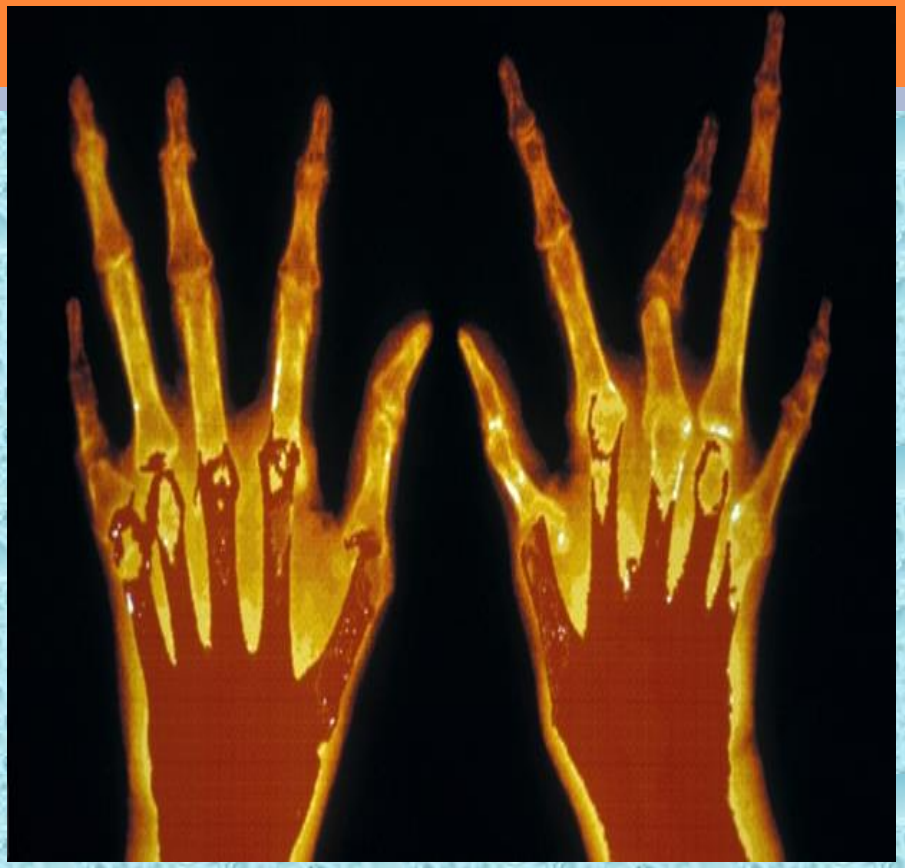
Disease Modifying Anti-rheumatic drugs



ILOS

At the end of the lecture the students should:

- Know the pathogenesis of rheumatoid joint damage
- Emphasize the rational for early treatment of RA
- Define and classify DMARDs
- Compare and contrast the advantages and disadvantages of NSAIDs, Steroids and DMARDs in treatment of RA
- Know some examples of drugs related to DMARDs.
- Explore the pharmacokinetic and pharmacodynamic aspects of the selected DMARDs
- Describe the mechanism of action , specific clinical uses, adverse effects of individual drugs.

EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

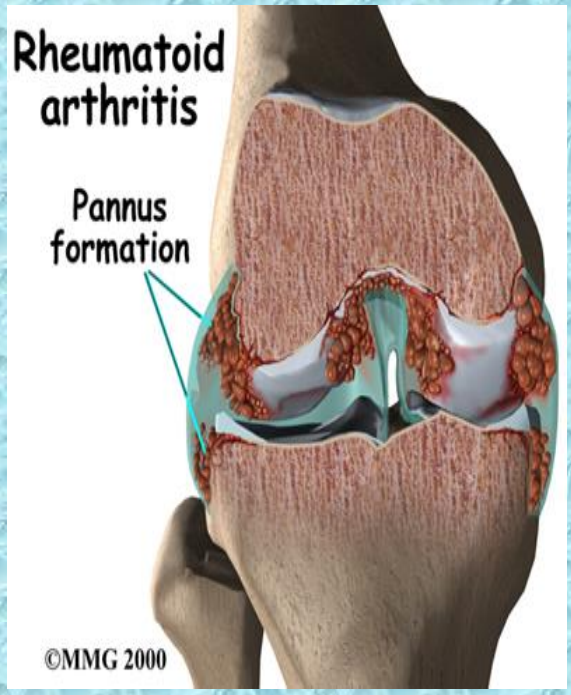
Affects 1-2 % of the adult population

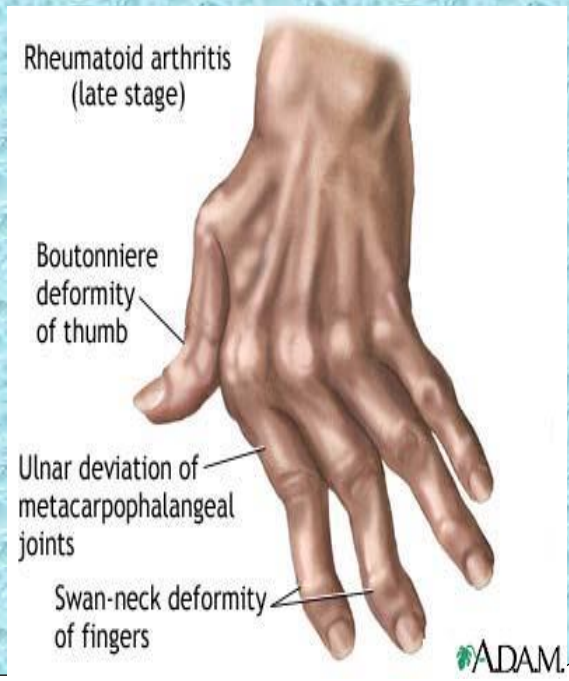
Is more common among women than in men (2-3 times)

Usually appears between ages 25 and 40 years

The incidence also increases with age, peaking between the 4th and 6th decades

Causes pain, disability and loss of function





RHEUMATOID ARTHRITIS

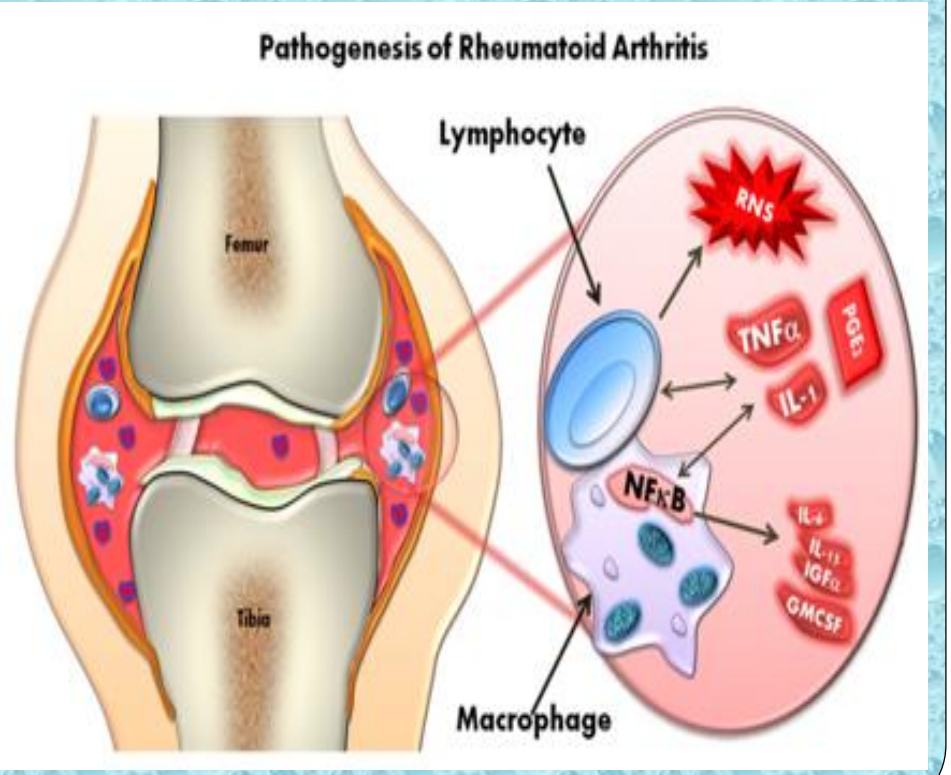
RA is a chronic **autoimmune** disorder in which the normal immune response is directed against an individual's own tissue leading to:-

Decline in functional status

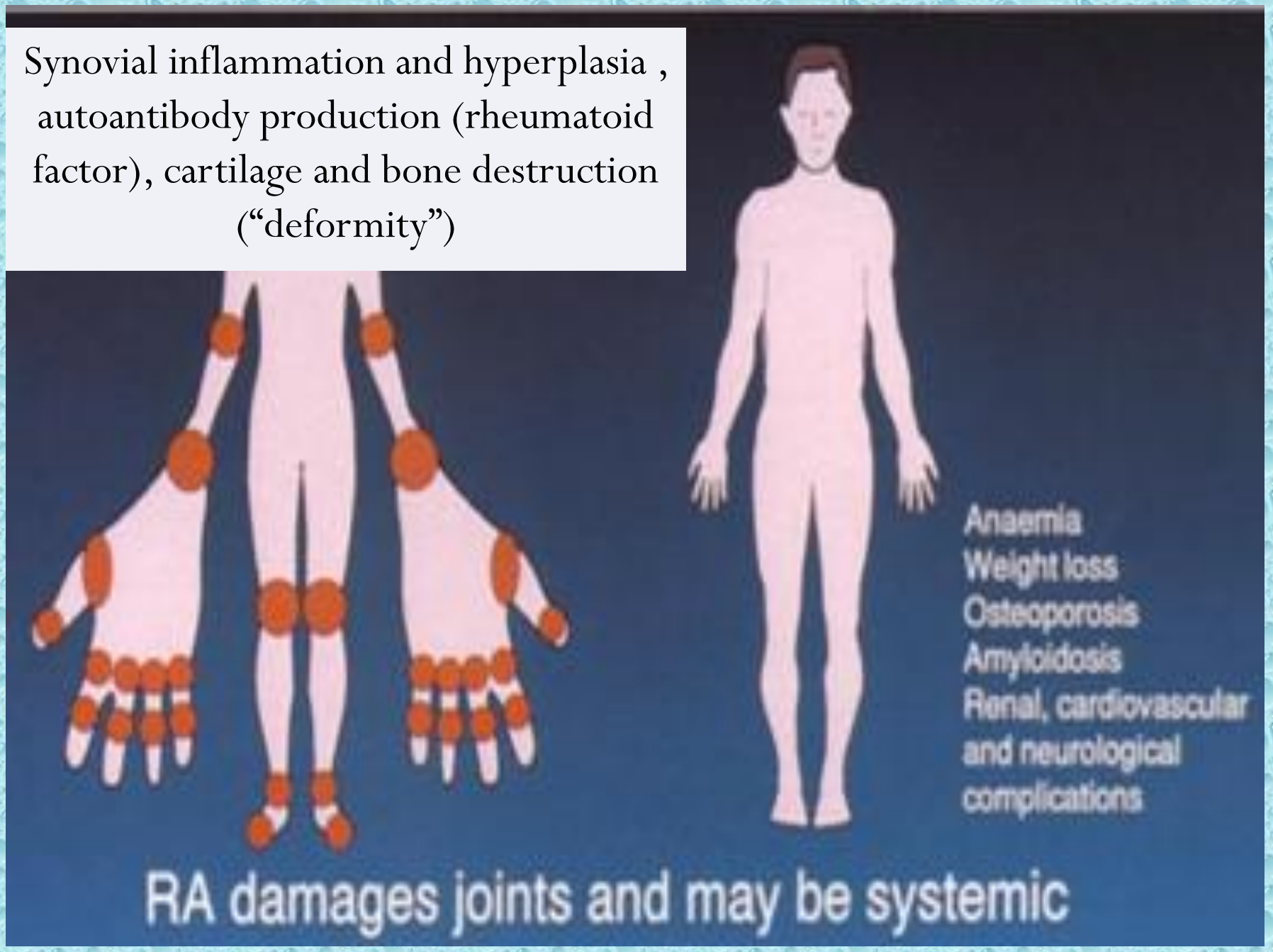
Work disability & socioeconomic costs

Systemic complications

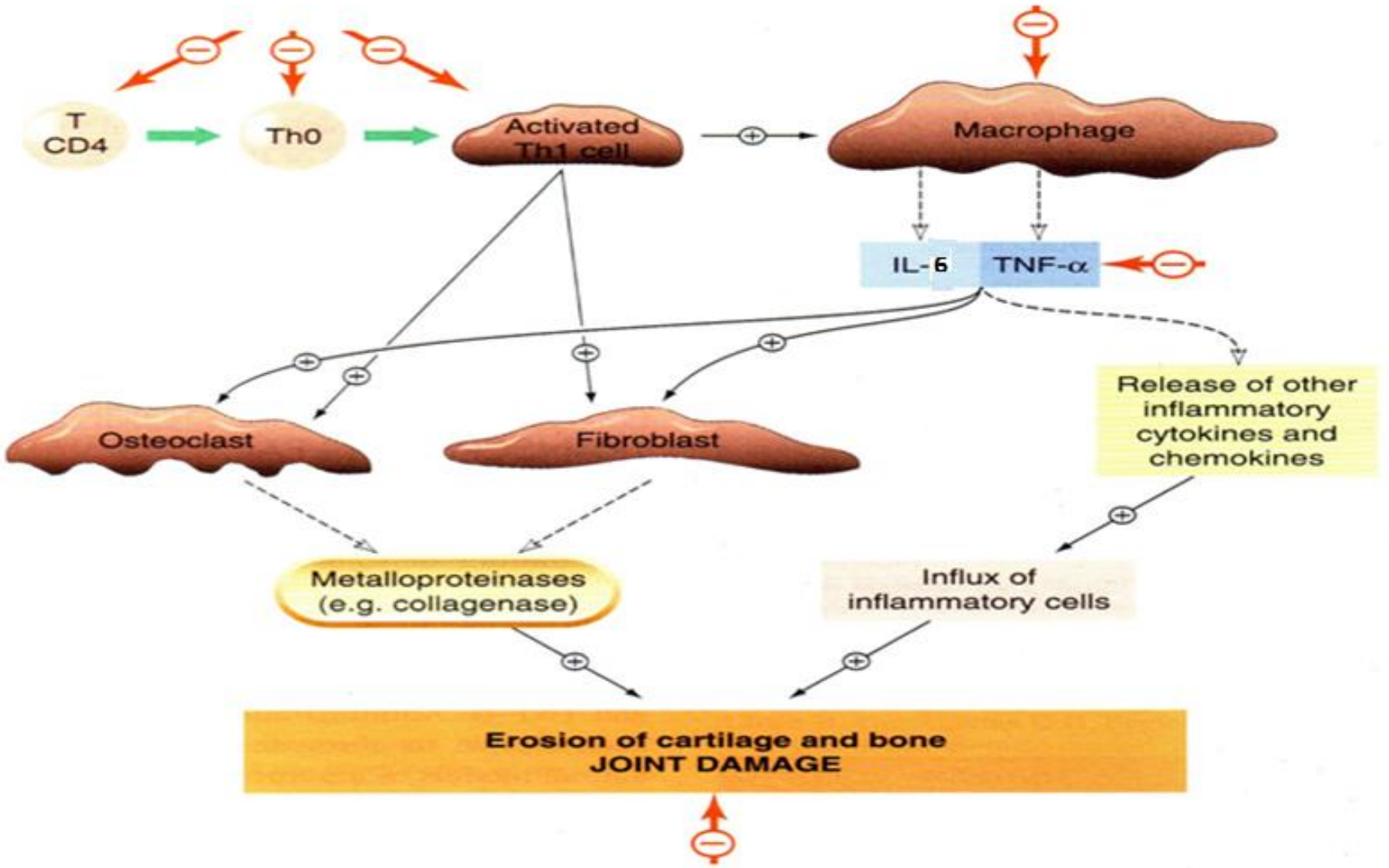
Co-morbidity & Increased mortality



Synovial inflammation and hyperplasia , autoantibody production (rheumatoid factor), cartilage and bone destruction (“deformity”)

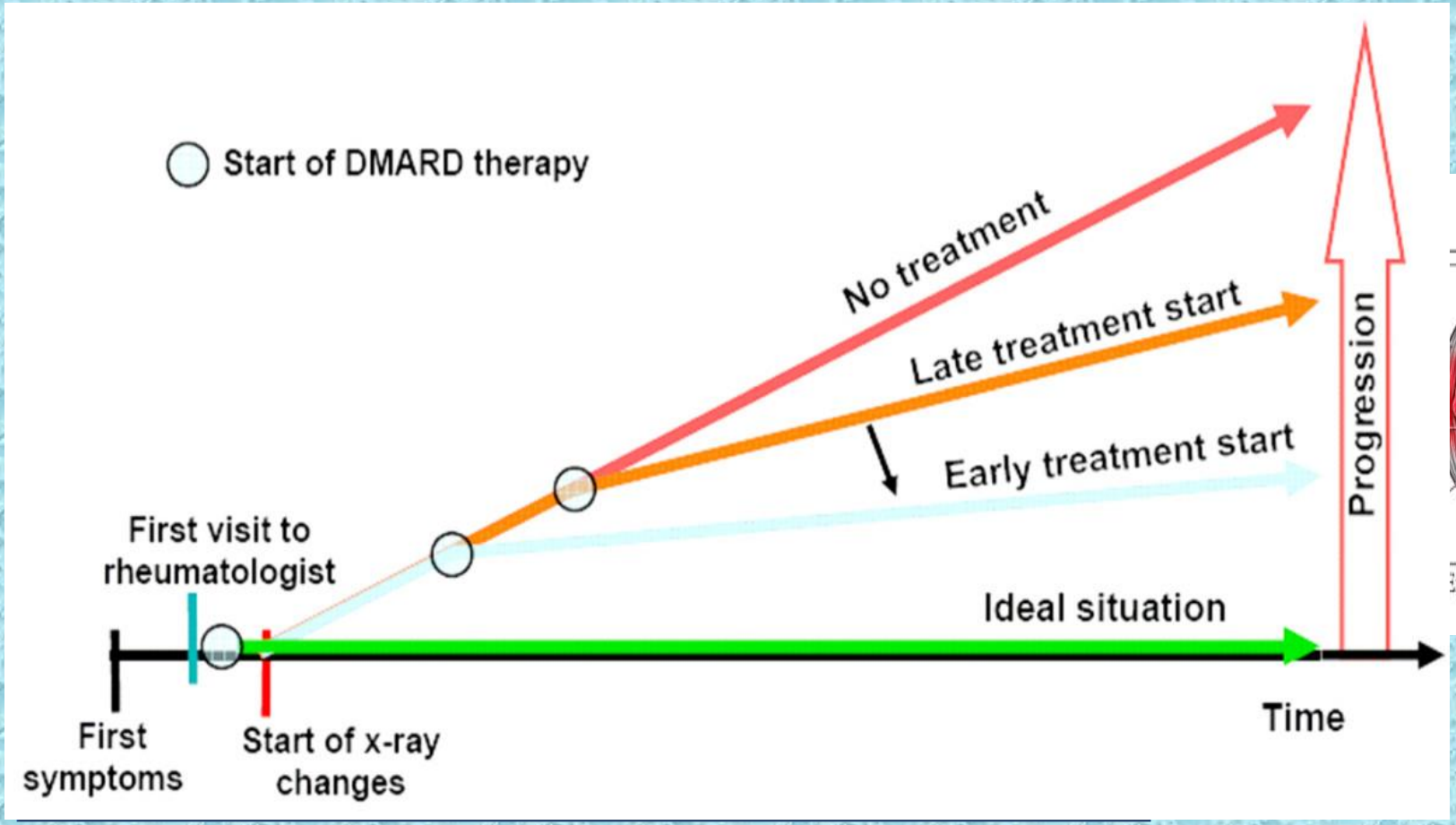


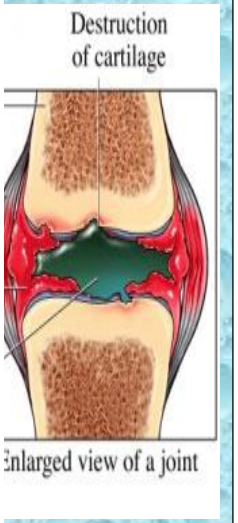
PATHOGENESIS



Mechanism of action: not clearly known

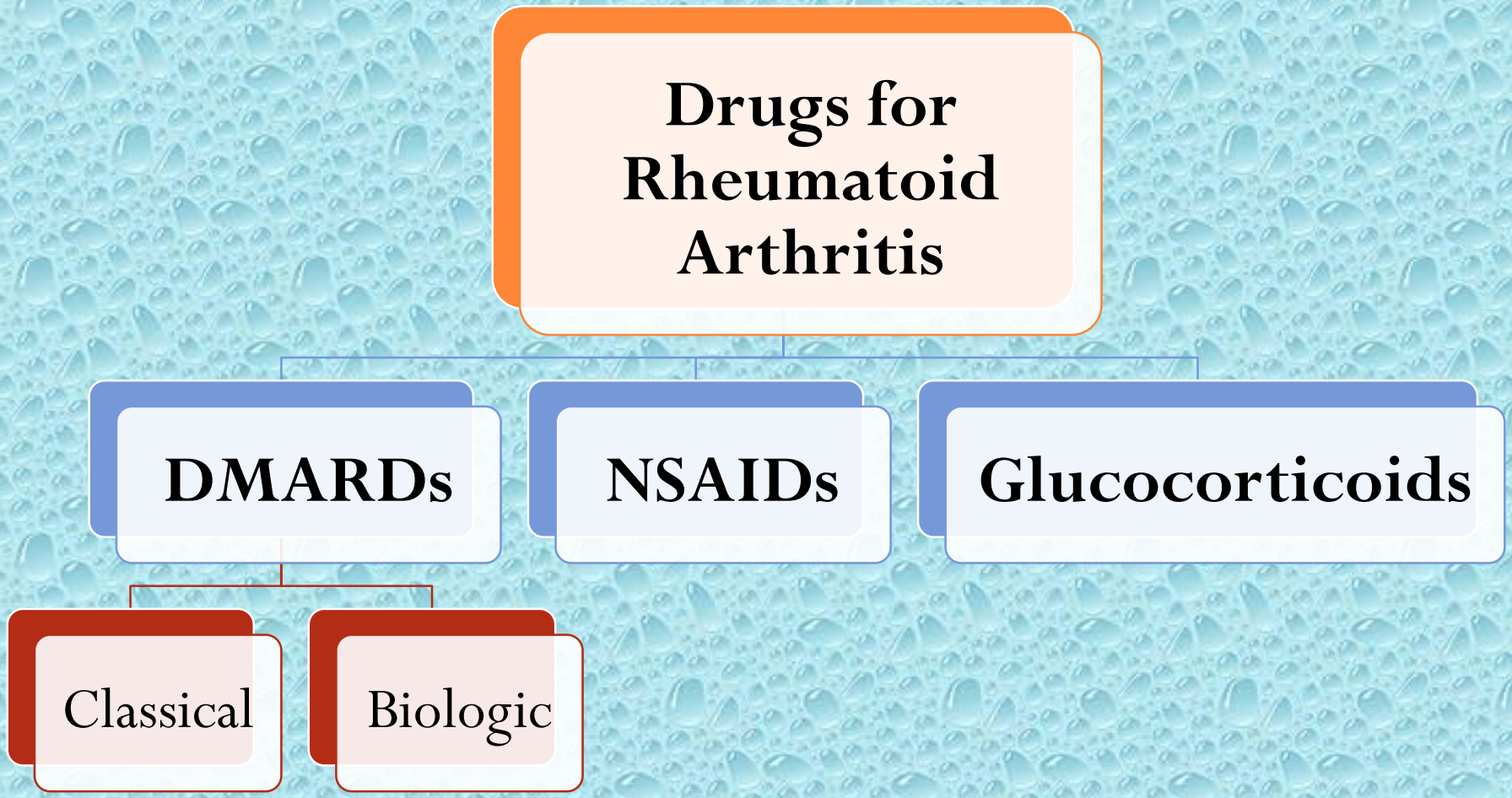
RATIONAL FOR EARLY TREATMENT





Early and aggressive treatment may have long-term benefits

CLASSIFICATION



NSAIDS

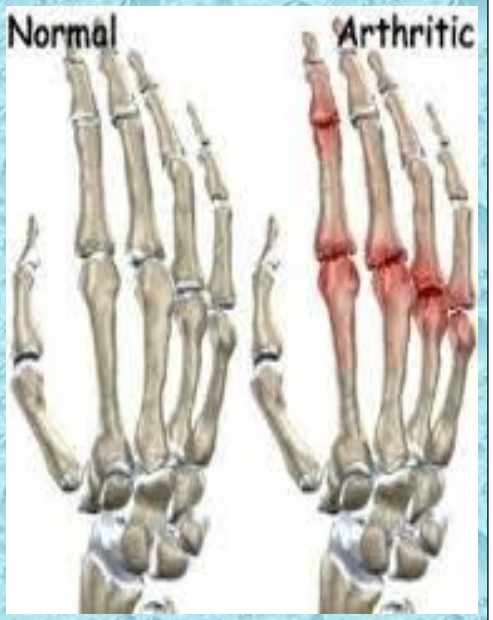
Rapid onset of action

Used in acute cases to relief inflammation & pain

Provide partial relief of pain and stiffness

Do not slow the progression of the disease

Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.



GLUCOCORTICOIDS

Anti-inflammatory drugs with an intermediate rate of action (slower than NSAIDs but faster than other DMARDs).

May be administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy

Reserved for temporary control of severe exacerbations and long-term use in patients with severe disease not controlled by other agents.

Corticosteroids are too toxic for routine chronic use

Comparison between NSAIDs & DMARDs

DMARDs	NSAIDs
• Slow onset of action	• Rapid onset of action
• Arrest progression of the disease	• No effect
• Prevent formation of new deformity	• Can not stop formation of new deformity
• Used in chronic cases when deformity is existing	• Used in acute cases to relief inflammation & pain

CLASSIFICATION OF DMARDS

DMARDs

act on the immune system to slow the progression of RA

Biologic

Infliximab
Tocilizumab

Classical

Methotrexate
Hydroxychloroquine

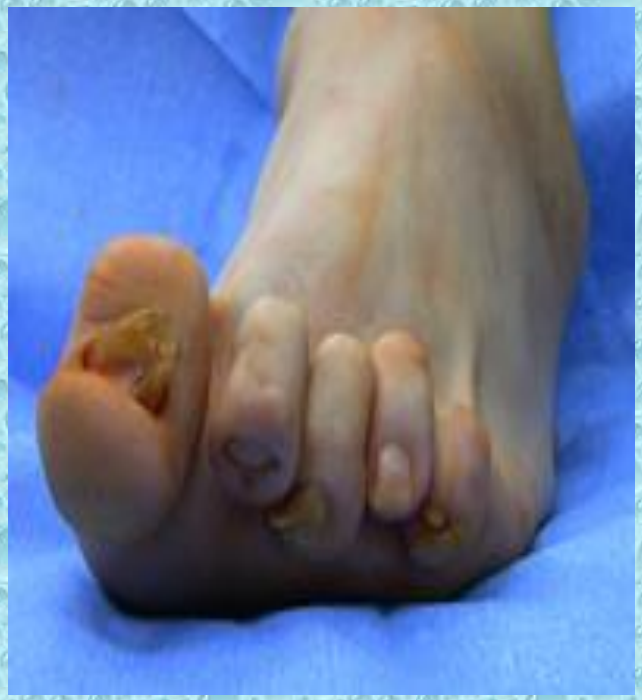
GENERAL FEATURES

Used when the disease is progressing & causing deformities

Can not repair the existing damage, but prevent further deformity

Have no analgesic effects

Their effects take from **6 weeks up to 6 months** to be evident



METHOTREXATE

"Gold standard" for DMARD therapy & is the first-line DMARD for treating RA and is used in 50–70% of patients

Active in RA at much lower doses than those needed in cancer chemotherapy

MECHANISM

Inhibits dihydrofolate reductase

Reduces thymidine & purine synthesis

But at the dosages used for the treatment of RA, methotrexate has been shown **to stimulate adenosine release from cells,** producing an anti-inflammatory effect.

Inhibition of polymorphonuclear chemotaxis

Inhibition of T-Cells (cell-mediated immune reactions)

METHOTREXATE

PHARMACOKINETICS

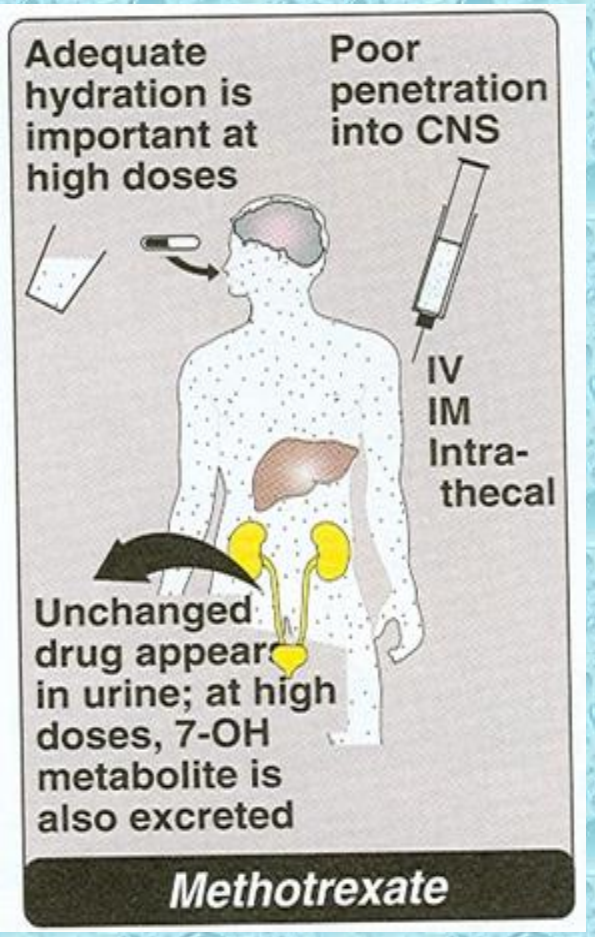
Approximately 70% absorbed after oral administration

Metabolized to a less active hydroxylated product

Half-life is usually only 6–9 hours

Excreted principally in the urine, but up to 30% may be excreted in bile.

Given 7.5 – 30 mg weekly



ADRS

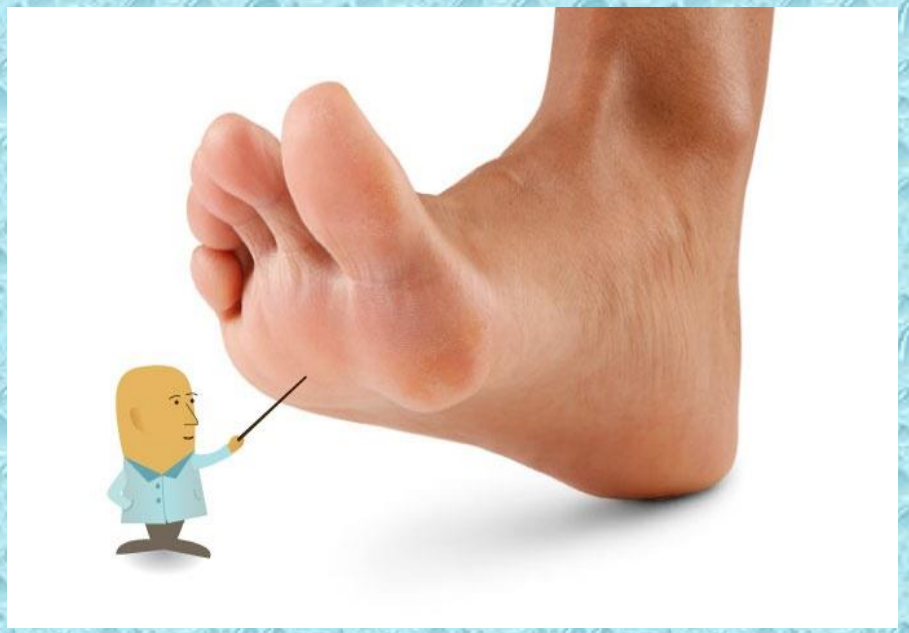
Bone marrow suppression

Dyspepsia, Mucosal ulcers

Hepatotoxicity

Pneumonitis

Teratogenicity



Leukopenia, anemia, stomatitis, GI ulcerations, and alopecia are probably the result of inhibiting cellular proliferation

Folic acid reduces GI & bone marrow effects

Monitoring:-Full blood count, ALT, Creatinine

HYDROXYCHLOROQUINE

MECHANISM

Stabilization of lysosomal enzyme activity

Trapping free radicals

Suppression of T lymphocyte cells response to mitogens

Inhibition of leukocyte chemotaxis

HYDROXYCHLOROQUINE

PHARMACOKINETICS

Rapidly absorbed and 50% protein-bound

Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes

Elimination half-life of up to 45 days

Highly concentrated within cells → increases intra-cellular pH

HYDROXYCHLOROQUINE

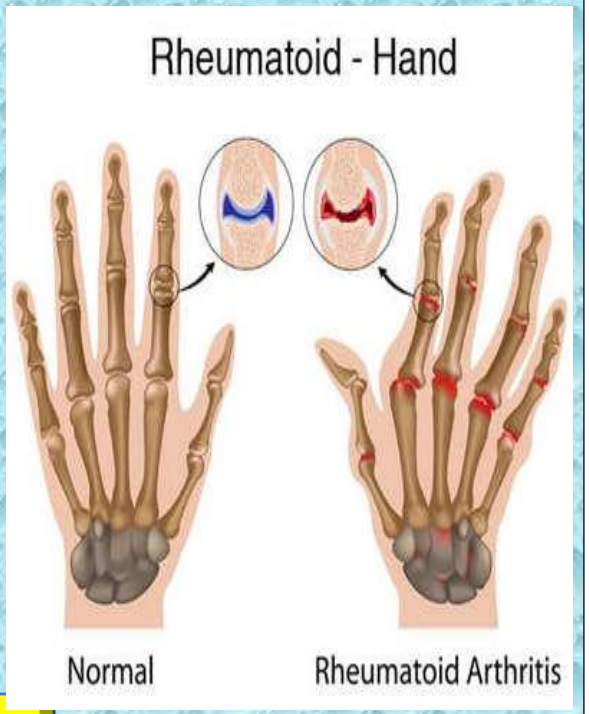
CLINICAL USES

Has not been shown to delay radiographic progression of disease

Generally used for treatment of early, mild disease or as adjunctive therapy in combination with other **DMARDs**.

Used in increasing methotrexate efficacy

6 month response, mild anti-rheumatic effect



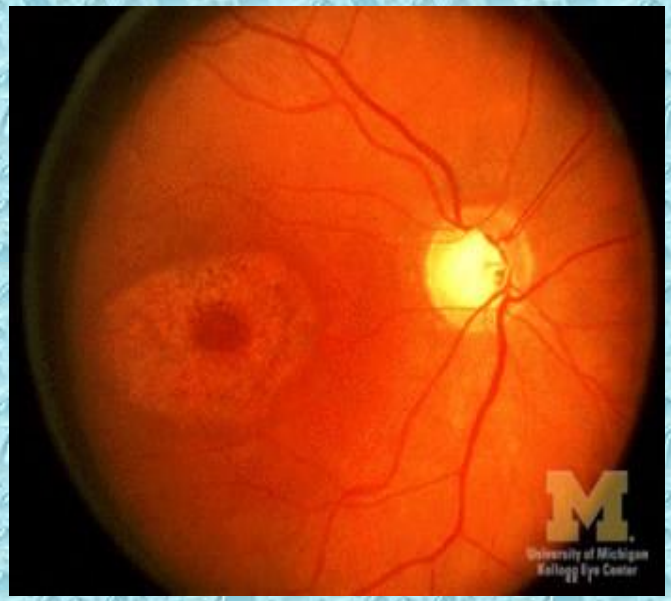
ADRS

Least toxic, no blood tests is required

Nausea & vomiting

Corneal deposits

Irreversible retinal damage



Ophthalmologic evaluation every 6 months

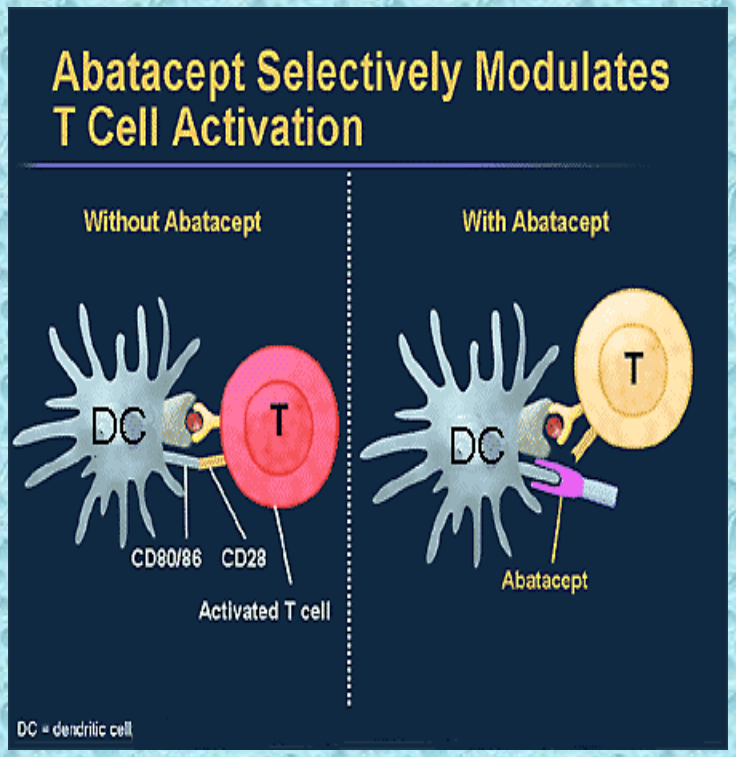
BIOLOGIC DISEASE MODIFIER

Genetically engineered drugs that are used to modify imbalances of the immune system in autoimmune diseases.

Some of these agents block, or modify the activity of selected cells in the immune system

Others work by blocking cytokines, that send signals between those cells

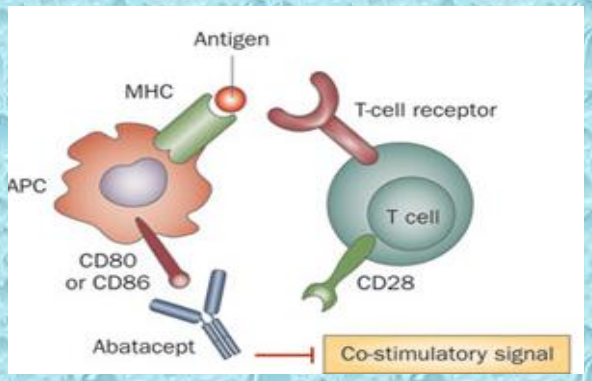
They are expensive

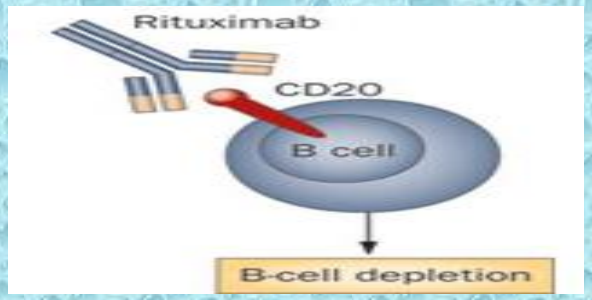


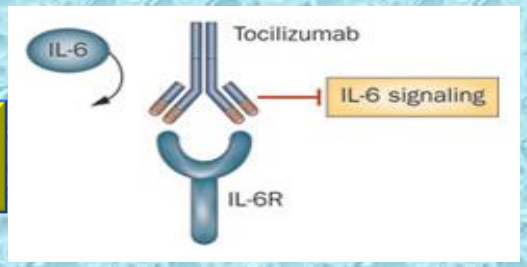
BIOLOGIC DISEASE MODIFIER

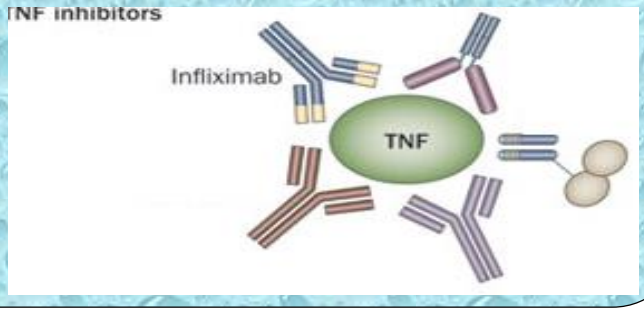
CLASSIFICATION

- ❖T-cell modulating drug (Abatacept)
- ❖B-cell cytotoxic agent (Rituximab)
- ❖Anti-IL-6 receptor antibody (Tocilizumab)
- ❖TNF- blocking agents (Infliximab)



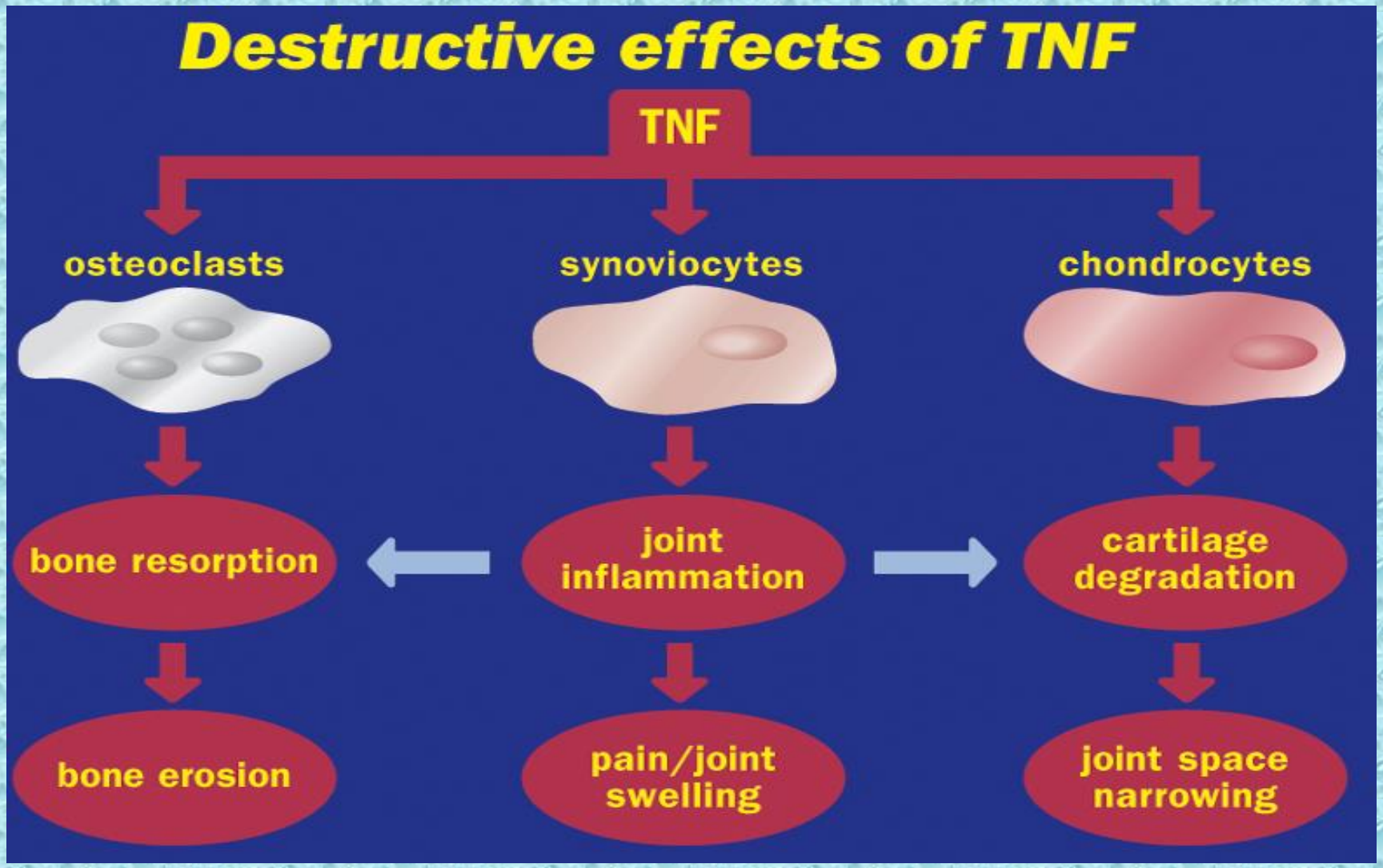






TNFα BLOCKING AGENTS

ROLE OF TNF ON JOINT DESTRUCTION



TNFα BLOCKING AGENTS

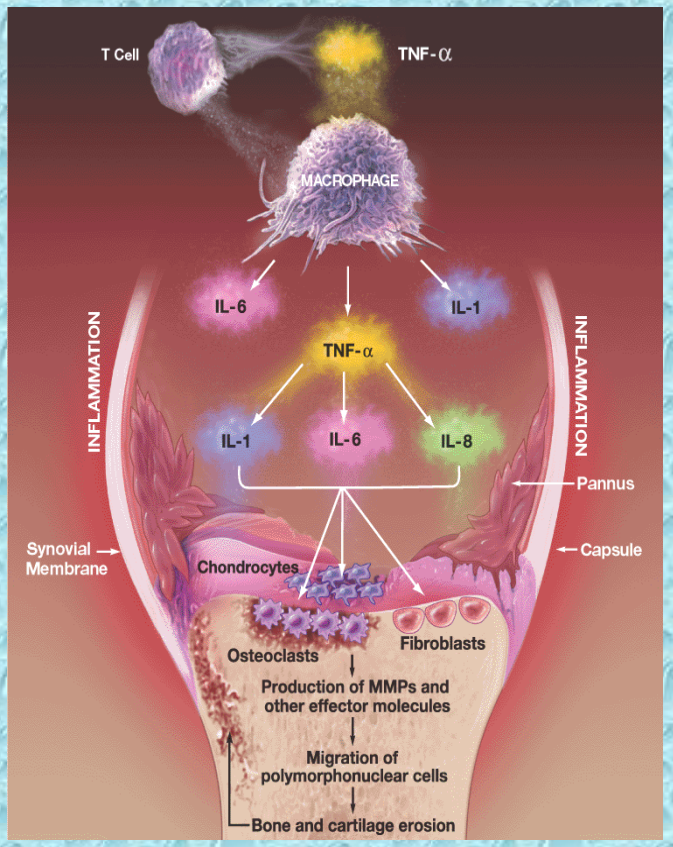
INFLIXIMAB

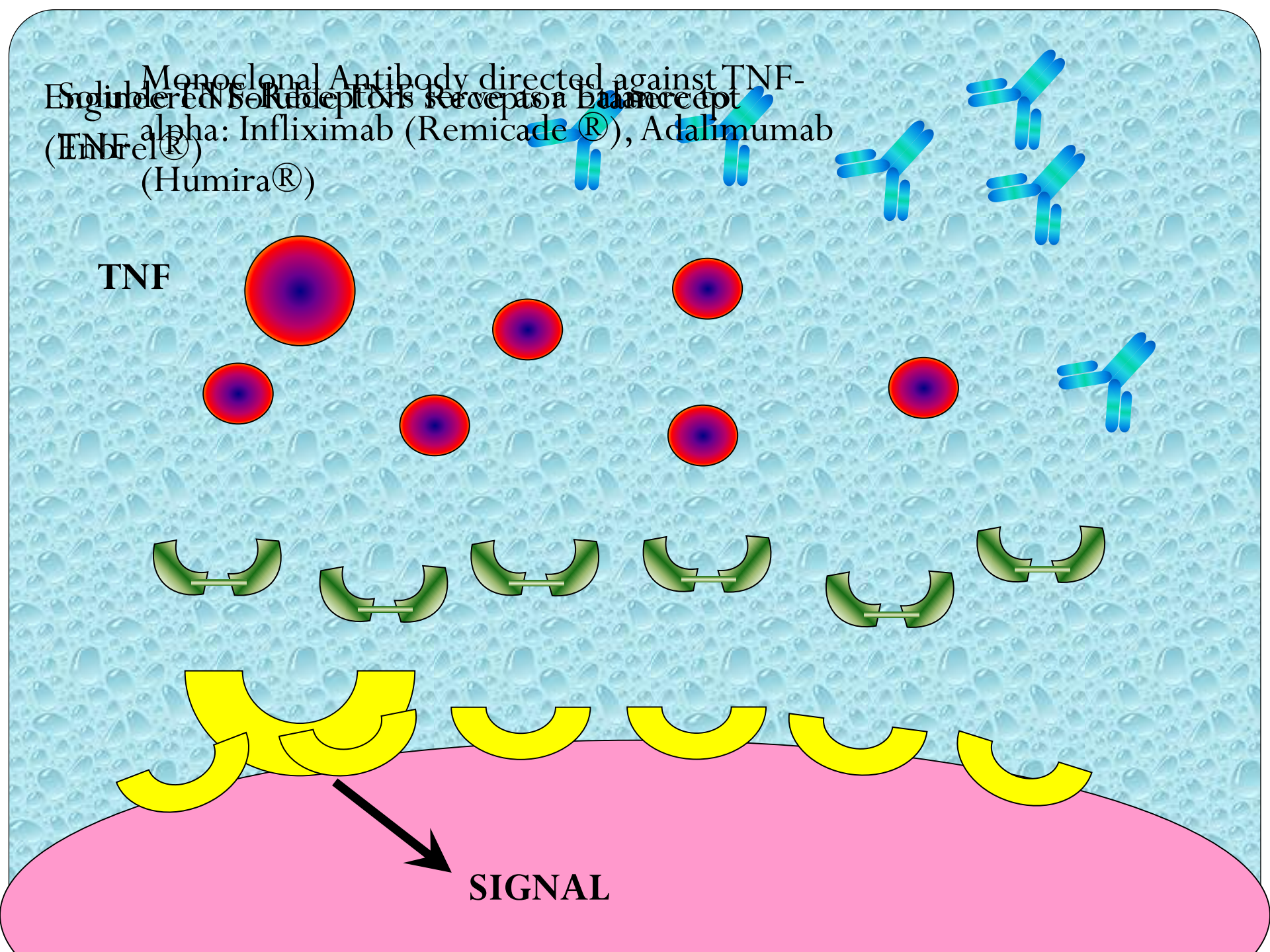
A chimeric IgG_1 monoclonal antibody (25% mouse, 75% human)

MECHANISM

It complexes with soluble TNF-α (and possibly membrane- bound TNF-α)and prevents its interaction with the cell surface receptors

This results in down-regulation of macrophage and T-cell function.




Monoclonal Antibody directed against TNF-alpha: Infliximab (Remicade ®), Adalimumab (Humira®)
Engineered Soluble TNF Receptor Fusion Protein (Enbrel®)
TNF
SIGNAL

INFLIXIMAB

PHARMACOKINETICS

Given as an intravenous infusion with "induction" at 0, 2, and 6 weeks and maintenance every 8 weeks thereafter,

Terminal half-life is 9–12 days

After intermittent administration elicits human antichimeric antibodies in up to 62% of patients

Concurrent therapy with **methotrexate** decreases the prevalence of human antichimeric antibodies

INFLIXIMAB

CLINICAL USES

Infliximab is approved for use in RA, Ankylosing spnodilytis, Crohn's disease, ulcerative colitis,

It could be combined with methotrexate, hydroxychloroquine and other non biological DMARDs

INFLIXIMAB

ADRS

- Upper respiratory tract infections
- Activation of latent tuberculosis
- Infusion site reaction
- Headache
- Cough
- Increase the risk of skin cancers—including melanoma

TOCILIZUMAB

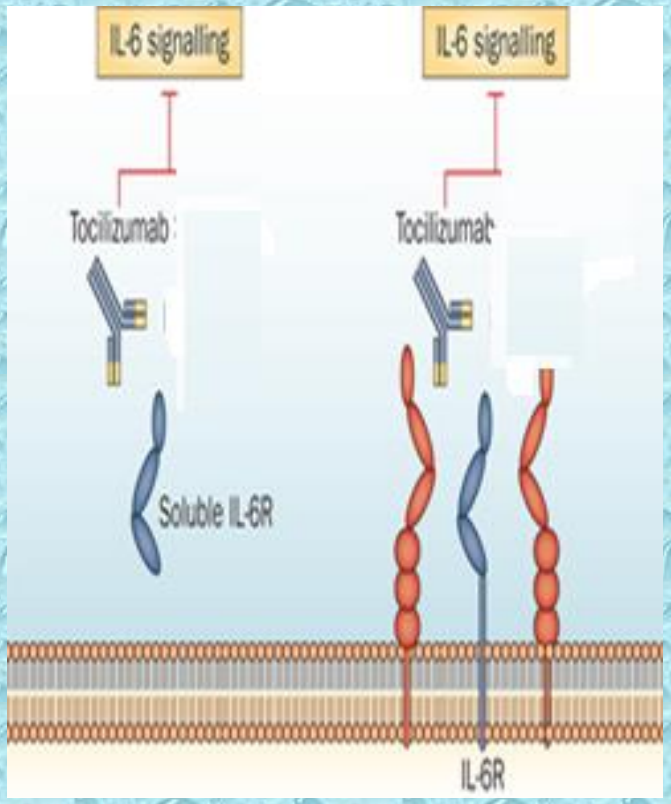
IL-6 is a proinflammatory cytokine implicated in the pathogenesis of RA,

With detrimental effects on both joint inflammation and cartilage damage

Tocilizumab binds to membrane IL-6 receptors, **blocking the activity of IL-6** in mediating signals that affect cytokine production, osteoclast activation

Half-life is dose-dependent

Given as monthly IV



TOCILIZUMAB

CLINICAL USES

Used as monotherapy in adult with rheumatoid arthritis or in children over 2 years with systemic juvenile arthritis

In combination with methotrexate or other non biologic anti-rheumatic drugs in patients with active rheumatoid arthritis not responding to TNF blockers or other biologic drugs

TOCILIZUMAB

ADRS

- Infusion reactions
- Serious infections (bacterial, tuberculosis ,fungal)
- Increase in cholesterol level
- Neutropenia, and thrombocytopenia (reversible upon stopping the drug)
- Decrease in WBCs
- Increase in liver enzymes
- Blood tests will be used monthly for increase in cholesterol, liver enzymes & decrease in WBCs

TOCILIZUMAB

DRUG INTERACTIONS

IL-6 inhibits CYP450

Tocilizumab restores the activity of the enzyme (essential for the metabolism of some drugs such as cyclosporine, warfarin).

BEST WISHES