

# **Disease modifying antirheumatic drugs (DMARDs)**



**Dr.Nashwa Abo-Rayah**  
**Associate prof. (clinical &experimental  
pharmacology)**  
**Mu'tah University- Faculty of Medicine-**  
**JORDAN**  
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# Objectives

- 1. Disease modifying anti-rheumatoid drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, D-penicillamine and gold salts.
- 2. Mechanism of action and profile of adverse effects of these drugs.
- 3. Brief discussion about biologic therapy in rheumatoid arthritis, e.g. anti-TNF- $\alpha$  drugs such as etanercept, infliximab, and adalimumab.
- 4. Other drugs such as interleukin antagonists such as anakinra, are also briefly discussed
- 5. JAK inhibitors are briefly discussed.

# Rheumatoid arthritis

- Chronic synovial inflammation
- Small joints : hands
- 70% females
- Symmetrical
- Autoimmune
- Cytokines which are responsible for: **inflammation & joint destruction**
  - ❑ **Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ )**
  - ❑ **Interleukins - 1,6,17**

## **ACPAs: anti-citrullinated proteins antibodies**

- **Conversion of the amino acid arginine into citrulline within a protein, a process often triggered by inflammation.**
- **This modification alters protein structure, leading to increased antigenicity.**
- **ACPAs are Diagnostic and Prognostic Markers:**
- ACPA, often detected as anti-CCP (cyclic citrullinated peptide), are present years before symptom onset and predict more severe joint damage.

# Pathophysiology of RA

Genetic predisposition + triggering factors: inflammation, smoking, diet, stress

Production of citrullinated proteins

Activation of T cells and B cells

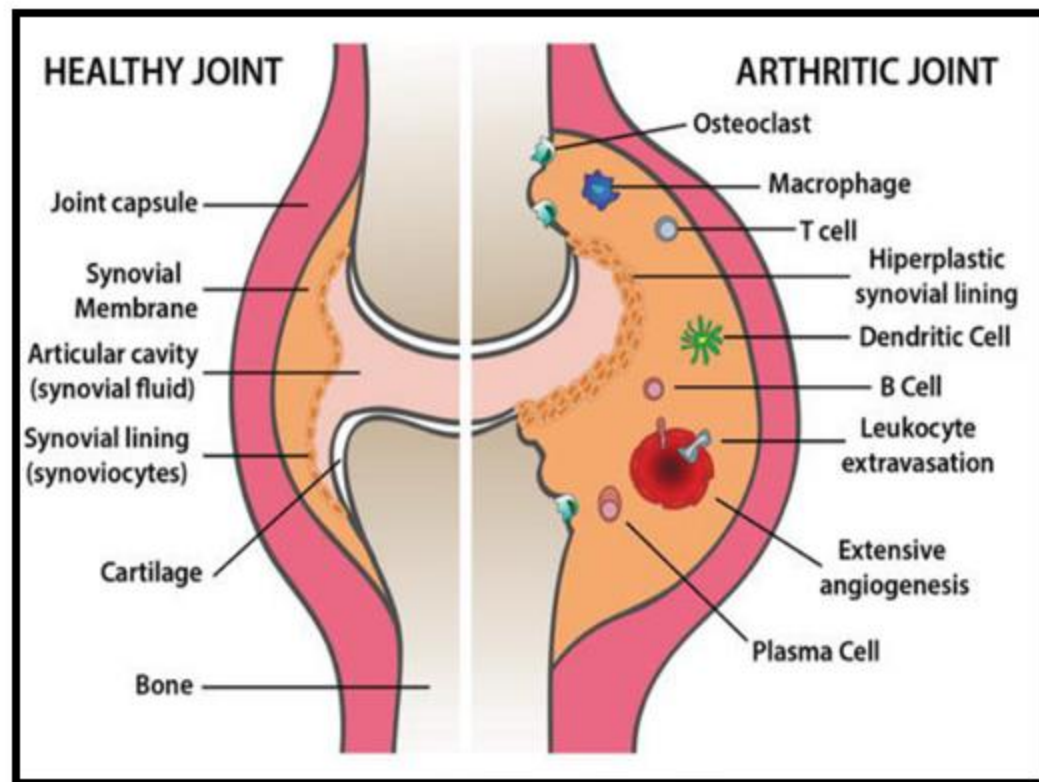
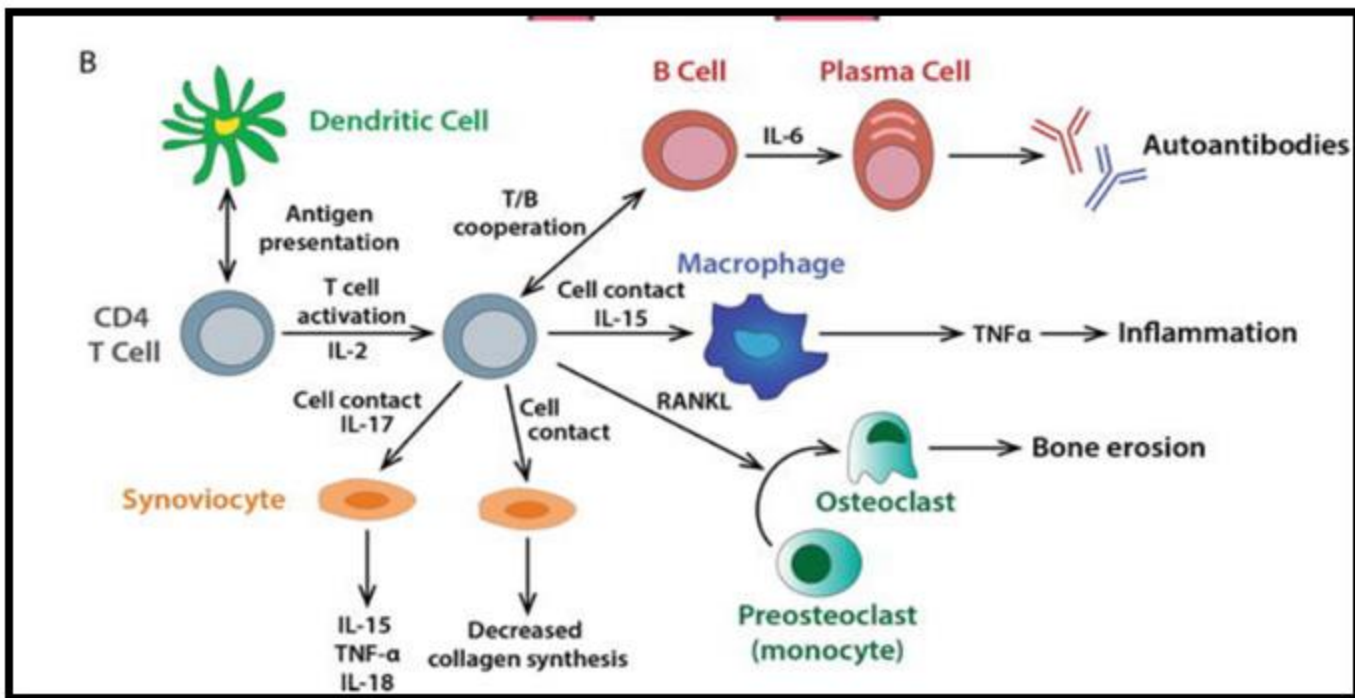
Autoantibodies attack the synovium

Activated macrophages, T cells and B cells in inflamed synovium release  $\text{TNF}\alpha$ , ILs 1, 6, 17

stimulation of osteoclasts

Bone resorption and cartilage damage + extra-articular manifestation s: CVS, rheumatoid nodules

# Pathology of RA



# Drug therapy of RA

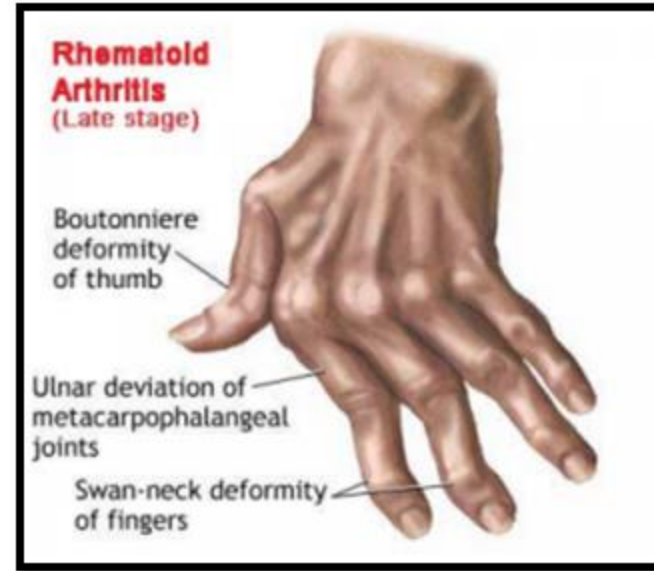
- **Start DMARDs therapy with one of the traditional drugs**, such as methotrexate.
- **Inadequate response to the traditional agents**: add one of newer DMARDs, such as: TNF-inhibitors eg: adalimumab, etanercept, and infliximab.
- **In case of failure of response to combination therapy with methotrexate plus TNF inhibitors, or other combinations**: treatment with rituximab or abatacept may be tried.
- **Most of these agents are contraindicated for use in:**
- pregnancy, breast feeding, liver disease, peptic ulcer, active infection, leucopenia and.

**90% of the joints involved in RA are affected within the first year**

**SO, start Treatment as EARLY as possible**

# Disability in Late RA (Too Late)

- **Damage**
  - Bones
  - Cartilage
  - Ligaments and other structures
- **Fatigue**
- **Not Reversible**



# Drugs for RA

- **Nonsteroidal anti-inflammatory drugs (NSAIDs):**  
**symptomatic**
- **Corticosteroids**  
**(symptomatic)**
- **Disease-modifying anti-rheumatic drugs (DMARDs)**
  - Conventional (traditional, synthetic)
  - Biologic

# NSAIDs

- **Non-selective COX inhibitors**
  - Ibuprofen
  - Diclofenac sodium
  - Add protective treatment for peptic ulcer
- **COX-2 inhibitors**
  - celecoxib

# COX-2 Inhibitors

- COX-2 inhibitors appear to be as effective as non-selective NSAIDs
- Associated with less GI toxicity
- However increased risk of CV events

# DMARDs

## Therapeutic effects of Disease Modifying Anti-Rheumatic Drugs:

- Reduce swelling & inflammation
- Improve pain
- Improve function
- Reduce radiographic progression (erosions)

## Effects on prognosis of the disease:

- 1- Slow the course of the disease
- 2- Induce remission
- 3- Prevent further destruction of the joints and involved tissues.

Combination therapy (using 2 to 3)  
DMARDs at a time works better than  
using a single DMARD

# Classification of DMARDs

## 1. Conventional Synthetic DMARDs

### (csDMARDs)

(MASLH)

- Methotrexate (first-line)
  - Leflunomide
- Hydroxychloroquine
  - Sulfasalazine
  - Azathioprine

## 2. Biologic DMARDs

### (bDMARDs)

**injectable (parenteral)** agents designed to target specific components of the immune system.

- **TNF Inhibitors:**  
Adalimumab, Infliximab  
Etanercept
- **IL-1 Inhibitors:** Anakinra
- **IL-6 Inhibitors:** Tocilizumab
- **T-cell Modulators:** Abatacept
- **B-cell Depleting Agents:**  
Rituximab

## 3. Targeted Synthetic DMARDs

### (tsDMARDs)

**oral drugs** act by targeting specific intracellular signaling pathways, primarily **Janus Kinase (JAK) inhibitors.**

- Tofacitinib
- Baricitinib
- Upadacitinib

# Key differences between conventional & biologic DMARDs

## Conventional

- **Mechanism:** affect the immune system broadly
- **Administration:** almost oral
- **Indication:** first line

## Biologic

- act selectively on specific cytokines or cellular pathways
- Injection or infusion (oral tsDMARDs)
- Unresponsive refractory cases

# Methotrexate

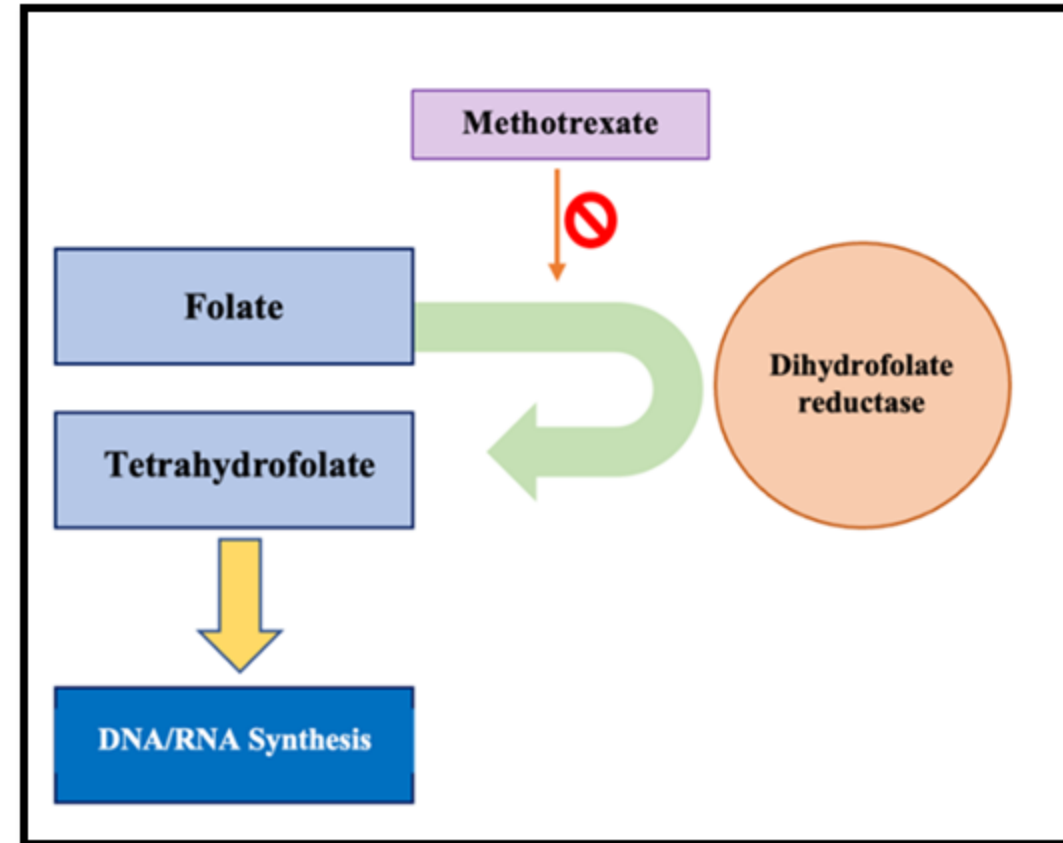
- **Antimetabolite** (chemotherapy agent) and **immunosuppressant**.
- **Indications:**
- **Autoimmune conditions** (rheumatoid arthritis, severe psoriasis, psoriatic arthritis, Crohn's)
- **Cancers:** breast, lung, and leukemia.
- Effective in 60% of RA patients
- **Onset of action:** sooner than usual for other slow-acting agents often **within 3-6 weeks of starting treatment.**

# Methotrexate

- **Methotrexate dose :**
- 7.5- 10 mg/ week: single weekly dose (2-3 tablets or injection):  
max. dose: 25 mg/ week
- **Folic acid dose**: to minimize adverse effects
- A common regimen is **5 mg of folic acid once a week**, often on the day after methotrexate (not on the same day) to avoid potential reduction in methotrexate effectiveness.
- Some regimens use 5 mg daily, excluding the day of methotrexate

# Methotrexate mechanism of action

- ❑ Methotrexate is folic acid analogue
- ❑ Inhibits dihydrofolate reductase (DHFR)
- ❑ Decreasing synthesis of tetrahydrofolate (THF)
- ❑ Reducing the synthesis of purines and pyrimidines required for DNA production in rapidly dividing inflammatory cells involved in pathogenesis of RA.
- ❑ Suppresses immune cell proliferation



# Methotrexate adverse effects

- **Due to decreased folic acid level**
- **The most common side effects:** GI mucosal ulceration: nausea, vomiting, diarrhea
- **Cytopenias** :bone marrow depression (particularly depression of the WBC count)
- **Hepatotoxicity**
- **Drug interactions:**
- **Non-Steroidal Anti-inflammatory Drugs (NSAIDs):** reduce methotrexate excretion, potentiating methotrexate toxicity.
- **Antibiotics:** penicillins and ciprofloxacin can increase methotrexate toxicity.
- **Hepatotoxic Drugs:** Alcohol, leflunomide, and azathioprine increase the risk of liver damage.
- **Folate Supplements:** High doses of folic acid may decrease the efficacy of methotrexate.

**Safety Monitoring:** Regular blood tests are required to monitor for potential side effects, such as liver or bone marrow toxicity.

# Leflunomide

- Effective as methotrexate
- **Mechanism of action:**
- **Immunosuppressive agent :**
- Inhibition of pyrimidine synthesis: inhibiting DNA synthesis in immune cells
- **Indications in RA:**
- 1- Monotherapy as an alternative to methotrexate
- 2- An additive in combination therapy.
- **Common Side Effects:** headache, alopecia, nausea, diarrhea

# Sulfasalazine

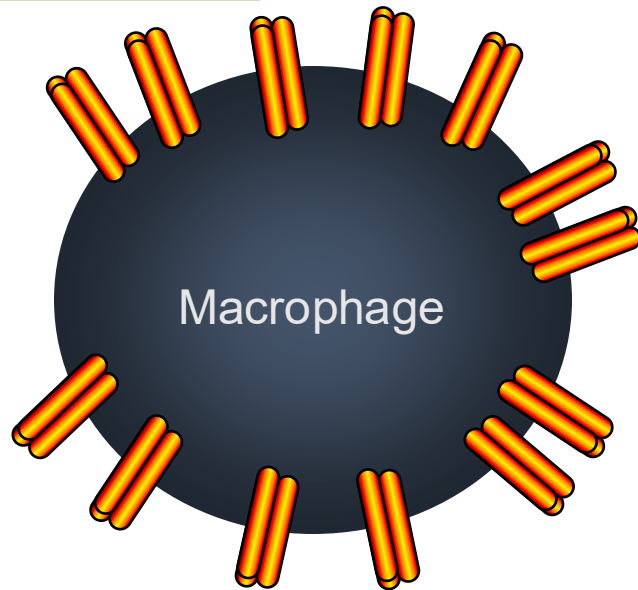
- **Sulfasalazine (SSZ)** is a **prodrug** composed of:
- broken down by bacteria in the colon into 5-aminosalicylic acid (5-ASA): immunosuppressant and sulfapyridine: antibacterial
- Mechanism of action: anti-inflammatory effects and immunomodulatory (exact mechanism unknown)
- **Indications:**
  - 1- Second line drug for milder cases
  - 2- Early mild RA in combination with hydroxychloroquine and methotrexate.
- **Adverse effects:**
  - **Common:** skin rash- yellow/orange discoloration of urine and skin
  - **Rare but serious:**
    - 1- Neutropenia/ thrombocytopenia: in about 10% patients
    - 2- Hepatitis      3- reversible decrease in sperm count

# Biologic DMARDs (bDMARDs)

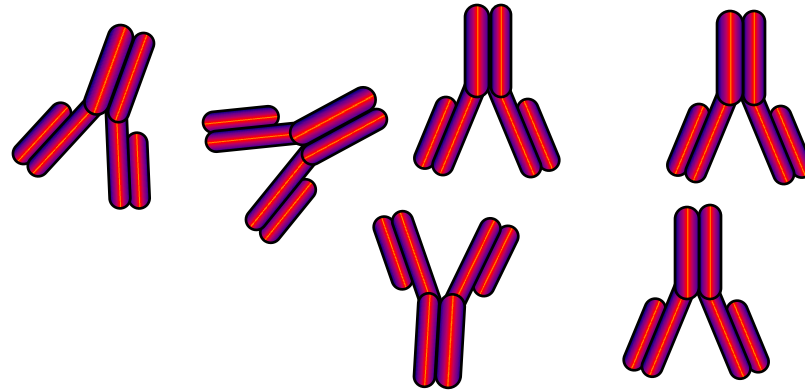
- **1. TNF  $\alpha$  inhibitors:**
- **Etanercept: TNF  $\alpha$  receptor blocker**
- **Infliximab Adalimumab: monoclonal antibodies**
- **2. IL-1 antagonist: Anakinra: short acting given daily and SC injection (disadvantage)**
- **Advantages:**
- 1- Very effective      2- Delay disease progression
- **Disadvantages:**
- 1- **Very expensive**, so try conventional therapy first
- 2- **Contraindicated in** patients with history of tumors esp. leukemia, viral hepatitis, immunocompromised patients, heart failure
- 3- Increased risk of certain skin cancers
- 4- Rare: drug-induced lupus or demyelinating diseases: MS
- 5- Injection site reactions (redness, pain, itching)

# Strategies for Reducing Effects of TNF

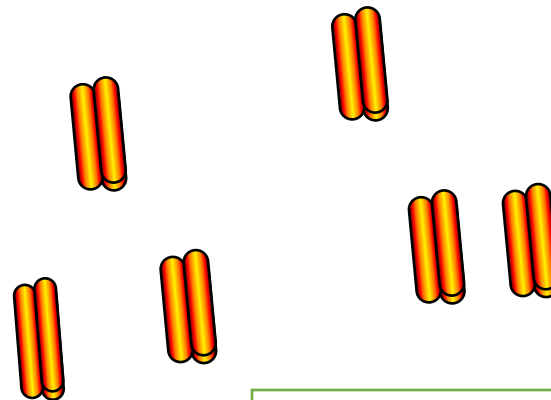
Trans-Membrane Bound TNF



Monoclonal Antibody (Infliximab & Adalimumab)



Soluble TNF



## Targeted Synthetic DMARDs (tsDMARDs) (JAK Inhibitors)

- Small-molecules, **daily oral medications** that **precisely target specific immune pathways** (e.g., JAK inhibitors) rather than suppressing the entire immune system
- **Advantage**: daily oral tablet compared to injectable biologics (bDMARDs)
- **Janus kinase (JAK) inhibitors** are the primary type, including baricitinib, tofacitinib, and upadacitinib
- **Disadvantages**: can increase the risk of infections, malignancies, and serious cardiovascular events

# JAK inhibitors

- **Janus kinase enzymes** (JAK1, JAK2, JAK3, and TYK2).
- These enzymes **promote inflammation**, and they are involved in some diseases:
- Arthritis, including rheumatoid arthritis (RA)
- Cancer
- Dermatological conditions like atopic dermatitis and alopecia areata
- Some bowel conditions like ulcerative colitis and inflammatory bowel disease
- Inflammation is limited when the enzyme signaling pathways are interrupted, which can help some autoimmune diseases.

## References

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**Thank you**