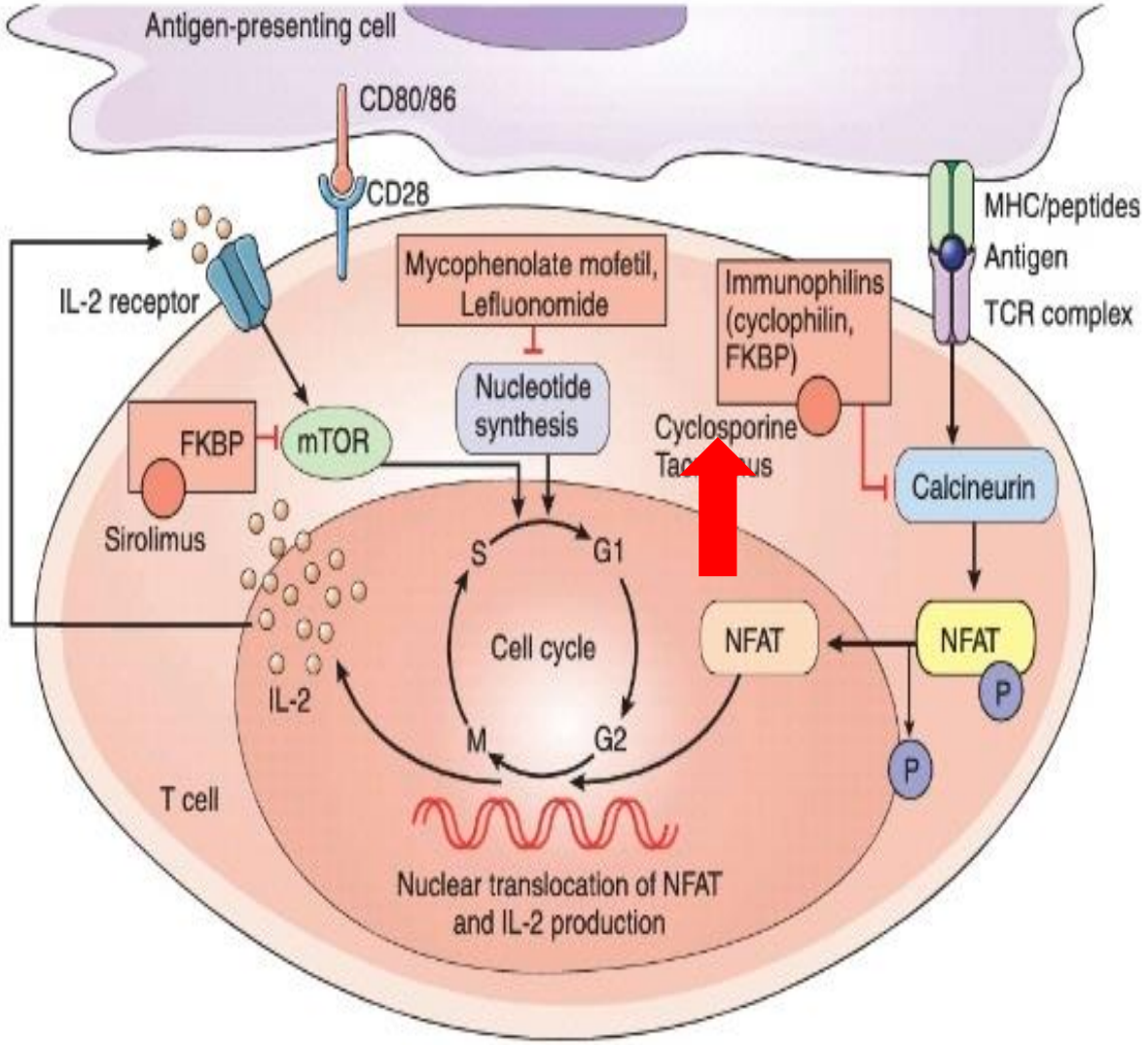
V. Cyclosporine

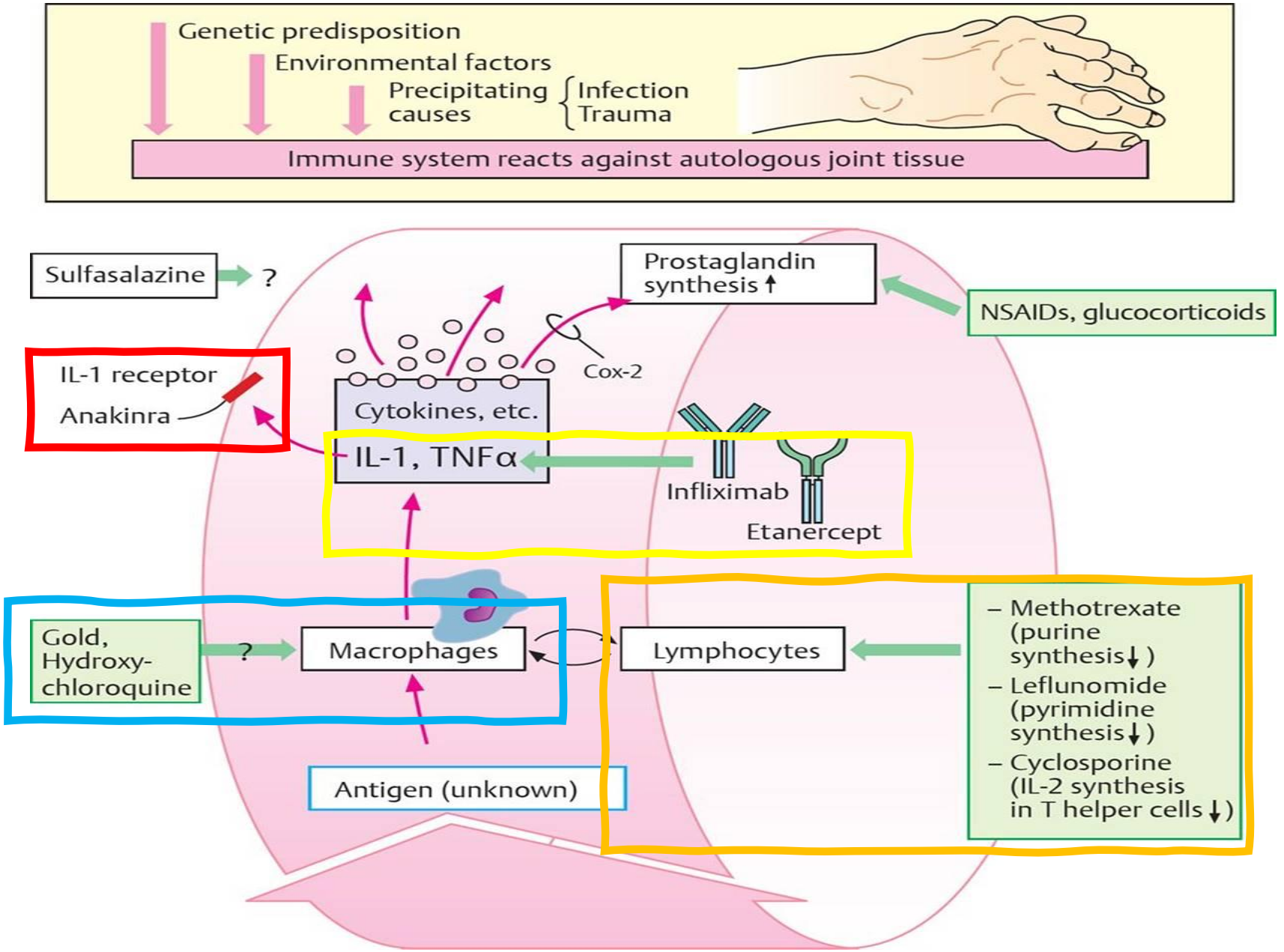
MOA:

Cyclosporine → bind cyclophilin → **inhibit calcineurin** → inhibit activation of NFAT (nuclear factor of active T cells) → **↓ biosynthesis of IL-2** → **inhibit T cell proliferation**.

Adverse effects:

- **Nephrotoxicity**
- 4H → **HTN**, **Hyperkalemia**, Hirsutism, gingival Hyperplasia

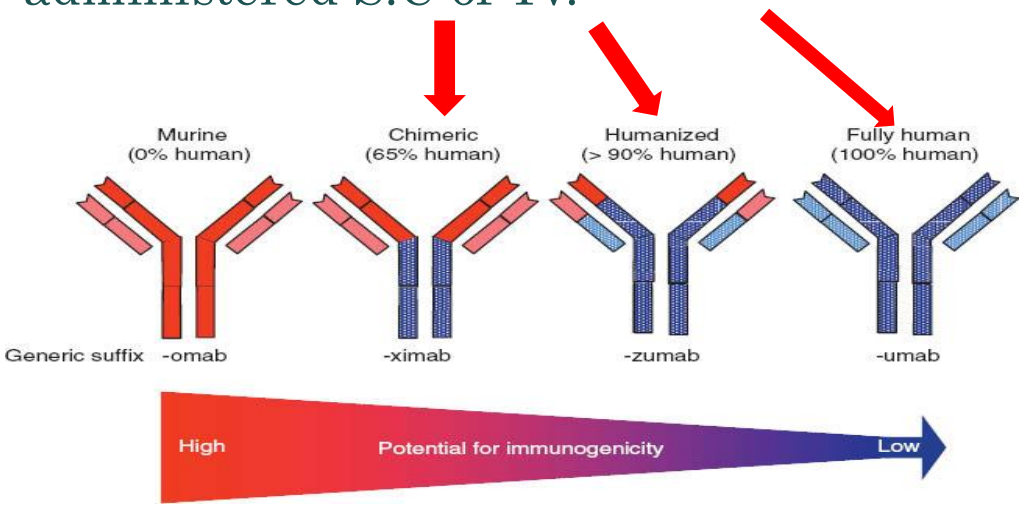


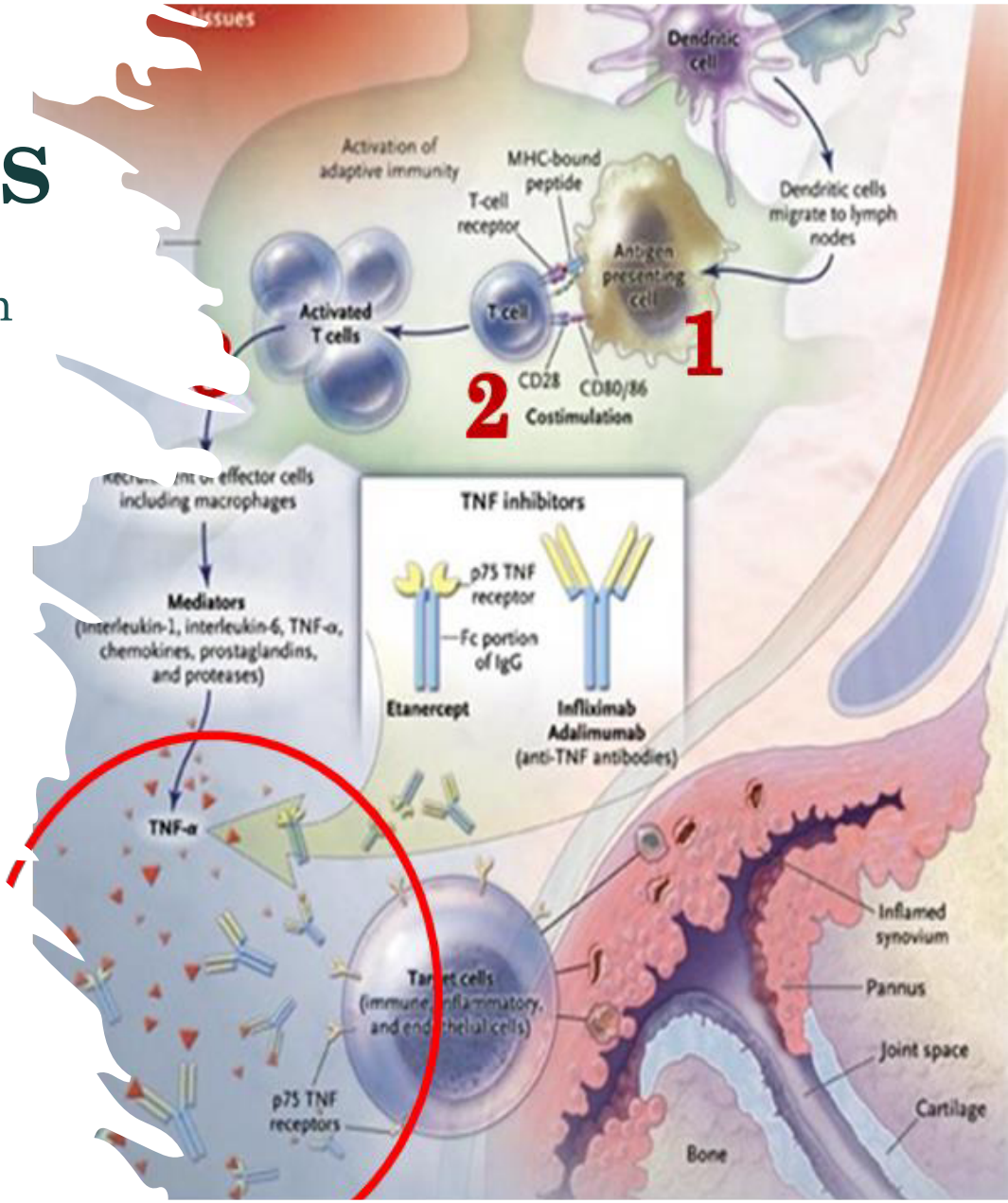

Genetic predisposition
Environmental factors
Precipitating causes
Infection
Trauma
Immune system reacts against autologous joint tissue
Sulfasalazine
?
Prostaglandin synthesis ↑
NSAIDs, glucocorticoids
IL-1 receptor
Anakinra
Cox-2
Cytokines, etc.
IL-1, TNFα
Infliximab
Etanercept
Gold, Hydroxy-chloroquine
?
Macrophages
Lymphocytes
– Methotrexate (purine synthesis ↓)
– Leflunomide (pyrimidine synthesis ↓)
– Cyclosporine (IL-2 synthesis in T helper cells ↓)
Antigen (unknown)

Biologic DMARDs

Inflammatory cytokines play a central role in RA.

Biological DMARDs are **antibodies and antibody fusion proteins** that inhibit the action of cytokines by blocking the cytokine from binding to its receptor → administered S.C or IV.





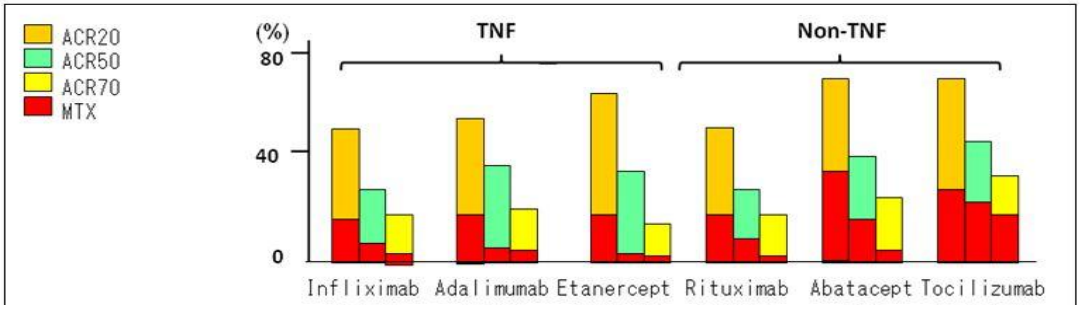
Biologic DMARDs

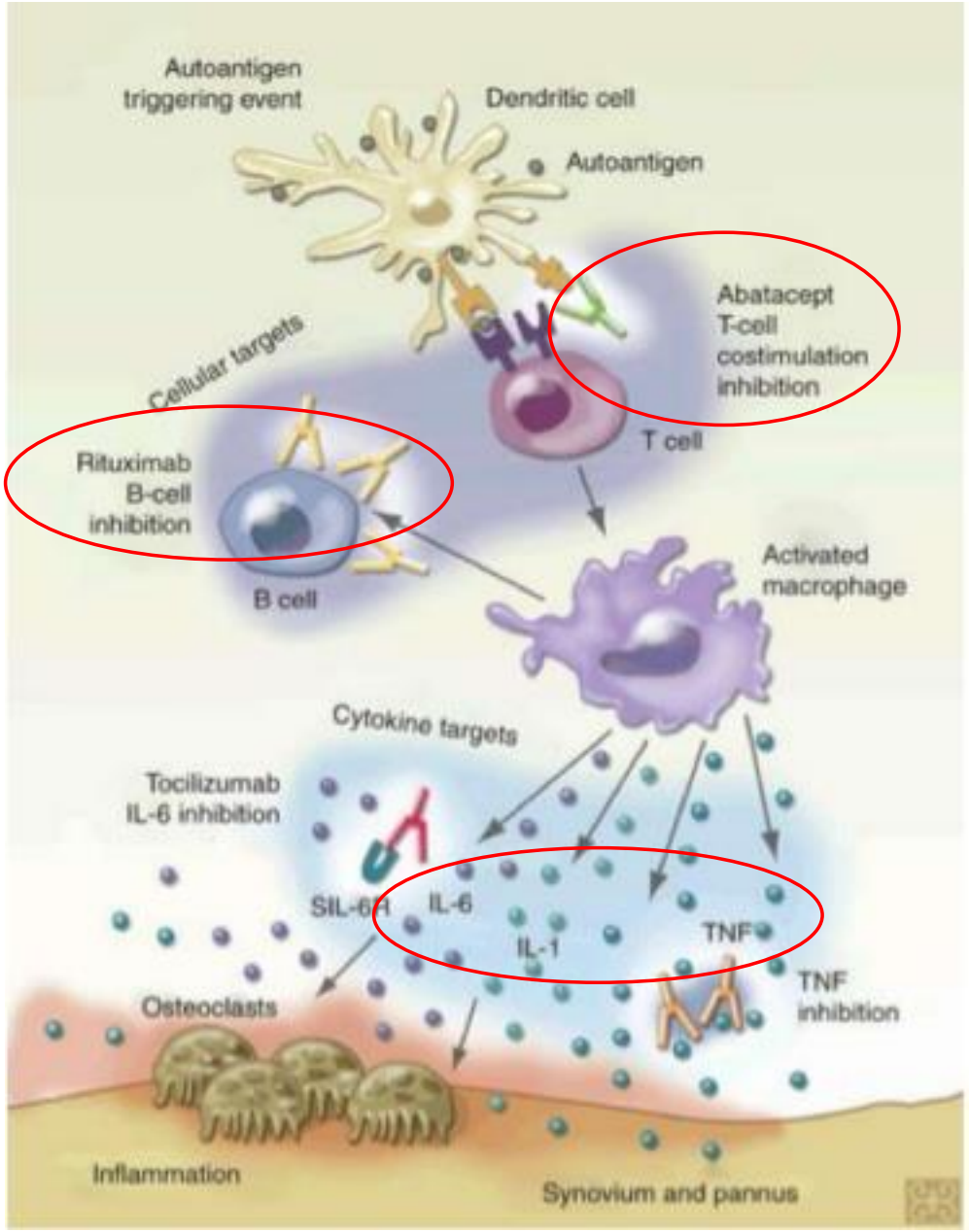
Cytokine inhibitors used in the treatment of RA are:

- Inhibitor of **IL-1 (anakinra),**
- Inhibitors of **TNF-α (infliximab, etanercept, and adalimumab)**
- Inhibitor of **IL-6 (tocilizumab).**

These drugs each have a stronger effect than methotrexate

Methotrexate + any biological agent → more effective than methotrexate alone.

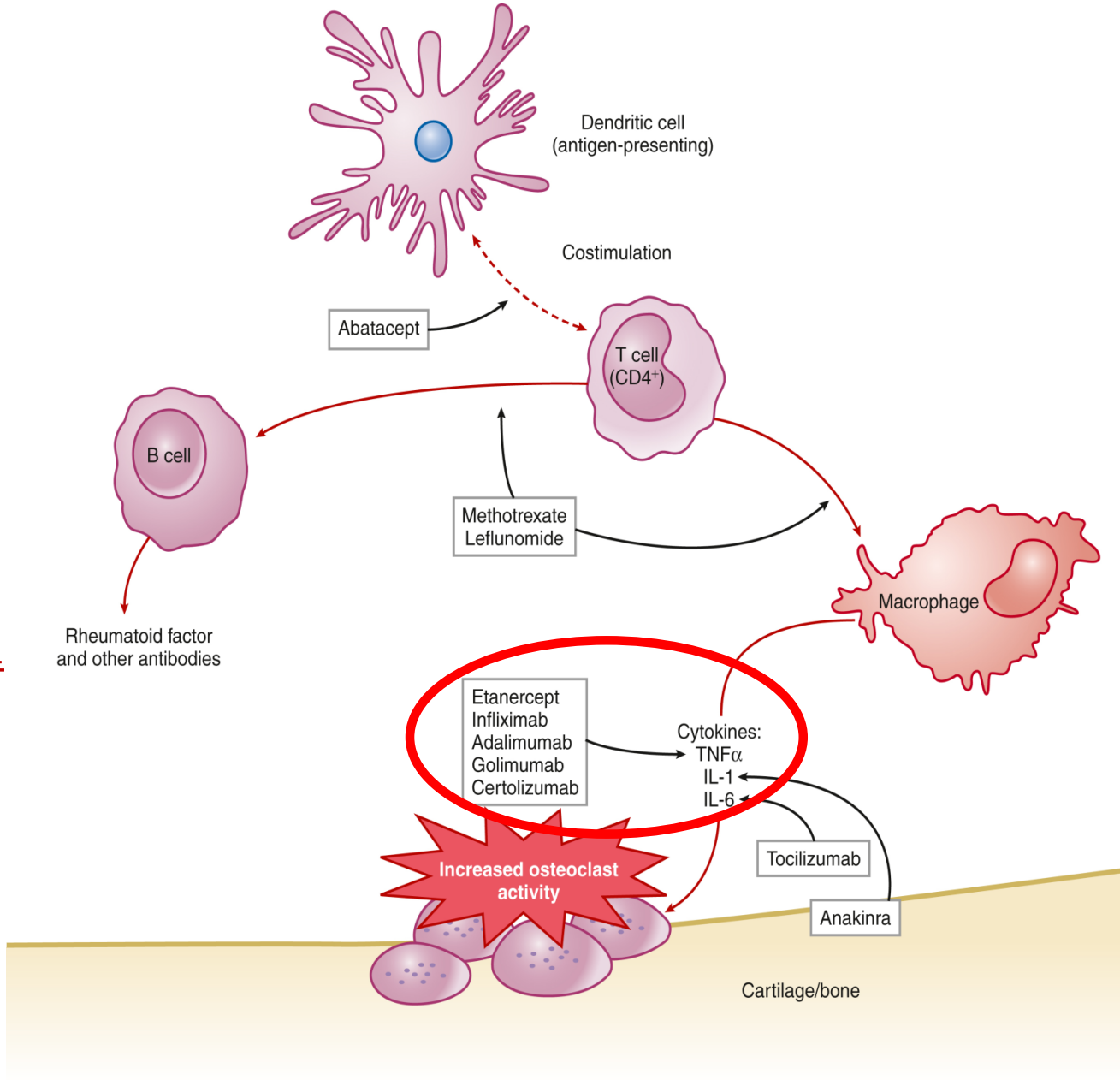




TNF-α inhibitors
(infliximab, etanercept, and adalimumab)

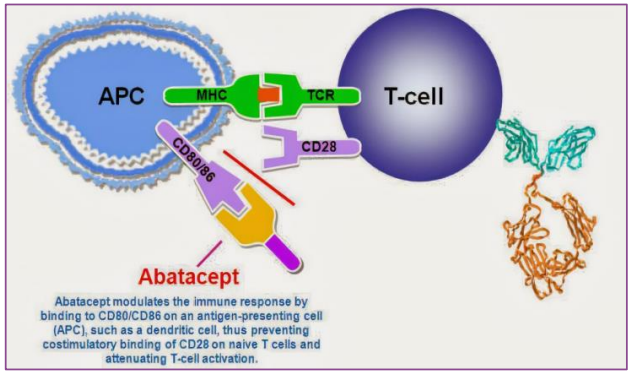
Immunomodulating drugs that exert their effects by **binding to and inactivating TNFα**

TNFα is one of the proinflammatory cytokines produced by macrophages.



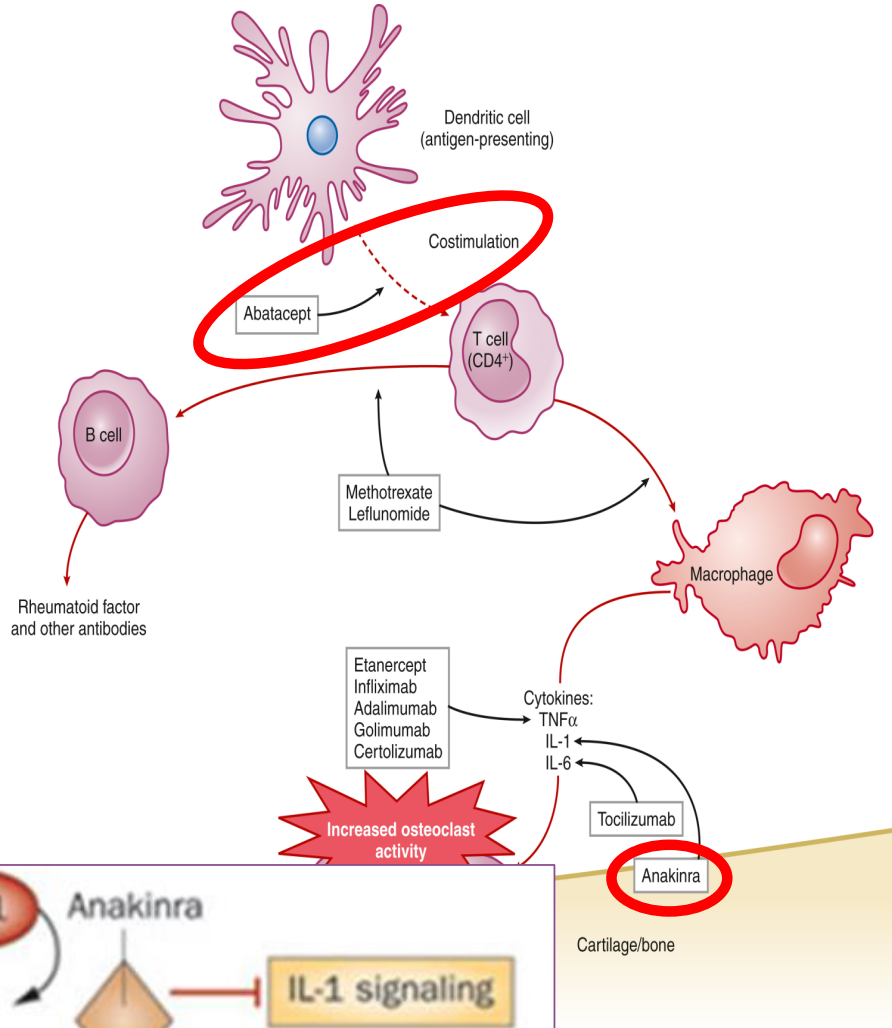
Abatacept

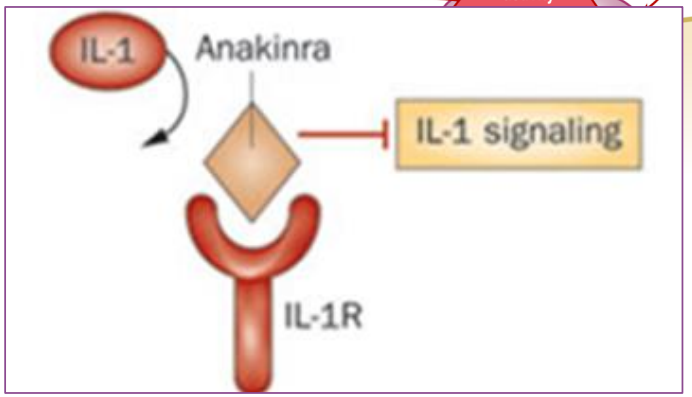
A selective **costimulation inhibitor** (CD80/86 inhibitor) → inhibits T-cell activation.

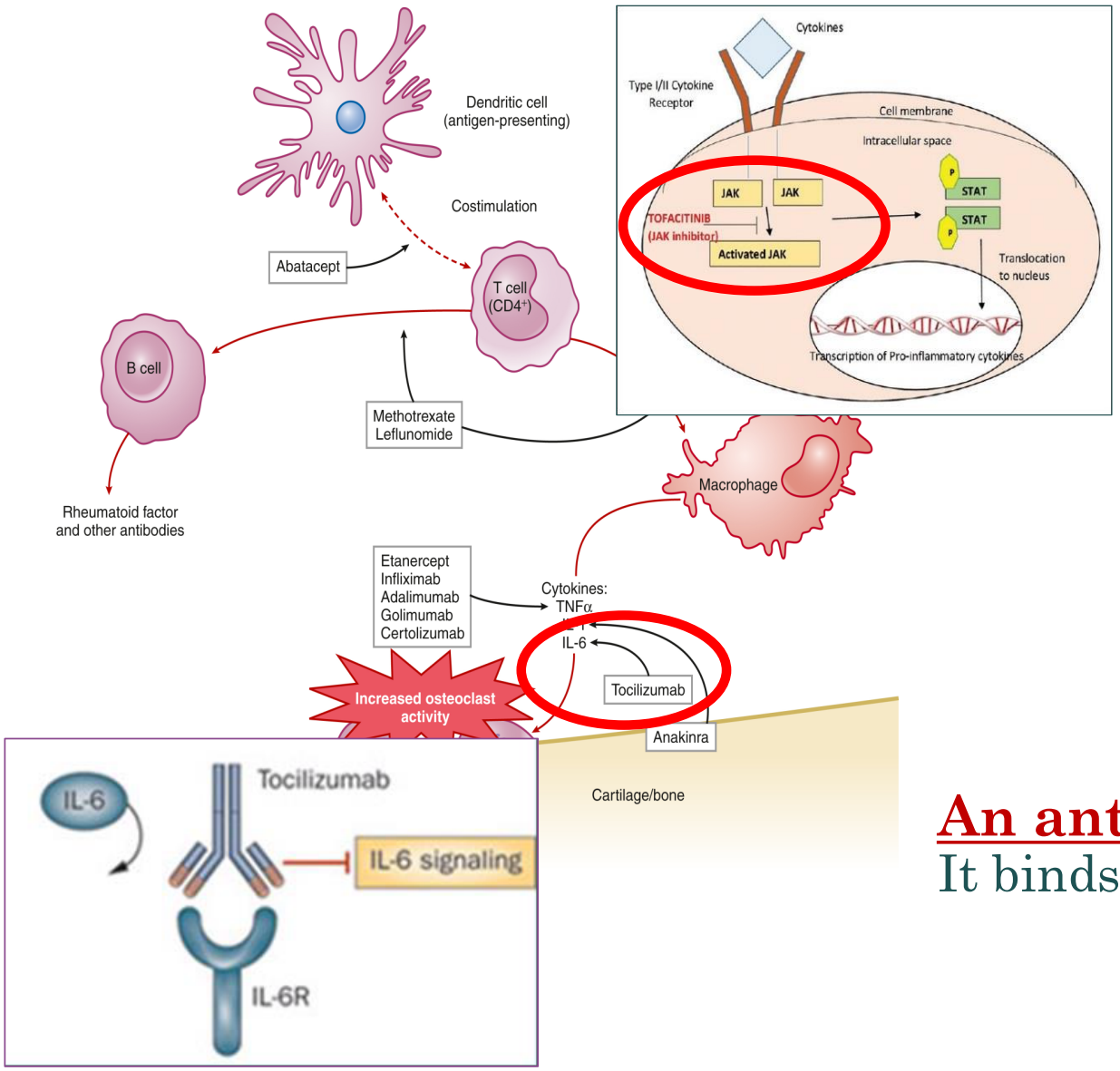


Anakinra

Interleukin-1 receptor antagonist (IL-1Ra) → competitively blocks IL-1 receptor (IL-1R).







Tofacitinib

A **Janus kinase (JAK) inhibitor**

JAK is an intracellular enzyme that initiates signal transduction to modulate immune cell function.

Tocilizumab

An anti–IL-6 receptor antibody → It binds selectively to IL-6 receptors and blocks IL-6 activity.

Biologic DMARDs

IL-1 inhibitor	**Anakinra**	A competitive IL-1 receptor antagonist	
TNFα inhibitors	**Infliximab**	Chimeric antibody	Complex with cytokine/cytokine receptor and prevent its interaction with corresponding receptor on immune cells.
	Adalimumab	Human antibody	
	Etanercept	Fusion protein	
IL-6 inhibitor	**Tocilizumab**	Humanized antibody of IL-6 receptor	
CD80/86 inhibitor	**Abatacept**	Fusion protein	Prevent T cell costimulation
CD20 inhibitor	**Rituximab**	Chimeric antibody	B cell depletion

Biologic DMARDs

Main side effects

1. Injection/infusion-related reactions
2. **Infections** (TB, fungal, sepsis, and reactivation of hepatitis B) → never use 2 biologic DEMARDs together.
3. Increased risk of **lymphoma** and other cancers.

Contraindications to the use of TNF-α inhibitors.

1. Acute and chronic **infections**
2. Recent **malignancies**
3. **Live virus** vaccination
4. Demyelinating disorders
5. Class III or IV **heart failure**

Questions

Q1

Rheumatoid arthritis is a relatively common autoimmune disease, with multiple treatment options. Which of the following is an example of a drug class that has been shown to halt or reverse the progression of this disease in most patients?

a. **Aspirin**
b. **Azathioprine**
c. **Everolimus**
d. **Methotrexate**
e. **Prednisone**

Q2

Which component of sulfasalazine is responsible for the therapeutic effect in rheumatoid arthritis ?

a. **Sulfapyridine**

b. **5–aminosalicylic acid**

c. **Both (a) and (b)**

d. **Intact sulfasalazine molecule**

Q3

JQ is a 40-year-old golfer who has developed a progressively more painful stiffness in her arms and legs over the past year. During her most recent medical checkup, her lab results reveal an elevated rheumatoid factor level. X-ray imaging confirmed diagnosis of RA and she is prescribed methotrexate. Which of the following best describes the mechanism of action of this drug?

a. **Increases adenosine levels**

b. **Inhibits dihydrofolate reductase**

c. **Inhibits IL-6 signal transduction**

d. **Small molecule kinase inhibitor**

e. **TNF-alpha receptor antagonist**

References

- **Stevens, Craig. Brenner and Stevens' Pharmacology. Available from: ClinicalKey Student, (6th Edition). Elsevier Limited (UK), 2022.**
- **Whalen , Feild, Carinda,, Radhakrishnan, Rajan,, K. Lippincott illustrated reviews: pharmacology. 2019.**
- **USMLE step 1 pharmacology lecture notes 2017.**


Thank you