DISEASE MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)

Dr.Nashwa Abo-Rayah
Associate prof. (clinical &experimental pharmacology)
Mu'tah University- Faculty of Medicine- JORDAN
2024/2025

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-α drugs such as etanercept, infliximab, and adalmumab.
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-α (TNF-α)**
  - **Interleukins - 1,6,17**

gout = any joint (big toe)
= males
= not always symmetrical.

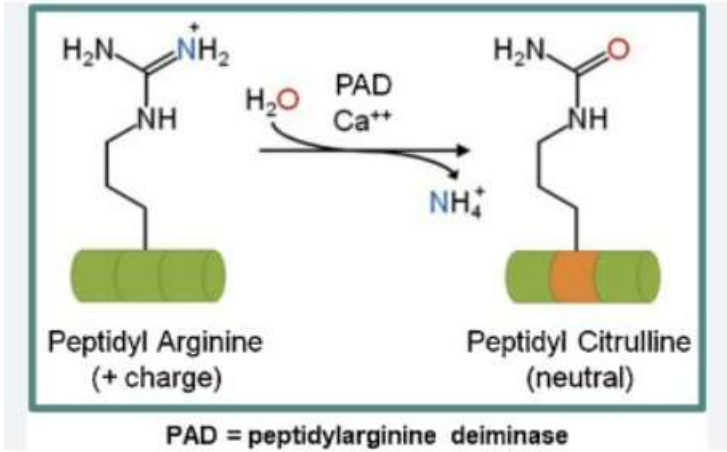
Pathogenesis

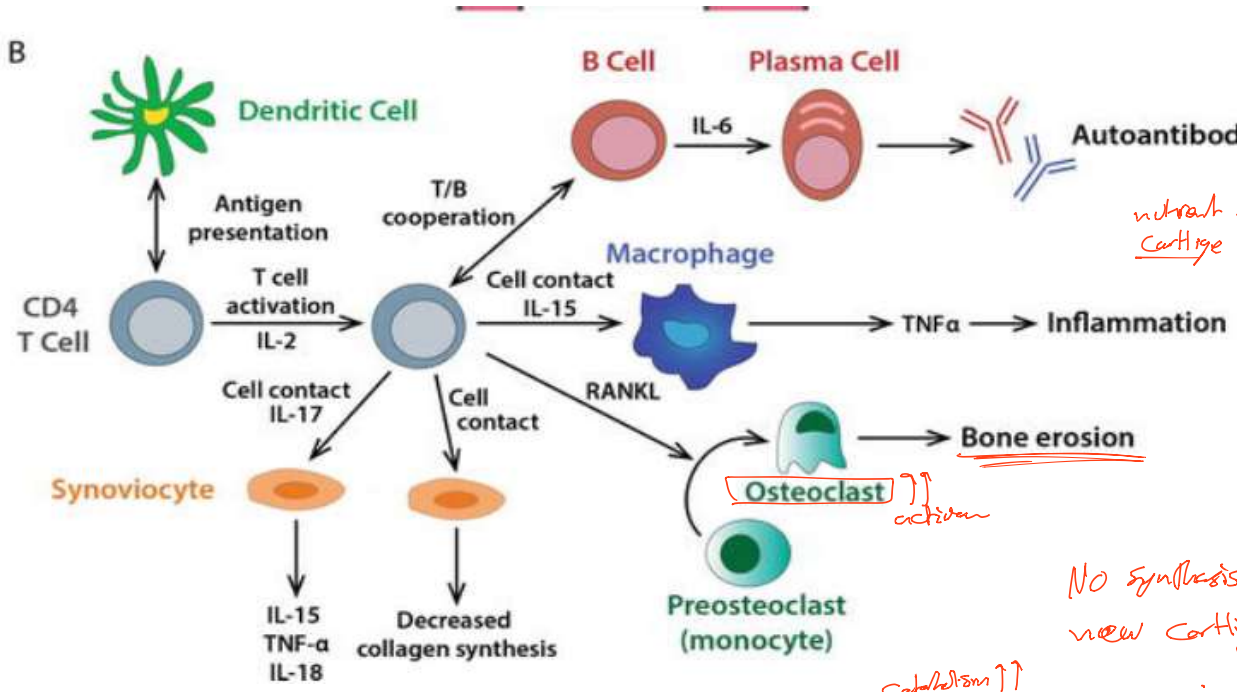
- **Genetic Susceptibilities:**
- RA is associated with class II major histocompatability (MHC) antigens, specifically the shared epitope found in HLA-DR4.
- In rheumatoid arthritis an **autoimmune response** develops against **citrullinated peptides** detected as **anti-citrullinated peptide antibodies (ACPA).**
- One of tests to detect these antibodies detects **anti-cyclic citrullinated peptides (anti-CCP)**, currently the most commonly used diagnostic test for them.
- 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.

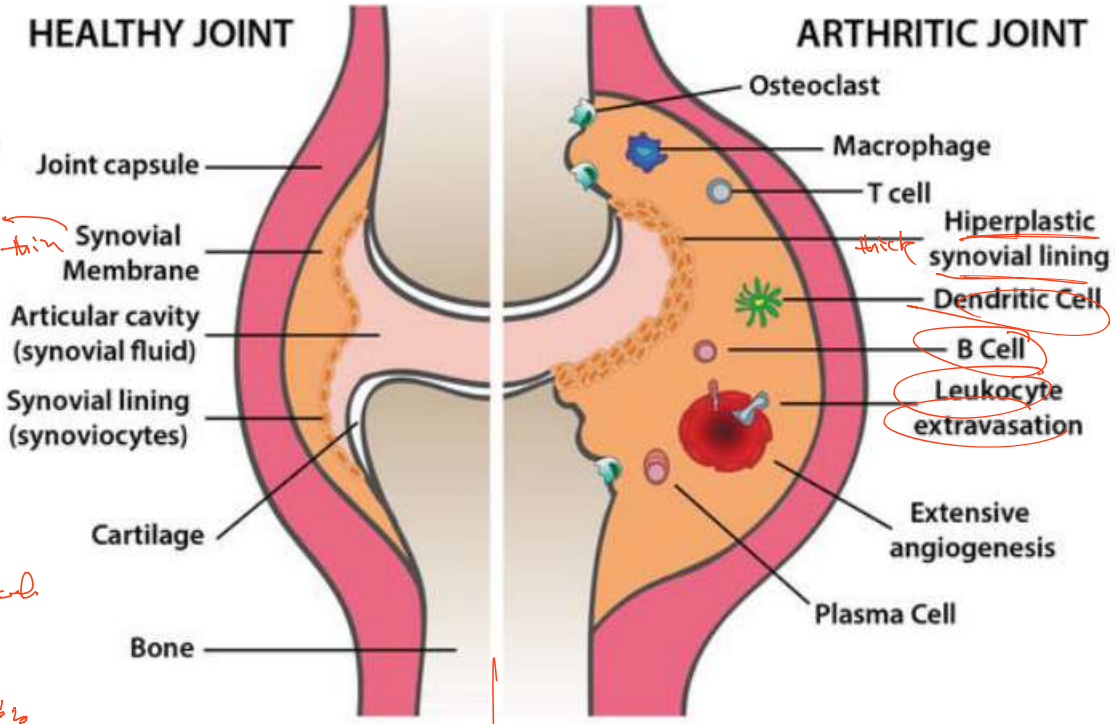
peptide (Arg) — NH3 deamination.

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

for normal skin function or other







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.

- 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.

Teratogenicity ↑.

!! Immunity

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 (Voltarin)
  - Add protective treatment for peptic ulcer ⟹ (As is disease is a chronic disease — for prolong used.)
- **Selective COX–2 inhibitors**
  - celecoxib

COX-2 Inhibitors

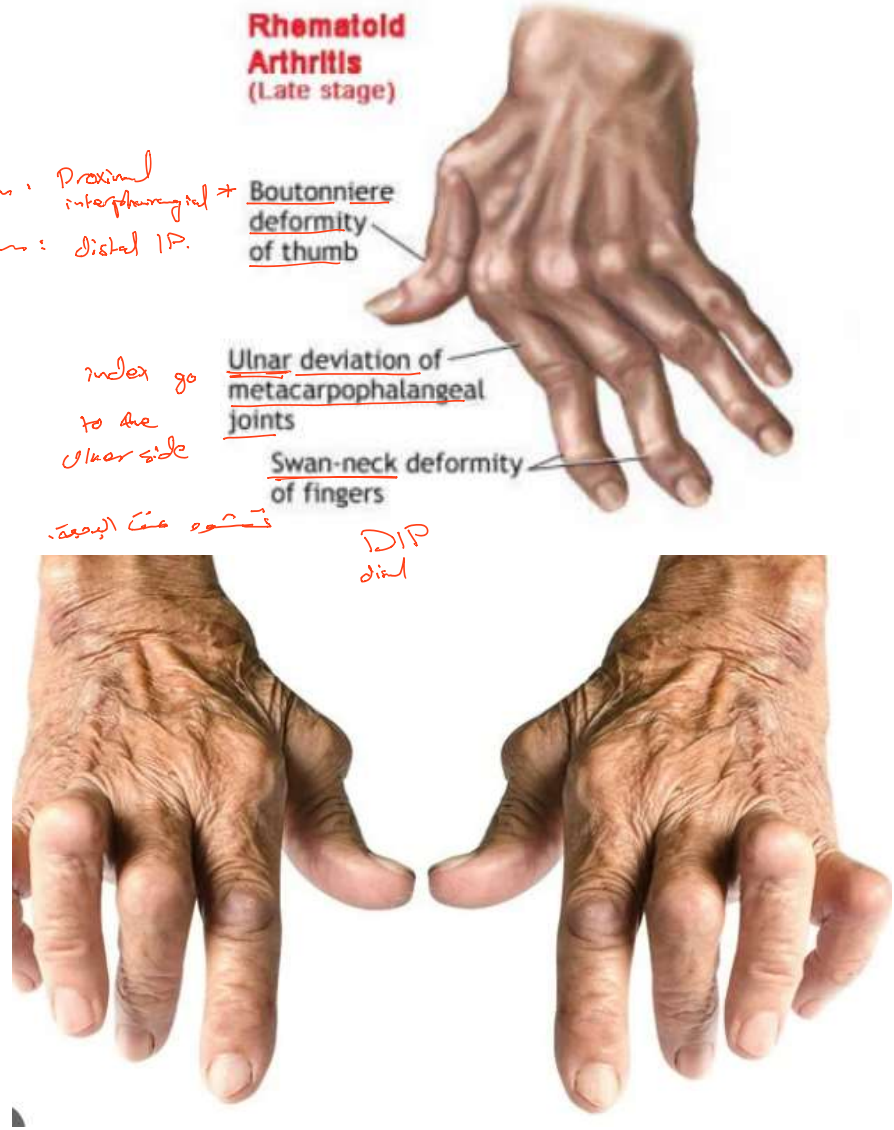
- COX-2 inhibitors are as effective NSAIDs
- Associated with less GI toxicity
- Associated with increased risk of CV events

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**

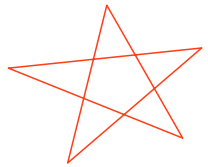


DMARDs

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.

DMARDs

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

Synthetic DMARDs

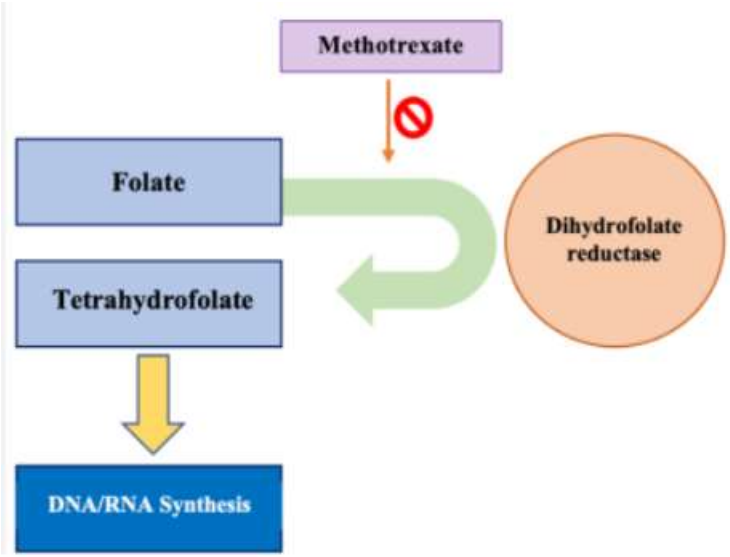
- Methotrexate
- Sulphasalazine
- Hydroxychloroquine, chloroquine
- Leflunomide
- Gold salts

Methotrexate: (immunosuppressant and cytotoxic)

- **Uses:**
- 1- Sever rheumatoid 2- Psoriatic arthritis.
- **Immunosuppressant**: effectiveness in arthritis (60% of patients), an autoimmune disease.
- **Onset of action**: sooner than is usual for other slow-acting agents often **within 3-6 weeks of starting treatment.**
- **Mechanism of action**: **folic acid antagonist** methotrexate is **folic acid analogue** also **inhibits dihydrofolate reductase (DHFR)**, decreasing synthesis of tetrahyrofolate (THF) and it inhibits formation of nucleic acids in immune cells involved in pathogenesis of RA.
- **Methotrexate dose :**
- **7.5- 10 mg/ week**: single weekly dose (2-3 tablets or injection): max. dose: 25 mg/ week
- Daily folic acid dose: 5 mg tablet: to reduce methotrexate adverse effects: **avoid the day of methotrexate administration**

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**.

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-errosive** 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)** (**immunosupressant**) linked to **sulfapyridine (antibacterial)**
- **Uses:It is used as a second line drug for milder cases:**
- Early, mild RA in combination with hydroxycholoroquine and methotrexate.
- **Adverse effects: few**
- 1- **Neutropenia/ thrombocytophenia** occurs in about 10% patients
- **2- Hepatitis**

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

stays in the body for years.

Biologic response modifiers (BRMs):

1.TNF α inhibitors:

Etanercept: TNF α receptor blocker

Infliximab Adalimumab (monoclonal antibodies)

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, immuncomprmised 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.

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

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THANK YOU