

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



# 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, 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. Rituximab
6. Abatacept

# Rheumatoid arthritis

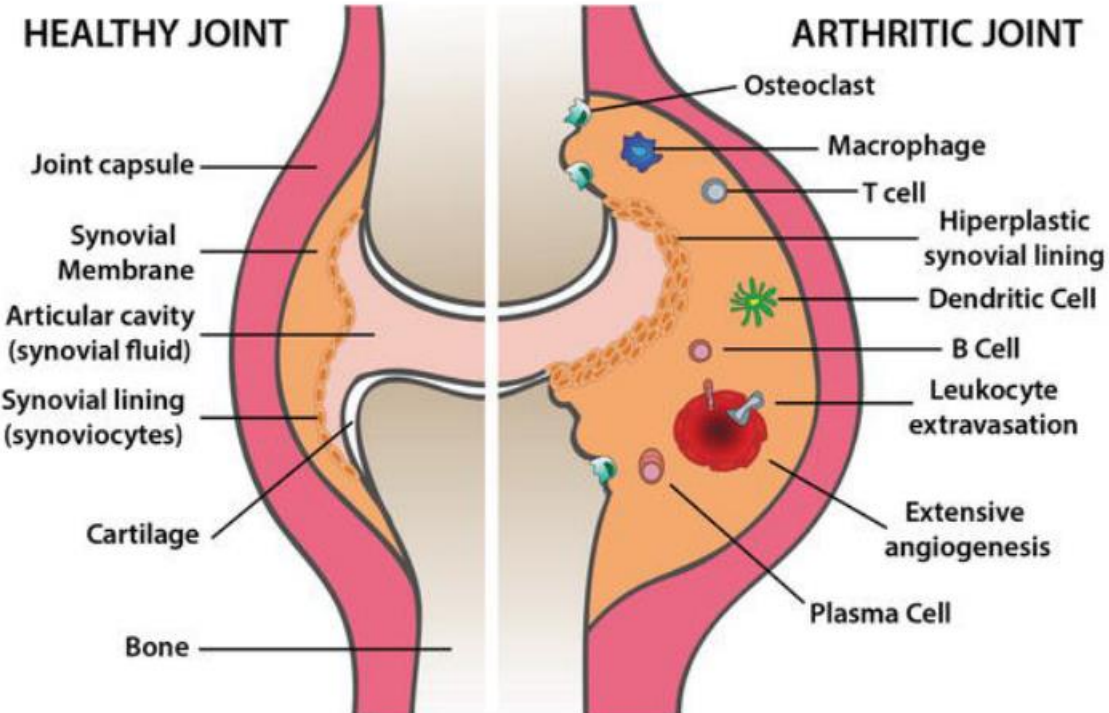
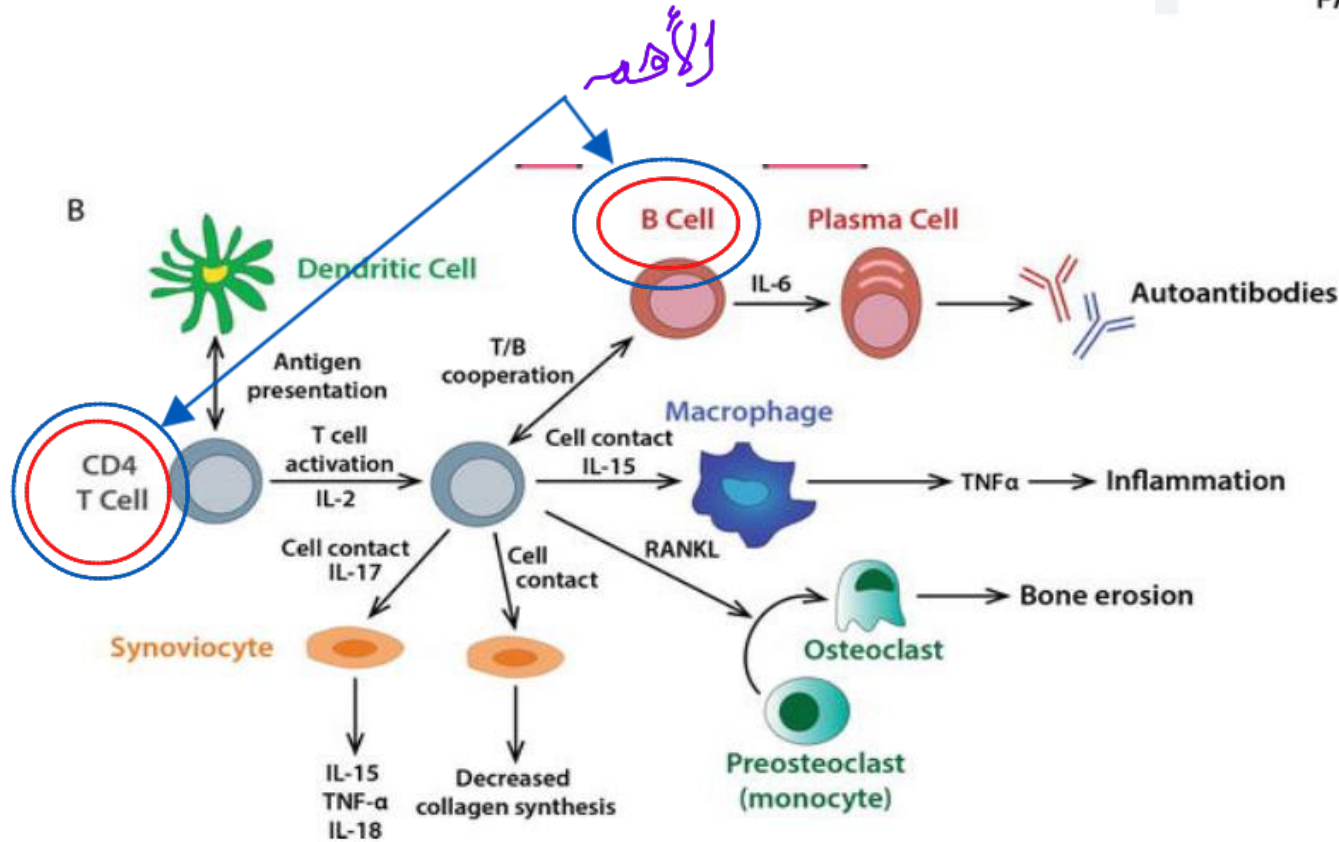
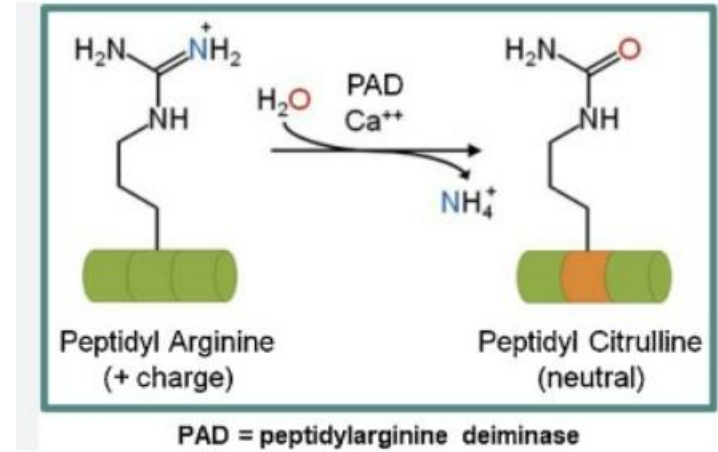
- Chronic synovial inflammation: immune mediated inflammatory disease (IMID)
  - Small joints : hands
  - 70% females
  - Symmetrical
  - Autoimmune
  - Cytokines which are responsible for: **inflammation & joint destruction**
    - ❑ Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ )
    - ❑ Interleukins - 1,6,17
- Gout*  
*Big Toe*  
*Males*  
*Asymmetrical*  
*Uric Acid Conc. ↑*
-

# Pathogenesis

- **Genetic Susceptibilities:**

- RA is associated with class II major histocompatibility (MHC) antigens, specifically the shared epitope found in **HLA-DR4**. → *Leukocyte*
- In rheumatoid arthritis an autoimmune response develops against citrullinated peptides detected as anti-citrullinated peptide antibodies (ACPA).
- One of tests to detect these antibodies detects anti-cyclic citrullinated peptides (anti-CCP), currently the most commonly used diagnostic test for them. *Specific for Rheumatoid A.*
- The presence of anti-CCP are >98% specific for the diagnosis of rheumatoid arthritis; however, not all patients with RA will develop anti-CCP antibodies.

**Citrullination or deimination is a posttranslational modification of protein in which arginine amino acid is converted into citrulline amino acid. This process is catalyzed by peptidylarginine deiminase (PAD) enzymes**



## Drugs used in treatment of rheumatoid arthritis

➤ Most experts begin RA therapy with one of the traditional drugs, such as **methotrexate** or **hydroxychloroquine**.

➤ Inadequate response to the traditional agents may be followed by addition of newer DMARDs, such as leflunomide, anakinra, and TNF-inhibitors eg: adalimumab, etanercept, and infliximab.

إذا الأدوية المعتادة أثبتت أنها لا تعالج، فهناك من يُعجّل "Accept"  
Abatacept

➤ In patients who do not respond to combination therapy of traditional drugs (methotrexate) plus newer drugs (TNF inhibitors) , treatment with rituximab or abatacept may be tried.

➤ Most of these agents are contraindicated in :

➤ pregnancy, breast feeding, liver disease, active infection, leucopenia and peptic ulcer.

# Drugs for RA

- **Nonsteroidal anti-inflammatory drugs (NSAIDs):**  
**symptomatic**
- **Corticosteroids**  
**(symptomatic & causative)**
- **Disease-modifying anti-rheumatic drugs (DMARDs)**
  - Synthetic
  - Biologic

# NSAIDs

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

Contraindication  
CV disease عند أمراض القلب



# COX-2 Inhibitors

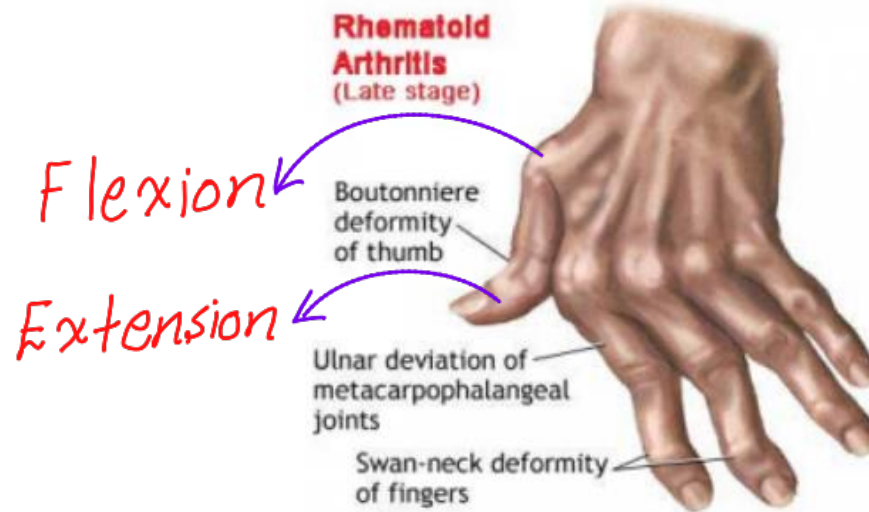
- COX-2 inhibitors are as effective NSAIDs
- Associated with less GI toxicity
- Associated with increased risk of CV events

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 of joint components:**
  - Bones
  - Cartilage
  - Ligaments and other structures
- **Fatigue**
- **Not Reversible**



# DMARDs

## Therapeutic effects of Disease Modifying Anti-Rheumatic Drugs: (symptomatic)

- Reduce swelling & inflammation
- Improve pain
- Improve function
- **Have been shown to reduce radiographic progression (erosions)**
- **Effects on prognosis of the disease: (causative)**
  - 1- Slow the course of the disease
  - 2- Induce remission
  - 3- Prevent further destruction of the joints and involved tissues.

همكنه يستمر لـ 15 "أو" 2 "سنة

# DMARDs

- **Synthetic**
- **Biologic**

# Synthetic DMARDs

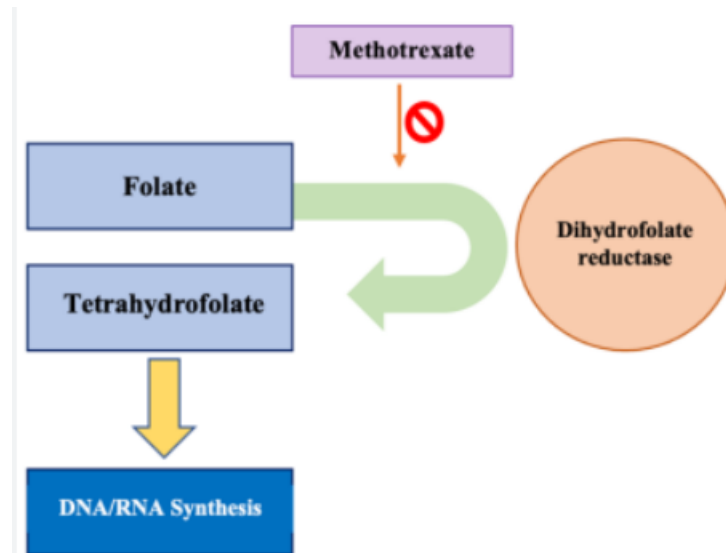


- Methotrexate
- Sulphasalazine
- Hydroxychloroquine, chloroquine
- Leflunomide
- Gold salts



## Adverse effects: due to decreased folic acid level

- **The most common side effects:** mucosal ulceration and nausea.
- **Cytopenias** :bone marrow depression (particularly reduction of the WBC count)
- **Hepatotoxicity**
- **Acute pneumonia-like syndrome** in chronic use





# Leflunomide

➤ effective as methotrexate

➤ Mechanism of action:

➤ Immunomodulatory and immunosuppressive agent :

➤ **inhibition of pyrimidine synthesis**: inhibiting DNA synthesis in immune cells

➤ Uses:

➤ 1- **Monotherapy** as an alternative to methotrexate

➤ 2- An addition to **methotrexate** in combination therapy.

الأفخيلة

## Hydroxychloroquine (and chloroquine): (antimalarial drug)

### Mechanism of action :

- 1- Inhibition of RNA and DNA synthesis in immune cells
- 2- Stabilization of lysosomal membranes

### Adverse effects:

- 1- **Renal** toxicity.
- 2- **Retinal** damage and **corneal opacity**: less common and reversible in case of hydroxychloroquine which **is preferred over chloroquine**

### ➤ **Uses:**

- 1- **Monotherapy**: **Milder non-erosive** disease especially when **only one or a few joints** are involved
- 2- Combined with **Mtx / sulfasalazine**.

# Sulfasalazine

- Sulfasalazine (SSZ) is a prodrug composed of **5-aminosalicylic acid (5-ASA)** (immunosuppressant) linked to **sulfapyridine (antibacterial)**
- **Uses: It is used as a second line drug for milder cases:**
- Early, mild RA in combination with hydroxychloroquine and methotrexate.
- **Adverse effects: few**
- 1- **Neutropenia/ thrombocytopenia** occurs in about 10% patients
- 2- **Hepatitis**

Most Effective

# Gold

- Gold is considered to be the most effective agent for **arresting the rheumatoid process** and preventing involvement of additional joints.
- it was the standard DMARD before **Methotrexate** regimen.

- **Mechanism of action:**

- It reduces chemotaxis, phagocytosis, macrophage and lysosomal activity : decreasing release of cytokines

- **It has no role in late cases**

- **Adverse effects:**

- Gold is heavily bound to plasma and tissue proteins especially in kidney: renal toxicity
- Dermatitis and stomatitis (oral ulcers)
- Bone marrow depression **CBC**

**stays in the body for years.**

Contraindicate  
in: →

Child Bearing

الأنتى في هذه الفترة  
لأنه يدخل في الجسم

الذهب

لما ألبسه بسبب

Dermatitis

وهو ثقيل "مثل الحصى"

يظهره خلايا الدم

وحصى الكلية

# Biologic response modifiers ( BRMs):

## 1. TNF $\alpha$ inhibitors:

**Etanercept: TNF  $\alpha$  receptor blocker**

**Infliximab Adalimumab (monoclonal antibodies)**

### Advantages:

- 1- Very effective
- 2- Delay disease progression

### Disadvantages:

متفطوي على وظائف الـ TNF- $\alpha$

- 1- Very expensive, so try conventional therapy first
- 2- Contraindicated in patients with **history of tumors esp. leukemia, viral hepatitis, immunocompromised patients**

**2. IL-1 antagonist: Anakinra: short acting given daily and sc injection  
(disadvantage: non-compliance)**

## 3- Rituximab

- is a monoclonal anti-CD20 antibody
- directed against the CD20 antigen found on the surface of **normal and malignant B lymphocytes**
- **Lysis of B lymphocytes:** near-complete depletion of peripheral B lymphocytes within 2 weeks after the first dose.

## 4- Abatacept

- **Abatacept** is the first in a new class of drugs known as Selective Co-stimulation Modulators.
- inhibit T-cell (T lymphocyte) activation by **binding to CD80 and CD86**, thereby blocking interaction with CD28.
- Blockade of this interaction has been shown to inhibit the second co-stimulatory signal required for optimal activation of T-cells.
- This results in the inhibition of autoimmune T-Cell activation that has been implicated in the pathogenesis of rheumatoid arthritis.

1<sup>st</sup> Stimulatory  
Signal CD80+CD86

2<sup>nd</sup> Stimulatory  
Signal (CD80+CD86)  
↓  
CD28

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



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THANK YOU

