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# **Disease-Modifying Antirheumatic Drugs (DMARDs)**

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# Types of Arthritis

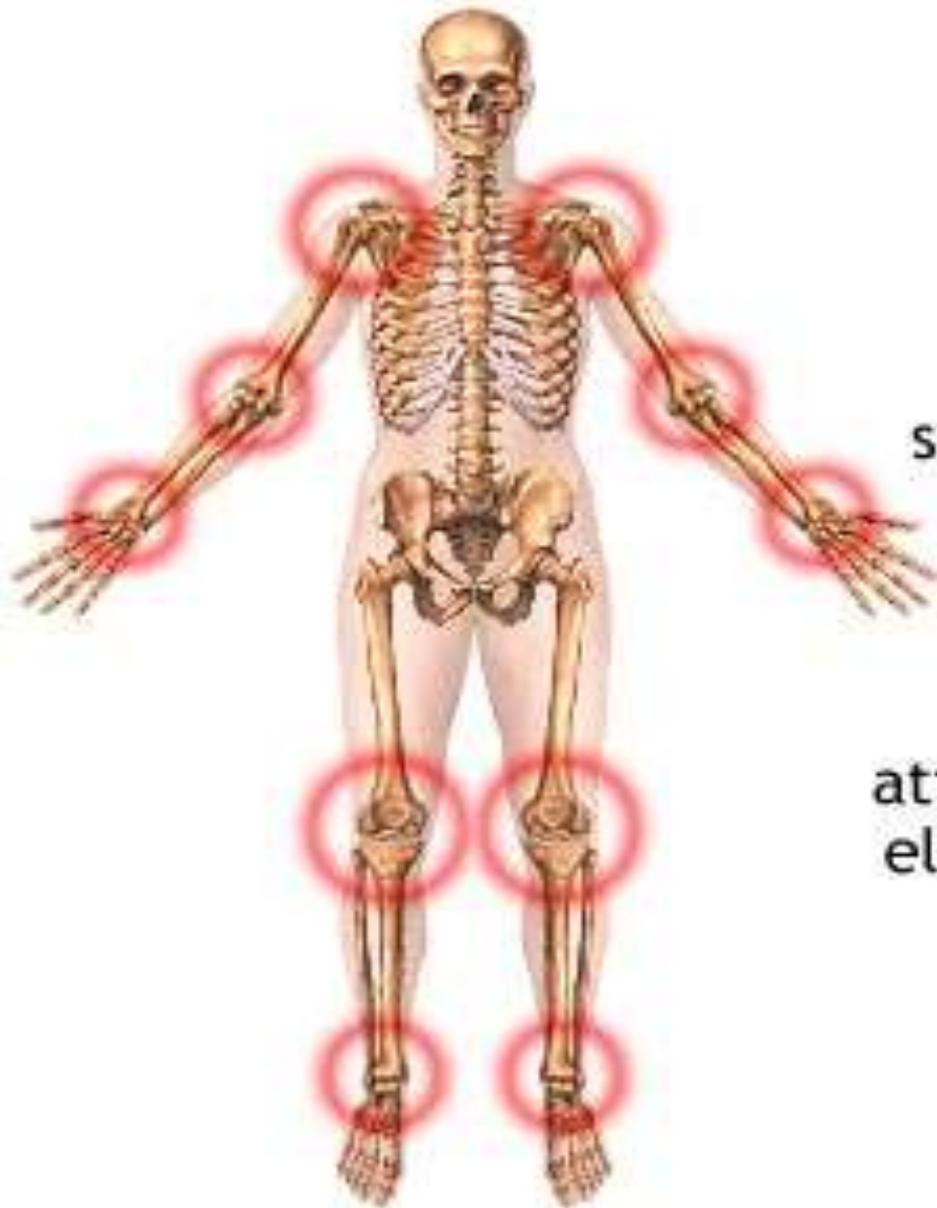
⇒ Most affected gender ⇒ Females.

Can affect any joint of the body

- Most common: Rheumatoid arthritis (RA)
- Less common of inflammatory arthritis:
  - Juvenile idiopathic arthritis (JIA) ⇒ mostly affected ⇒ children.
  - **Spondyloarthritis** (ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease) ⊕ Early sign? Pain
- Joint pains (arthralgia) is common in connective tissue diseases (SLE, scleroderma)
- Endocrine diseases (hypo- & hyperthyroidism)  
(T<sub>3</sub>, T<sub>4</sub>, TSH)

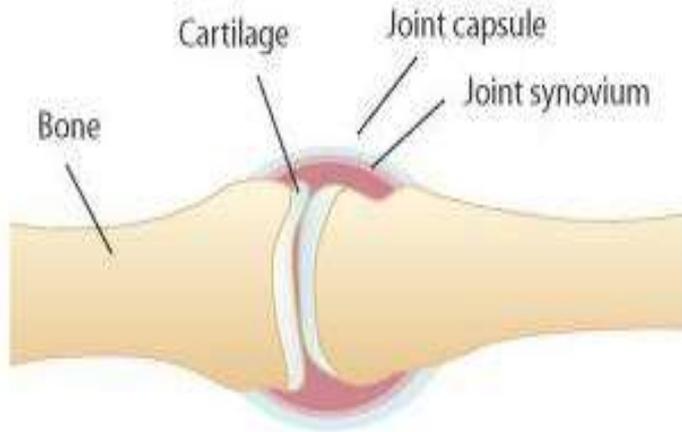
# Rheumatoid arthritis (RA)

- is an **autoimmune disease** that can cause **chronic inflammation of joints & other areas of the body**
- Fatigue
- Joint pain, tenderness, swelling, redness, warmth
- **Stiffness of joints**, particularly worse in the morning
- Many joints affected (**polyarthritis**) *Shoulder ⇒ Elbow ⇒ Wrist ⇒ Fingers*
- Both sides of the body affected (**symmetric**)

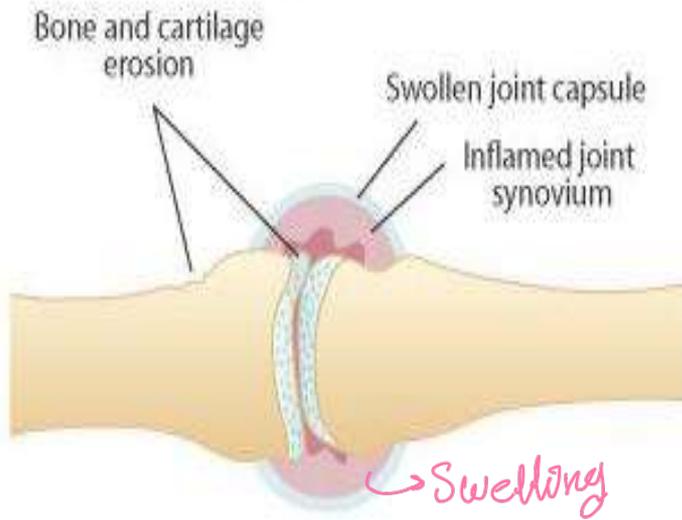


Rheumatoid arthritis usually affects joints symmetrically (on both sides equally), may initially begin in a couple of joints only, and most frequently attacks the wrists, hands, elbows, shoulders, knees and ankles

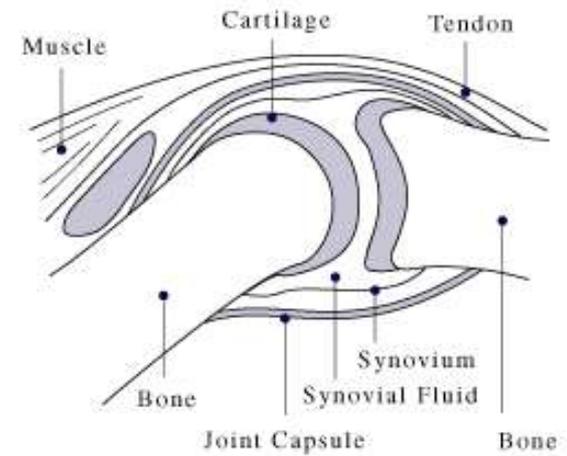
### Normal joint



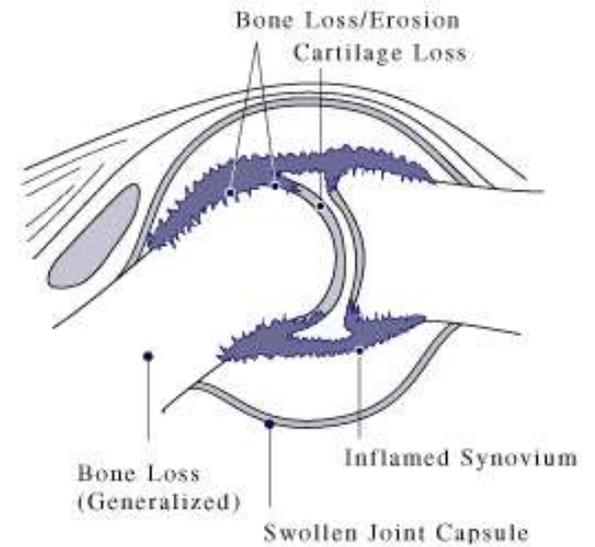
### Joint affected by rheumatoid arthritis



### Normal Joint



### Joint Affected by Rheumatoid Arthritis



- Patient's priority is relief of **joint pain, swelling & stiffness**
- There is no cure for arthritis
- Successful treatment requires **multidisciplinary approach** with DMARDs, pain management (NSAIDs) & low-dose corticosteroids, physiotherapy

- it's the known clinical approach to cure the patients with best possible way that can be accomplished. by Using DMARD's + NSAID's + Cortico + Physiotherapy

↳ magic drug ⇒ but associated w/ many ADRs

# DMARDs

- Are immunomodulators that restore more normal immune environment within joint synovium
- They are used primarily for rheumatic disorders in which inflammatory disease does not respond to cyclooxygenase inhibitors

# DMARDs

- **Slow course of disease** ⇒ Depends on the Severity of the disease.
- **Can cause remission**
- **Prevent further destruction of joints & involved tissues**
- **Early initiation of DMARDs is recommended to control signs & symptoms and to limit joint damage** ⇒ To lead to the best outcome.
- If you can't fix it with drugs and physiotherapy (too severe), the patient will have to do joint replacement.

# DMARDs

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## ➤ **Immunosuppressants:**

<sup>low dose</sup>  
(Methotrexate, leflunomide, azathioprine, ciclosporin, cyclophosphamide)

## ➤ **Hydroxychloroquine** ⇒ can be used w/ mild to moderate cases.

## ➤ **D-Penicillamine**

## ➤ **Gold Salts**

## ➤ **Biological agents: cytokine modulators**

New!

↓  
IV infusion  
↓  
Needs Hospital submission.

# DMARDs

- They have a long onset of action, require 2-6 months for full therapeutic response
- Choice of DMARDs:
  - No one DMARD is efficacious and safe in every patient
  - Start with **traditional small molecules agents**, such as **methotrexate or hydroxychloroquine** (efficacious, well tolerated, well-known side-effects profiles)

# DMARDs

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- Inadequate response, newer drugs such as **leflunomide, anakinra, TNF inhibitors** (etanercept, infliximab, adalimumab)
- **Combination therapies are both safe & effective**
- In most cases, *→ careful! Heavy ADRs! so leave it to be the last option* methotrexate is combined with one DMARDs (**TNF inhibitors**)
- **Combination of MTX plus rituximab**  
*methotrexate*

# 1. Methotrexate

- It is an immunosuppressant (RA is autoimmune disease)
- First line treatment in RA & PA
- Used alone or in combination therapy in patients with moderate to severe rheumatoid or psoriatic arthritis who have not responded to NSAIDs
- It acts by competitive inhibition of enzyme dihydrofolate reductase
- Inhibits purine synthesis

# 1. Methotrexate

- Slows appearance of new erosions within involved joints on radiographs
- **Response to MTX occurs sooner than with other agents within 3 to 6 weeks**
- In high doses, used in **solid & haematological malignancies**
- Doses in RA are lower than those needed in cancer chemotherapy, **7.5 mg once a week orally**

# 1. Methotrexate

## ➤ Adverse effects:

- **Most common:** Mouth ulcer & nausea
- **Bone marrow toxicity:** Pancytopenia (WBCs)
- Hepatic toxicity: Liver cirrhosis with long-term use
- Acute pneumonia-like syndrome, after chronic administration
- It is teratogenic
- Taking **leucovorin (folinic acid)** reduces severity of side effects
- **Monitoring side effects:** CBC, liver enzymes, signs of infections

## 2. Leflunomide

- It is an immunomodulatory agent that causes cell arrest of T lymphocytes through its action on **dihydroorotate dehydrogenase (DHODH)**
- Inhibits pyrimidine synthesis & prevent T-cell proliferation which is thought to be important in pathogenesis of RA

## 2. Leflunomide

- Reduces pain, inflammation & slow progression of structural damage
- Can be used in **monotherapy** as alternative to MTX or **an addition to MTX**
- Pharmacokinetics:
  - Administered orally
  - Long half-life of 14 to 18 days

## 2. Leflunomide

### ➤ Adverse effects:

- **Most common:** headache, diarrhea, nausea
- Weight loss, allergic reactions (skin rash, alopecia)
- **Teratogenic, is contraindicated during pregnancy**
- Should be used with caution in liver disease

## 3. Hydroxychloroquine

- **Advaquenil**
- Is used in treatment of malaria (antimalaria actions)
- Used in early & mild RA
- When used alone, it dose not slow joint damage, **it is often used in combination with MTX**
- Accumulate within lymphocytes, macrophages & inhibit phagocyte function

### 3. Hydroxychloroquine

- It is used for arthralgia associated connective tissue diseases e.g. SLE
- **They cause serious adverse effects:**
  - Retinal damage (rare)
  - Skin discoloration
  - Alopecia
  - Bleaching of hear
  - GI upset

## 4. D-Penicillamine

- It reduces **rheumatoid factor & concentration of immune complexes in plasma & synovial fluids**
- Rarely used
- **Serious side effects:** GI upset, impairment of taste, dermatological, **nephritis, aplastic anemia**, allergic reactions

# Biological Therapies (Cytokine modulators)

- **Interleukin-1b (IL-1b) & tumor necrosis factor-alpha (TNF-alpha)** are pro-inflammatory cytokines involved in pathogenesis of RA
- Drug antagonists of cytokines are effective in treating RA

# Cytokine modulators

- When secreted by **synovial macrophages**, they **stimulate synovial cells** to **proliferate & synthesize collagenase**, thereby **degrading cartilage**, stimulating **bone resorption**

- **TNF inhibitors decrease signs & symptoms, reduce progression of structural damage, improve physical function**
- **Clinical response within 2 weeks**
- **TNF inhibitors increase risk of infections (TB, sepsis), fungal infections, pancytopenia**
- **Live vaccinations should be avoided**
- **Cautious in patients with heart failure**

- **TNF- alpha inhibitors:**  
**(Etanercept, infliximab, adalimumab)**
- **IL-1 receptor antagonist: anakinra**
- **Monoclonal antibody: rituximab**

# 1. Etanercept (Enbrel)

- Genetically engineered fusion protein
- **Used alone or in combination with MTX**
- Is given in moderate to severe RA, ankylosing spondylitis, psoriatic arthritis
- **Mechanism of action:** 
  - It binds to TNF molecules & prevents them from binding to cell surface TNF receptors
  - Is given **Sc twice a week, (half-life 115 hrs)**
  - **Side effects:** local inflammation at site of injection

## 2. Infliximab (Remicade)

- Is monoclonal antibody that binds to TNF-alpha, thereby neutralizing that cytokine
- Approved for treatment of **RA, Crohn's disease & ulcerative colitis, psoriasis, ankylosing spondylitis**
- **Not indicated for use alone**, because of development of anti-infliximab antibodies
- **It is often used in combination with MTX**, in patients who had inadequate response to MTX
- Is infused IV over 2 hrs *⇒ needs Hospital admission*
- Half life 9.5 days

➤ **Adverse effects:**

- **Pancytopenia:** leukopenia, neutropenia, thrombocytopenia
- **Infusion reactions:** fever, chills, pruritus, urticaria
- May predispose to **life-threatening infections**

# 3. Anakinra (kineret)

- Is an IL-1 receptor antagonist
- It binds to IL-1 receptor, thus preventing IL-1 action
- Is used alone or in combination with other DMARDs in patients who failed to response to DMARDs
- Is given Sc
- It causes neutropenia

## 4. Rituximab ⇒ last option!

- Monoclonal antibody against CD20 antigen found on surface of B lymphocytes, resulting in B-cell depletion
- B cells in RA causes activation of T lymphocytes, producing of autoantibodies (anti-CCP cyclic citrullinated peptide antibody), RF & TNF alpha, IL-1
- **Used in severe RA with no response to TNF inhibitors**
- Is given by IV infusion needs hospital submission
- **Side effects:** infusion reaction (urticaria, hypotension, angioedema)

# Intra-articular injection of corticosteroids

Hide Behind Dex ONE

- Hydrocortisone, prednisolone & dexamethasone
- Benefit from one injection may last many weeks
- Aseptic precautions for introducing infection



# Intra-articular injection of corticosteroids

- Too frequent injections may promote joint damage by removing protective limitation conferred by pain
- Injections in a single joint would not exceed three per year

# Role of systemic corticosteroids

- Use for systemic corticosteroids is reluctant because of its adverse effects
- **In extreme severity, high dose prednisolone (20- 40 mg/d) very effectively suppress inflammation**
- **Where DMARDs have failed or produced intolerable adverse effects**  
e.g. prednisolone 7.5 mg once daily orally

# Different ways of using DMARDs

- Drugs may be administered in sequence (to find most effective)
- Alternatively, up to three DMARDs may be given in combination, with drugs added progressively or all started at same time
- Some patients fail to all the standard treatments, they may benefit from long-term maintenance on prednisolone (2- 4 years)