

A stylized, colorful illustration of a landscape. The foreground features rolling green hills with dark brown soil. On the left, there is a green tree, a purple flower, and an orange flower. A small red bird is flying in the sky above the tree. The background consists of layered, wavy blue and white bands representing a sky or distant hills.

Antirheumatoid Drugs

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Background – Rheumatoid arthritis

- Autoimmune disorder
 - Joint inflammation
 - Non-Suppurative Proliferative Synovitis
 - Articular cartilage destruction
- Disabling Arthritis - pain, swelling, stiffness and loss of function in the joints ..
- Systemic Manifestations
- Prevalence - 1 to 2% , increases with age – 5% women over age 55

Rheumatoid arthritis - Mechanism

- Immune complexes composed of IgM activates Complements
- Release of cytokines – mainly TNF α , IL-1 – chemotactic for neutrophils
- Inflammatory cells secrete lysosomal enzymes – Cartilage damage and erosion of bones
- PGs produced – Vasodilatation and pain

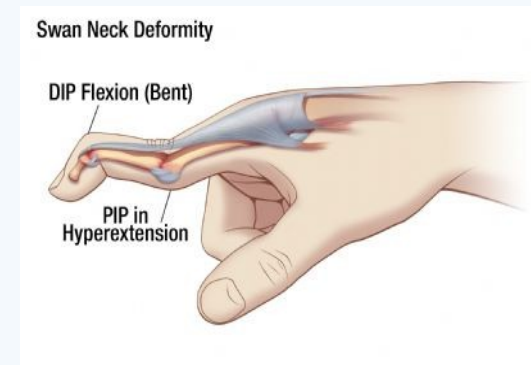
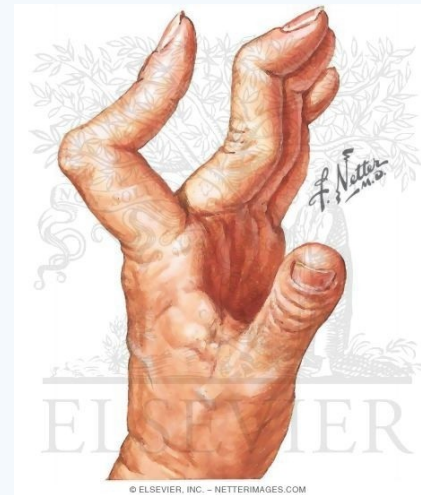
Rheumatoid arthritis – Patient presentation



- Chronic progressive **crippling** (unable to move properly) with **waxing** and **waning** course (alternate increases and decreases)
- Pain and swelling of joints, morning stiffness, immobility etc.
- Symptoms can be divided into 3 types:
 - ✓ **General:** fatigue, malaise, depression, occasional fever
 - ✓ **Articular:** persistent symmetrical joint swelling for long
 - ✓ **Extra articular:** **Rheumatoid Nodules** - extensor surfaces of the arms and elbows - rarely in visceral organs (lungs, heart)
- 70% of patients disease begins with general symptoms like weakness, loss of appetite, vague muscle aches, tiredness
- **NSAIDS are the first line drugs**

Deformities in advance cases

- **Swan neck deformity:** PIP Hyperextension and DIP flexion
- **Boutonniere deformity:** PIP flexion and DIP Hyperextension
- **Z like deformity:** DIP Hyperextension and fixed flexion and subluxation of the MCP
- **Hammer toe (claw toe):** Curling and stiffening of position of toes
- **Carpel tunnel syndrome**



Extra-articular Manifestations



- Skin – Rheumatoid nodules – vasculitis – splinter haemorrhages
- Eye - keratoconjunctivitis sicca
- Oral - Oral dryness and salivary gland swelling
- GIT - mesenteric vasculitis leading to intestinal infarction – bleeding and perforation
- Pulmonary - Pleural effusions
- Cardiac - thickening of the artery walls (atherosclerosis) and heart attacks
- Renal - mesangial glomerulonephritis
- Haematological: anaemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia etc.
- Neurological – Peripheral neuritis

Antirheumatoid Drugs

- Drugs which (except corticosteroids) can suppress the rheumatoid process and bring about a remission, but do not have nonspecific antiinflammatory or analgesic action - **Used in addition to NSAIDs**
- Disease Modifying Antirheumatoid Drugs (**DMARDs**) or Slow acting Antirheumatoid Drugs (**SAARDs**)
 - Slow onset and relapses
- Biologic Response Modifiers (BRMs)

Role of NSAIDs

- First line of Drug
- Symptomatic relief in pain, swelling, morning stiffness, immobility
- Preserve function

But

Little effect on the progression of bone and cartilage destruction

Available drugs for treatment

- **DMARDs:**

1. Immunosuppressants: Methotrexate, Azathioprine and Cyclosporine
2. Sulfasalazine
3. Chloroquine/Hydroxychloroquine
4. Leflunomide
5. Gold sod. Thiomalate, Auranofin
6. D-Penicillamine

- **BRM:**

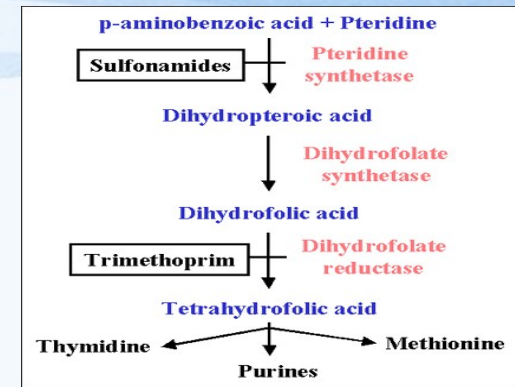
1. TNF α inhibitors: Etanercept, Infliximab and adalimumab
2. IL-1 antagonist: Anakinra

- **Adjuvant:** Corticosteroids, Prednisolone and others

Treatment Goals

1. Relief of pain
2. Reduction of swelling & stiffness
3. Protection of articular structures – cartilage damage
4. Maintenance of function
5. Control of systemic involvement

Methotrexate (Mtx)



- One of the oldest and highly efficacious antineoplastic drug
- Primarily kills cells in *S₁ phase* – inhibits DNA synthesis – also RNA and protein
- **Repeated doses** – Bone marrow toxicity - Megaloblastic anaemia, high doses - pancytopenia, desquamation and bleeding in GIT
- **Basically** - Inhibitor of **dihydrofolate reductase** enzyme (**50,000 times**) – immunosuppressant and potent antiinflammatory (blocks conversion of **DHFA** to **THFA** – de novo purine synthesis and amino acid interconversion) – affects lymphocyte and macrophage function

Methotrexate (Mtx)

- **MOA (antirheumatic):**

- Inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells
- Inhibition of proinflammatory cytokine production, chemotaxis and CMI reactions

- **Kinetics:** Absorbed orally (variable) - 70%, affected by food. Binds to plasma protein 50%, little metabolized and largely excreted unchanged in urine – renal diseases, interaction with **aspirin** and **probenecid** (plasma protein bound)

- **Dose:** 7.5 to 15 mg weekly Vs **15-30 mg per day**

- Takes **4- 6 weeks** for onset of action – preferred for initial treatment – including juvenile RA

Mtx – contd.

- **ADRs:** Nodulosis, Oral ulceration, GI disturbances, Hepatotoxicity, Megaloblastic anaemia – Bone marrow depression Inj. **Leucovorin** 24 hrs after each dose
 - **Cirrhosis** on prolonged administration – also chest infection
 - **CI:** pregnancy, lactation, liver disease, active infection, peptic ulcer etc.
- **Uses:**
 - **Autoimmune diseases:**
 - RA, Psoriasis, Pemphigus, Chronic active hepatitis, Myasthenia gravis
 - **Cancer:**
 - Choriocarcinoma, Leukemia, NHL, Ca Breast, Bladder, Head & neck Cancer, Osteogenic Sarcoma

Azathioprine

- Purine antimetabolite – acts after getting converted to 6-mercaptopurine by enzyme Thiopurine methyl transferase (TPMT)
- **MOA:** Suppressions of CMI – selectively affects differentiation and function of T-cells and natural killer cells – also suppresses inflammation
- **Drawback:** Smaller percentage of success rate of treatment – less commonly used
- **Uses:** Along with Corticosteroids - Steroid sparing effect – however not to be combined with Mtx
- **ADRs:** Bone marrow suppression, GI disturbances, infection risk, Lymphomas, fever, rash, and hepatotoxicity

Sulfasalazine

- Compound of **sulfapyridine** and **5-amino salicylic acid (5-ASA)** – antiinflammatory – used in **ulcerative colitis**
- **MOA:** **sulfapyridine** splits off in colon by bacterial action and active compound gets (**5-ASA** is active in ulcerative colitis) absorbed systemically – generation of **superoxide** radicals and **cytokine** liberation suppressed
- **Uses:** 2nd line of drug in RA
- **ADRs:** Neutropenia, Thrombocytopenia, Hepatitis

Chloroquine and hydroxychloroquine

- Antimalarial drugs – 50% of patients of RA remission
- Low toxicity but low efficacy – bony erosion not prevented
- Takes 3 - 6 months to for onset of action
- **MOA:**
 - Suppression of T-lymphocyte responses to mitogens
 - Decreased leukocyte chemotaxis
 - Stabilization of lysosomal enzymes
 - Trapping of free radicals (free radical scavenging)
- Accumulates in tissues (prolonged administration) – toxicity – retinal and corneal opacity
- **ADRs:** Rashes, graying of hair/loss, IBS, myopathy and neuropathy
- **Uses:** Mild no-responsive diseases – when 1 or few joints involved – combined with Mtx

Leflunomide

- **Immunomodulator** – comparable efficacy with Mtx – onset 4 weeks - can retard the disease progression
- **MOA:** Converted to active metabolite with long $t_{1/2}$ (2 weeks) – inhibits dihydrofolate reductase and pyrimidine synthesis
 - Antibody production by B-cells are depressed
 - Active metabolite- long half life – 2 weeks
 - Given in loading dose 100 mg 3 days followed by 20 mg OD
- **ADRs:** Diarrhoea, nausea, rashes, loss of hair, thrombocytopenia, leucopenia, chest infection and hepatic damage

The Gold Therapy



- Once very popular – before Mtx
- Used for arresting RA process and involvement of additional joints
- **MOA:** Reduces chemotaxis, phagocytosis, macrophage and lysosomal activity and inhibits **CMI**
- **Kinetics:** Bound to plasma and tissue proteins and stays in body **for years**
- **ADRs:** hypotension, dermatitis, stomatitis, kidney and liver damage and bone marrow depression - **diarrhoea**
- **Auranofin:** 29% gold - 25% bioavailability
- **D-Penicillamine:** gold like action – not used now - toxicity

BRMs – General points

- $\text{TNF}\alpha$ has key role in RA – activates membrane bound receptors TNFR_1 and TNFR_2 on surface of T-cells and macrophages etc.
- Exogenously administered inhibitors or antibodies can neutralize it and interrupt reaction
- Mainly suppress Macrophage and T-cells
- Inflammatory changes and bone erosion – slowed down and also new erosions slowed down
- Effective as monotherapy, but given with Mtx – in low Mtx responsive and highly rapidly progressing cases
- Few side effects – but opportunistic infections

Etanercept

- Recombinant fusion protein of **TNF-receptor** and **Fc portion of human IgG** – administered SC
 - Binds TNF- α molecules and also inhibits lymphotoxin- α
 - 50 mg weekly subcutaneously

Infliximab

- Infliximab is a **chimeric** (25% mouse, 75% human) IgG1 monoclonal antibody
- Binds with high affinity to soluble and membrane-bound TNF- α .
- 3–5 mg/kg every 8 weeks intravenous infusion
- **ADRs:** Acute reactions – fever, chills, urticaria, bronchospasm, anaphylaxis
 - Susceptibility to respiratory infections
- **Combined with Mtx – improved result**

Adalimumab

- Fully human IgG1 anti-TNF monoclonal antibody
- Complexes with soluble **TNF- α**
- Down-regulation of macrophage and T cell function
- 40 mg every 2 weeks; subcutaneously
- Advantage of combining with MTx:
 - Formation of human anti mAb is reduced
 - Duration of action increases

Common toxicities of BRMs

- Bacterial infections and macrophage-dependent infection (TB and other opportunistic infections)
- Leukopenias and vasculitis
- Demyelinating syndromes (multiple sclerosis)
- Hepatitis, activation of hepatitis B
- Infusion/ injection site reactions
- Rarely lymphomas

IL-1 antagonist

- **ANAKINRA**
- Recombinant human IL-1 receptor antagonist
- Clinically less effective than TNF inhibitors
- Used in refractory RA

Corticosteroids and RA

- Potent immunosuppressant and anti-inflammatory
- Any stage – 1st line as well as 2nd line
- Potent antiinflammatory action required – DMARD + NSAIDs + steroids
- Prompt symptomatic relief
- Low dose (5-10 mg prednisolone or equivalent)
- Symptomatic relief - do not arrest RA process – slows down joint destruction and bony erosion
- High dose steroids – severe systemic manifestations – organ threatening disease, vasculitis etc.
- Intra-articular steroids
- **REMEMBER!!! LONG TERM USE OF CORTICOSTEROIDS CARRIES SERIOUS DISADVANTAGES**

Remember !

- RA - There is no known way to prevent it !
- Methotrexate is one of the oldest highly efficacious antineoplastic drug and is also 1st line of drug in RA at low dose
- BRMs are usually combined with Mtx



Thank you

