Disease-Modifying Antirheumatic Drugs (DMARDs)

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Types of Arthritis

- **Most common: Rheumatoid arthritis (RA)**
- **Less common of inflammatory arthritis:**

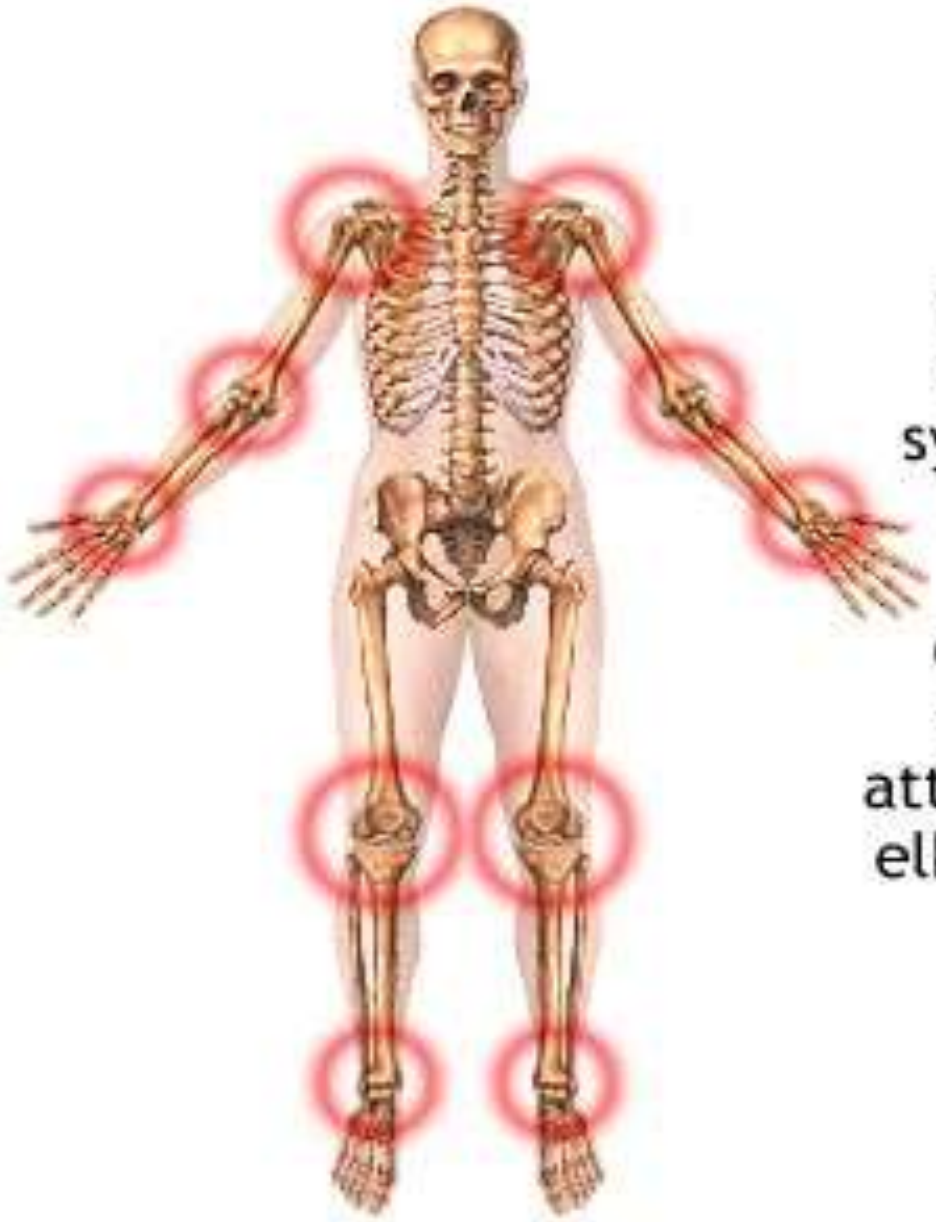
- Juvenile idiopathic arthritis (JIA)

- Spondyloarthritis (ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease)

- **Joint pains (arthralgia)** is common in **connective tissue diseases (SLE, scleroderma)**
- **Endocrine diseases (hypo- & hyperthyroidism)**

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)
- 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

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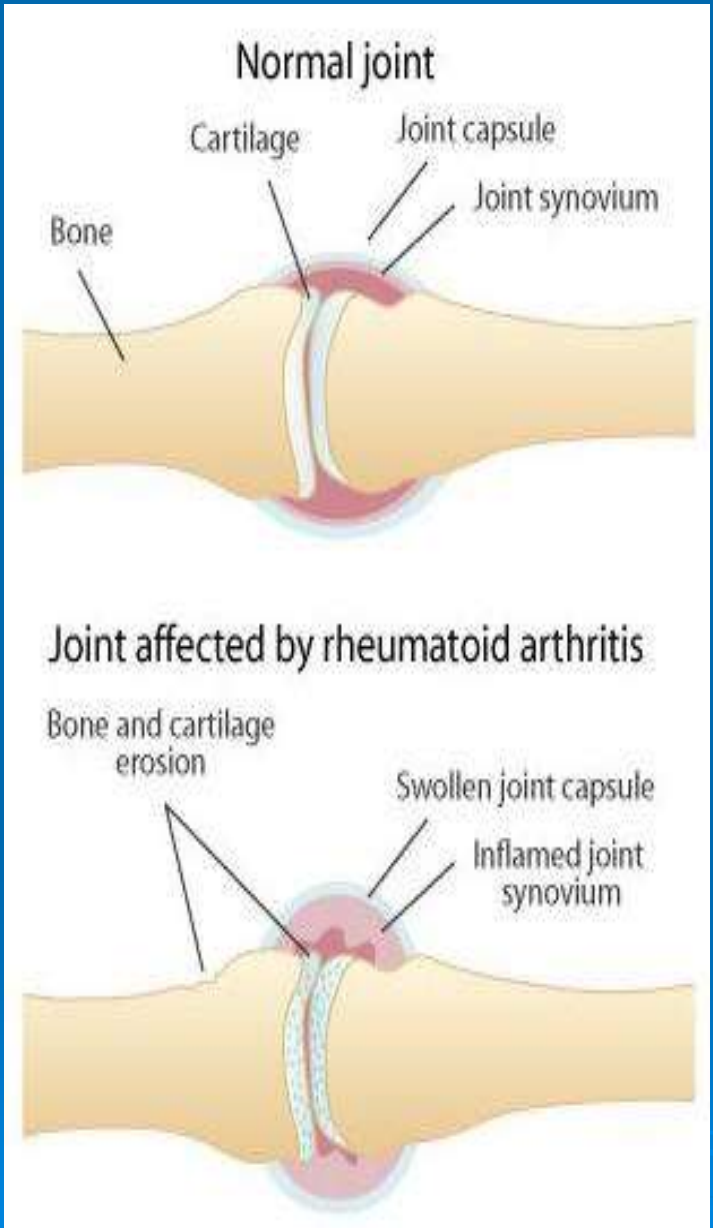
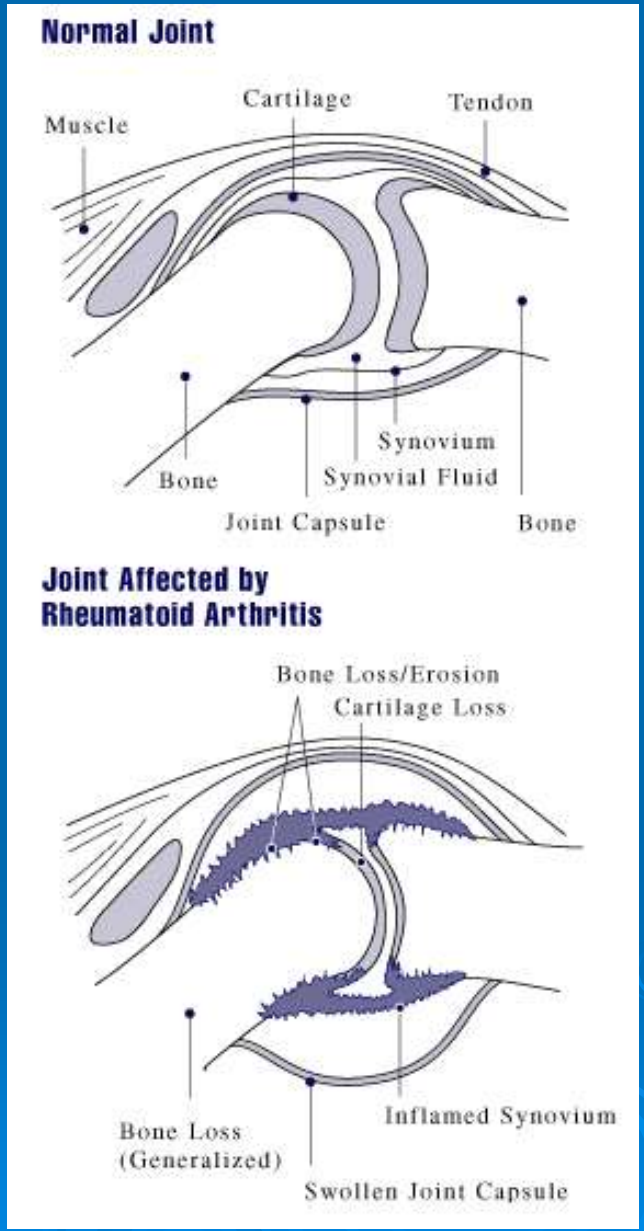

Normal joint
Cartilage
Joint capsule
Joint synovium
Bone
Joint affected by rheumatoid arthritis
Bone and cartilage erosion
Swollen joint capsule
Inflamed joint synovium


Normal Joint
Muscle
Cartilage
Tendon
Synovium
Bone
Synovial Fluid
Joint Capsule
Bone
Joint Affected by Rheumatoid Arthritis
Bone Loss/Erosion
Cartilage Loss
Bone Loss (Generalized)
Inflamed Synovium
Swollen Joint Capsule

- **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**

DMARDs

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

DMARDs

- **Slow course of 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

DMARDs

- **Immunosuppressants:**

  (Methotrexate, leflunomide, azathioprine, ciclosporin, cyclophosphamide)
- **Hydroxychloroquine**
- **D-Penicillamine**
- **Gold Salts**
- **Biological agents: cytokine modulators**

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

- **Inadequate response**, **newer drugs** such as **leflunomide, anakinra, TNF inhibitors (etanercept, infliximab, adalimumab)**
- **Combination therapies** are both **safe & effective**
- **In most cases**, **methotrexate is combined with one DMARDs (TNF inhibitors)**

- Combination of MTX plus rituximab

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-life115 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
- 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

- 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
- Side effects: infusion reaction (urticaria, hypotension, angioedema)

Intra-articular injection of corticosteroids

- **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 reluctance 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)**