# Drug treatment of rheumatoid arthritis

## Learning objectives

1. Aim of drug therapy
2. Use of non-steroidal anti-inflammatory drugs (NSAIDs)
3. Disease modifying anti-rheumatic drugs (DMARDs) and pharmacological details
4. Role of corticosteroids in rheumatoid arthritis
5. Use of anti-TNFα agents

**Rheumatoid arthritis** is a systemic autoimmune inflammatory disorder that is characterized by inflammation within synovial joints, causing pain, swelling and stiffness, it may progress to erosion and eventually to joint destruction.

Drug therapy is used:
1. To relieve pain, inflammation & muscle stiffness with NSAIDs
2. To modify course of disease or induce remission

**I. NSAIDs** are drugs of first choice in rheumatoid arthritis, they relieve symptoms but not slow disease progression.
e.g. aspirin (2-6g/day), indomethacin, piroxicam
***Gastric intolerance & PU may be reduced by concomitant use of $H_2$ antagonists or misoprostol, or using selective COX-2 inhibitors.**

**II. Disease modifying anti-rheumatic drugs (DMARDs)**
Are agents that reduce disease activity & prevent radiologically determined disease progression. They require 4-6 months of treatment for a full response.
*They decrease ESR, C-reactive protein & RF (rheumatoid factor) titer.

**A. Methotrexate (Rheumatrex)**
Is used as first line treatment in rheumatoid arthritis in 60% of patients at lower doses than those needed in cancer chemotherapy
**Mechanism of action**
It inhibits folate-dependent enzymes involved in purine biosynthesis, thus reducing lymphocyte proliferation. In recent years, it is thought that it inhibits 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, this will lead to increase the amount of AICAR that inhibits the degradation of adenosine. The increased plasma concentrations of adenosine, is

thought to mediate many anti-inflammatory effects like decreased TNFα production.
*It is the most rapid acting disease modifying drug, its therapeutic effect develops in 3-6 weeks, $t_{1/2}$=6-9h, is given orally once weekly & gradually increase the dose as bone marrow & liver function allows. Parenteral administration is possible, but is mainly used in pediatrics.
It is excreted mainly in urine & 30% in bile

**Clinical uses**

1. rheumatoid arthritis
2. as a cytotoxic drug (in high doses)
3. psoriatic arthritis
4. less commonly in connective tissue diseases like SLE

**Adverse effects** the most serious side effects are bone marrow toxicity, hepatic toxicity and pneumonitis.
***Regular (at least monthly) monitoring of full blood count and liver function test, is recommended.**
Mouth ulcers and nausea are common, and can be improved by co-administration of folic acid (5mg).

**Contraindications**

1. Moderate to severe renal impairment
2. Liver disease
3. Pregnancy because it is embryotoxic (both male & female patients should avoid conception for at least 6 months after cessation of methotrexate)
4. Breast feeding
5. Active infection

**B. Sulfasalazine** is a conjugate of mesalazine (5-aminosalicylic acid) coupled to sulfapyridine.
*It is poorly absorbed from gut but is cleaved by bacterial azoreductases in colon to release mesalazine & sulfapyridine.
*Mesalazine a) inhibits both COX & lipo-oxygenase enzymes
b) scavenge free radicals
c) inhibits production of pro-inflammatory cytokines & immunoglobulins
*Sulfapyridine component is the active moiety in rheumatoid arthritis, it reduces rheumatoid factor titers, inhibits IL-2 induced T-cell proliferation.

**Adverse effects** nausea, vomiting, headache & rash (common), hemolytic anemia , methemoglobinemia & SLE like syndrome(rare), it causes reversible infertility in male & not in female & is not teratogenic.

**C. Leflunomide**

It inhibits dihydro-orotate dehydrogenase, a mitochondrial enzyme required for synthesis of pyrimidines. It arrests proliferation of activated T-cells. It is licensed for treatment of rheumatoid arthritis and psoriatic arthritis.

**Adverse effects** diarrhea is the commonest, allergic reactions, alopecia, hypertension, leucopenia and hepatitis.

**D. Gold salts**

Its use is decreased as a result of its toxicity & increased use of methotrexate & more recently anti-TNFα biological agents

**e.g. Sodium aurothiomalate** by deep i.m. injection

**Auranofin** orally, is less effective but has less severe adverse effects

**Adverse effects**

Mouth ulcers, irreversible skin pigmentation, proteinurea, blood dyscrasias, hepatitis, peripheral neuropathy and pulmonary fibrosis.

**Contraindications** hepatic & renal disease, pregnancy & lactation.

**E. Hydroxychloroquine (antimalarial drug)**

Is used as an adjunct to other disease modifying drugs. The mechanism of action is unclear but in vitro found to reduce production of pro-inflammatory cytokines including TNFα & IL-β.

It is best to be used in mild disease. It is relatively non toxic.

**Adverse effects**

It is well tolerated, low incidence of side effects like GIT disturbances & rashes. Retinal toxicity rarely occurs with long term use.

**Cautions & contraindications**

Hepatic & renal impairment, G6PD deficiency, breast feeding.

**III. Adrenal corticosteroids**

They may be considered as DMARD because they reduce disease severity & associated damage but its clinical effects are noticeable within 24h.

*Is usually given orally (Prednisone & Prednisolone)

Steroids are used for the following conditions:

1. To provide in-term relief of inflammatory symptoms during weeks that is taken by DMARDs
2. In severe cases like vasculitis or rheumatoid lung
3. During failure of DMARDs or development of intolerable side effects
4. Intra-articular injection of steroids when one or two joints are involved

**IV. Other immunosupressants**

Azathioprine, cyclosporin, cyclophosphamide, are used in resistant cases

**V. Interference with cytokine expression or signaling**

Cytokines play a central role in immune response & in rheumatoid arthritis, TNF-α appears to be at the heart of inflammatory process.

**Anti-TNFα agents** include:

**1. Infliximab** is humanized monoclonal IgG1 Abs, causes down regulation of macrophages & T-cell function, given with methotrexate by iv infusion.

**2. Etanercept** is a recombinant molecule, licensed to be used sc in rheumatoid arthritis in adults.

**Short essay questions**

1.Interference with cytokine expression can be utilized in treatment of rheumatoid arthritis. Comment

2.What is meant by DMARDs? Give 2 examples. Write on the mechanism of action of both

**MCQ**

1.Drugs useful in rheumatoid arthritis

**F** a.Colchicine
**T** b.Methotrexate
**F** c.Allopurinol
**T** d.Hydroxychloroquine
**F** e.Abciximab

2.DMARDs which are relatively sage in pregnancy

**F** a.Methotrexate
**T** b.Hydroxychloroquine
**F** c.Gold salts
**T** d.Sulfasalazine
**F** e.Probenecid