Disease-modifying antirhumeatic drugs DMARDS

EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

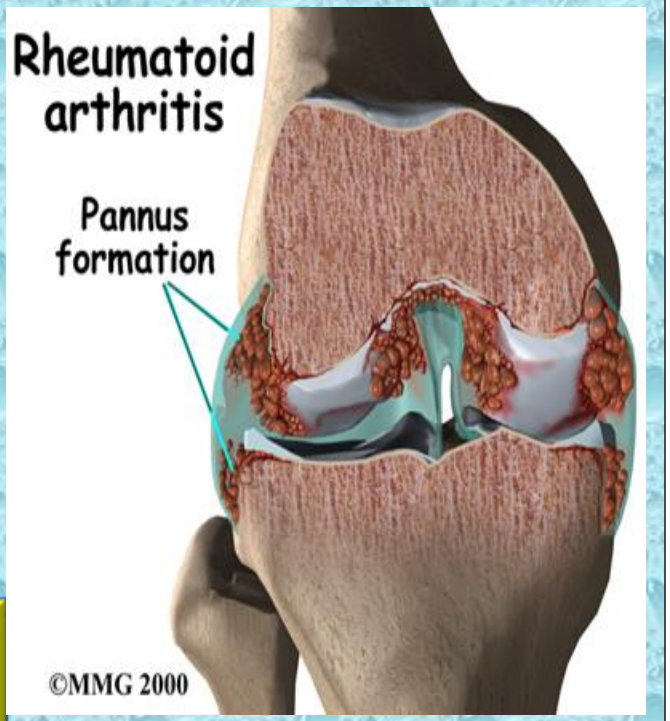
Affects 1-2% of the adult population

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

Usually appears between ages 25 & 40 years

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

Causes pain, disability & loss of function



DMARDS

ILOS

Define DMARDs & Emphasize the rational for early treatment of RA

Classify drugs used for treatment of RA

Compare & contrast the advantages and disadvantages of NSAIDs, Steroids & DMARDS in treatment of RA

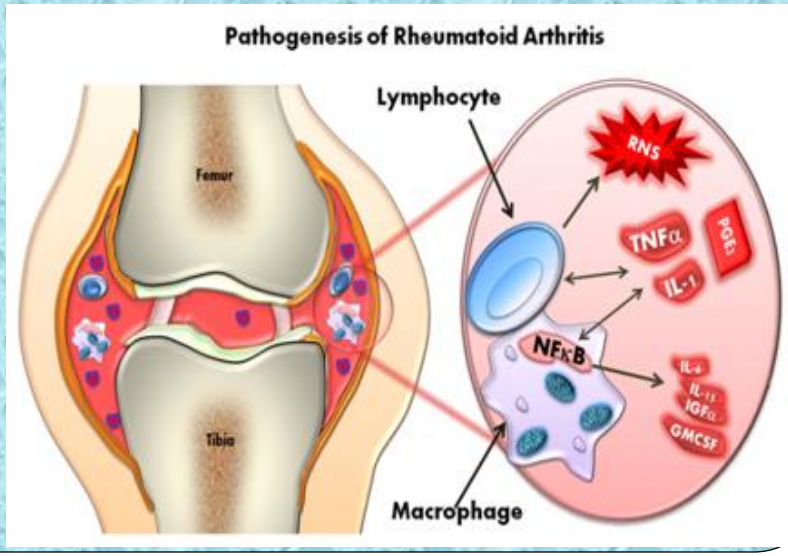
Explore the pharmacokinetic aspects & pharmacodynamic effects of selected DMARDs

DMARDs are a class of drugs indicated for the treatment of several inflammatory arthritis, including rheumatoid arthritis (RA), as well as for the management of other connective tissue diseases.

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
- Co-morbidity
- Increased mortality



RATIONAL FOR EARLY TREATMENT

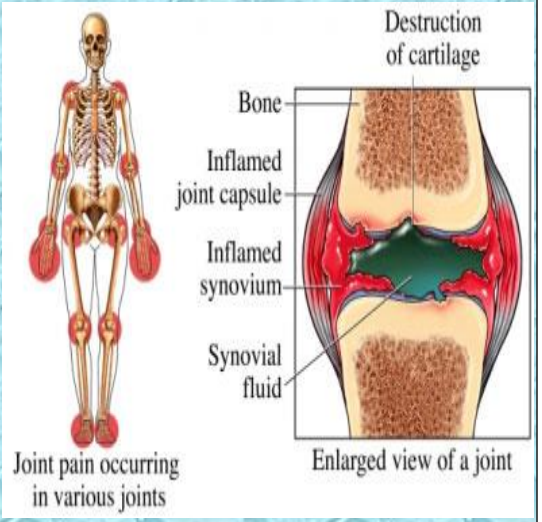
Joint damage is an early phenomenon of rheumatoid arthritis

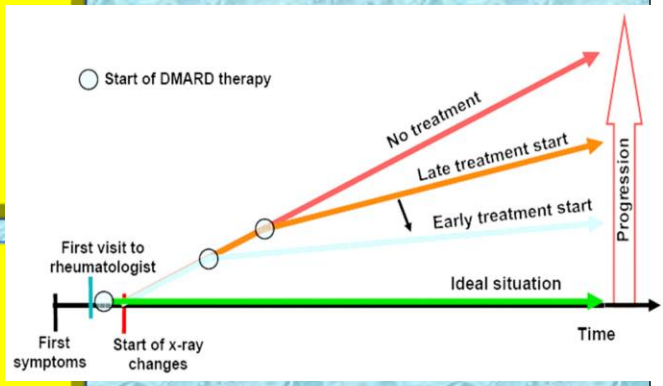
Joint erosions occur in up to 93% of patients within less than 2 years of disease activity

Disability occurs early – 50% of patients with RA will be work disabled at 10 years

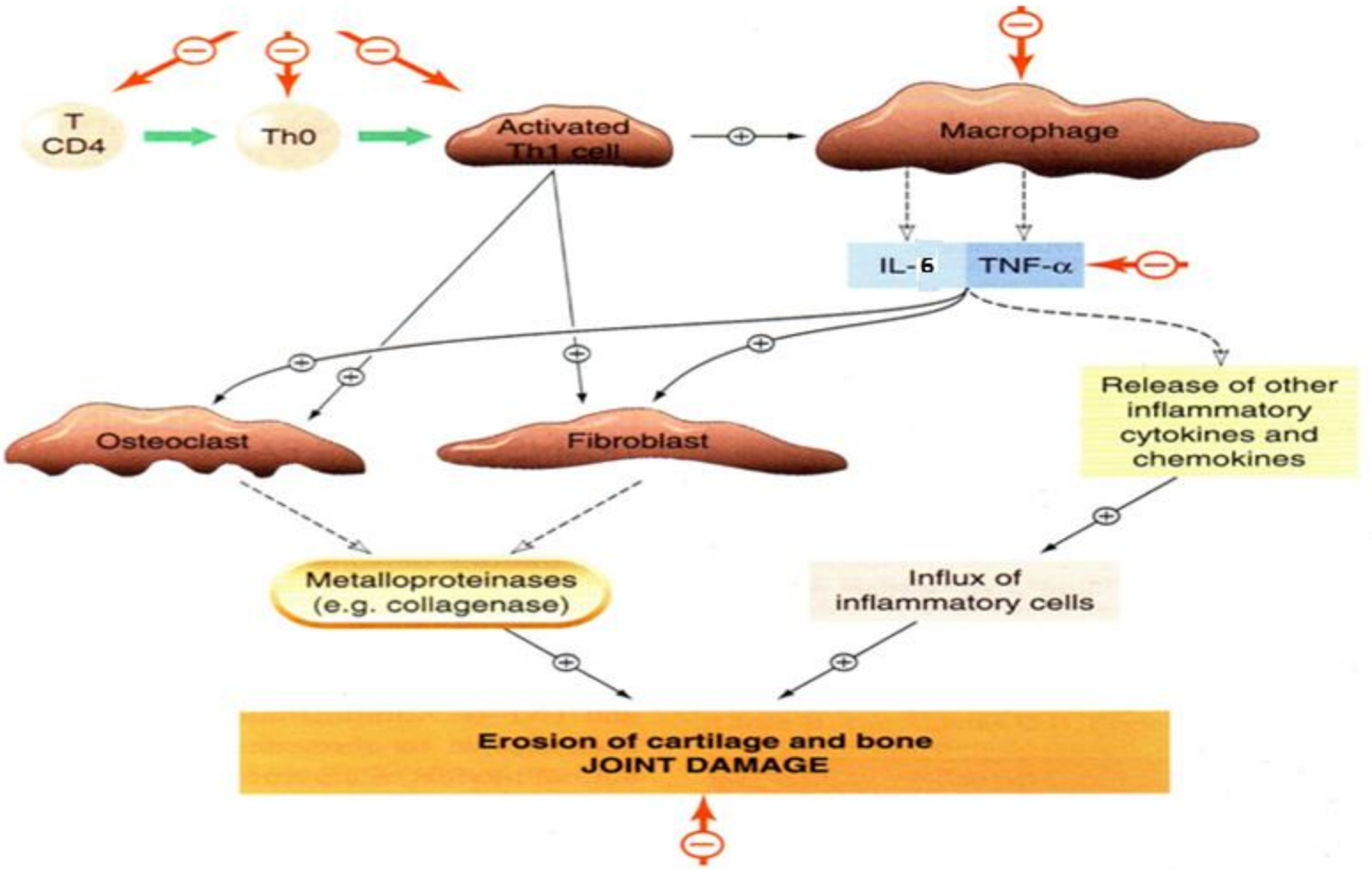
Severe disease is associated with increased mortality

Early & aggressive treatment may have long-term benefits



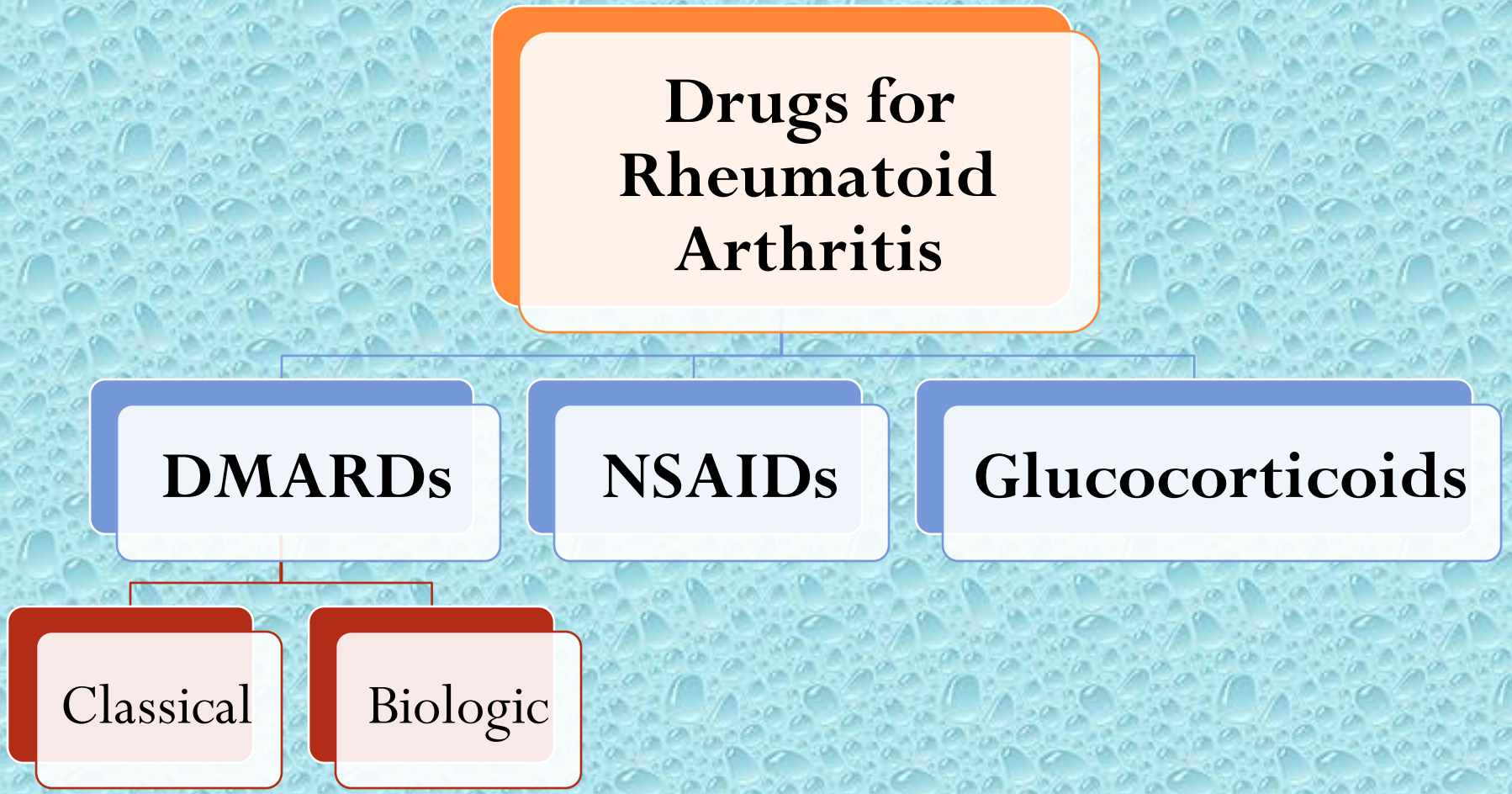


PATHOGENESIS



Mechanism of action: not clearly known

CLASSIFICATION



NSAIDS

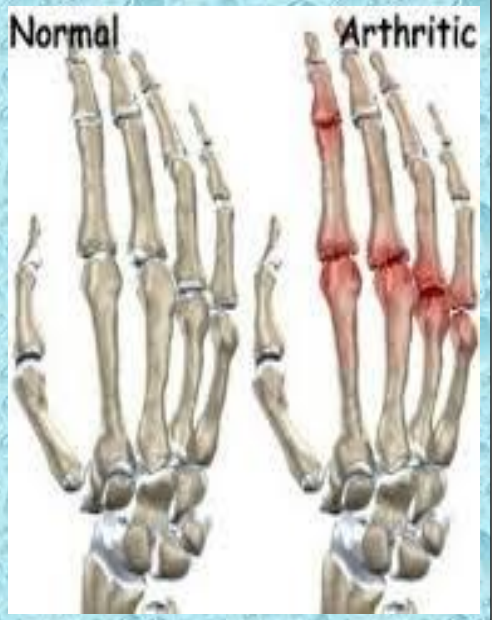
Do not slow the progression of the disease

Provide partial relief of pain and stiffness

Rapid onset of action

Used in acute cases to relief inflammation & pain

Chronic use should be minimized due to the possibility of side effects, including gastritis, peptic ulcer disease & 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 & long-term use in patients with severe disease not controlled by other agents

Corticosteroids are too toxic for routine chronic use.

CLASSIFICATION OF DMARDS

DMARDS

Biologic

Infliximab

Tocilizumab

Classical

Methotrexate

Hydroxychloroquine

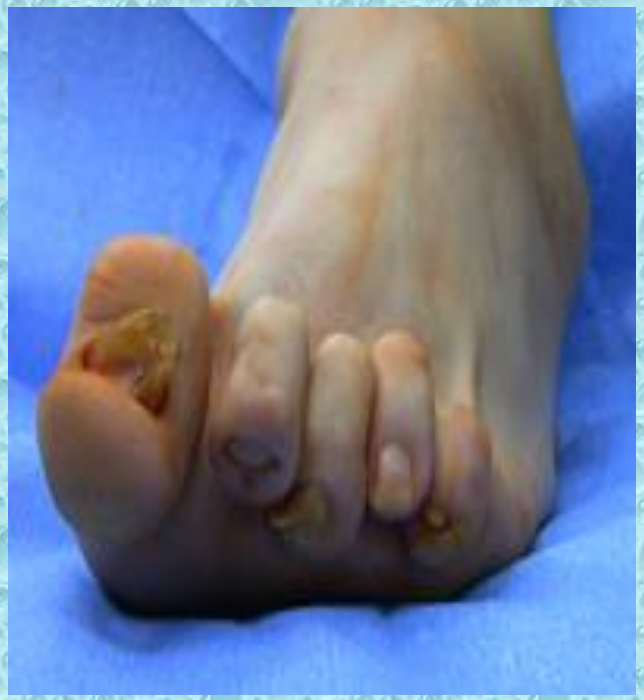
GENERAL FEATURES

Used when the disease is progressing & causing deformities

Can not repair the existing damage, but prevent further deformity

Have no analgesic effects

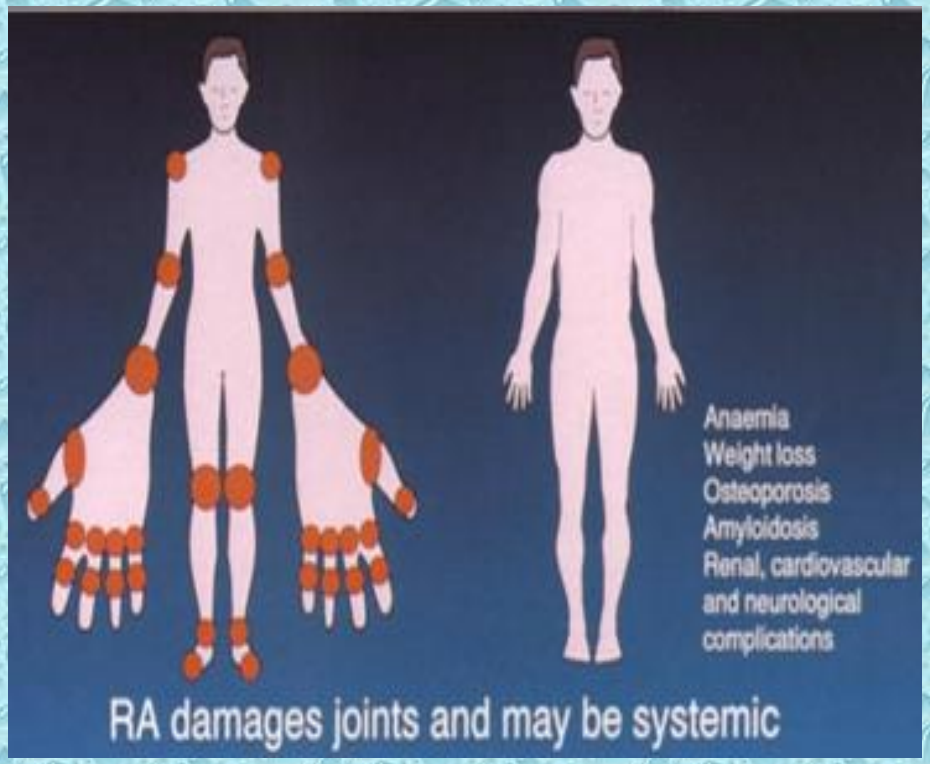
Their effects take from 6 weeks up to 6 months to be evident



METHOTREXATE

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

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



METHOTREXATE

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 chemotaxis of polymorphonuclear leukocytes
- Inhibition of T-Cells (cell-mediated immune reactions).

METHOTREXATE

PHARMACOKINETICS

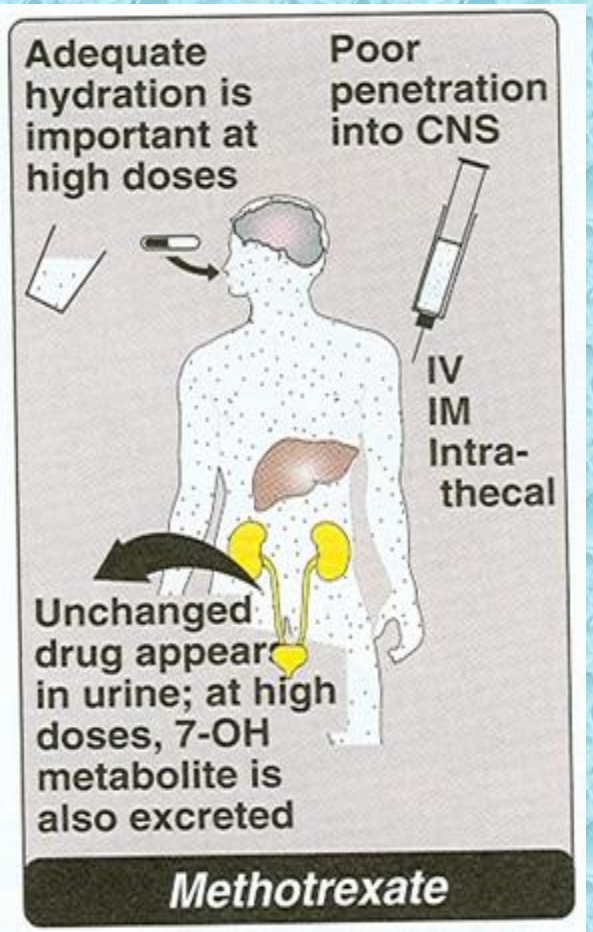
Approximately 70% absorbed after oral administration

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

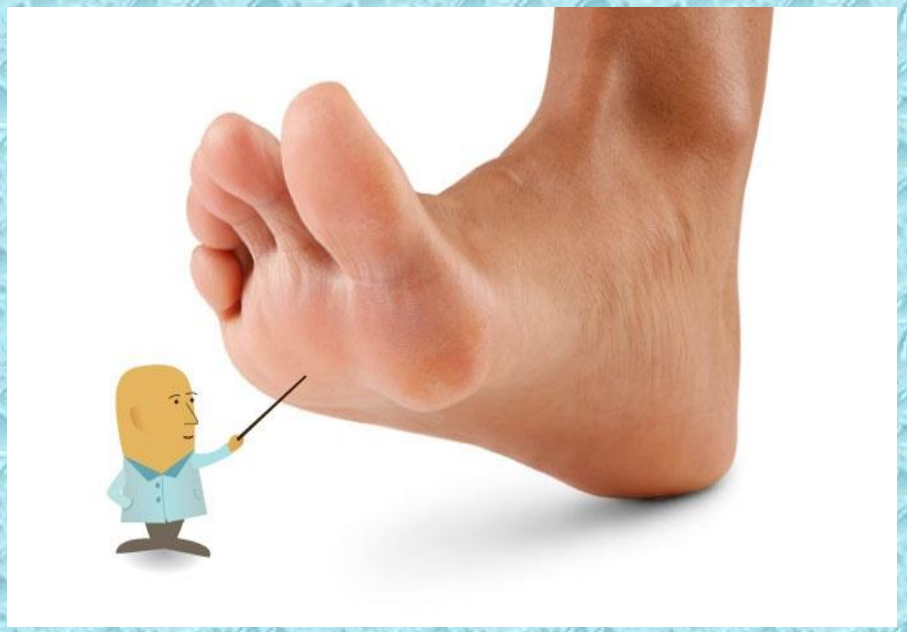
Bone marrow suppression

Dyspepsia, Mucosal ulcers

Hepatotoxicity

Pneumonitis

Teratogenicity



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

* Give Folic acid to reduce 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

Dampens antigen–antibody reactions at sites of inflammation.

HYDROXYCHLOROQUINE

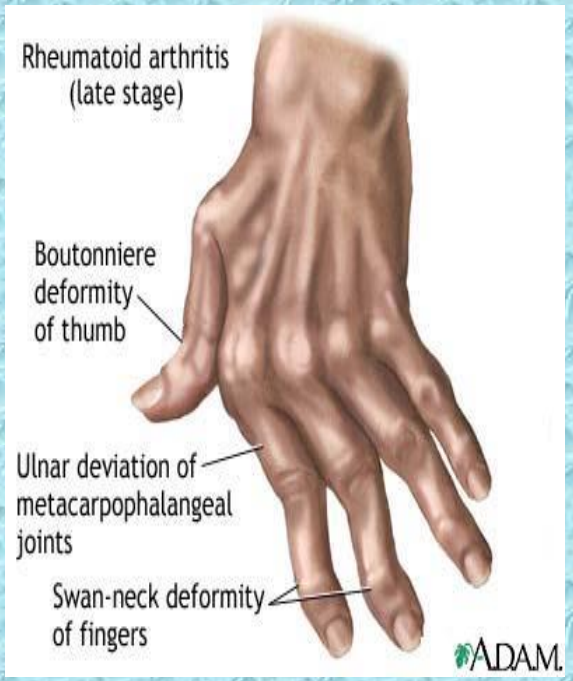
PHARMACOKINETICS

Rapidly absorbed & 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 intracellular pH



HYDROXYCHLOROQUINE

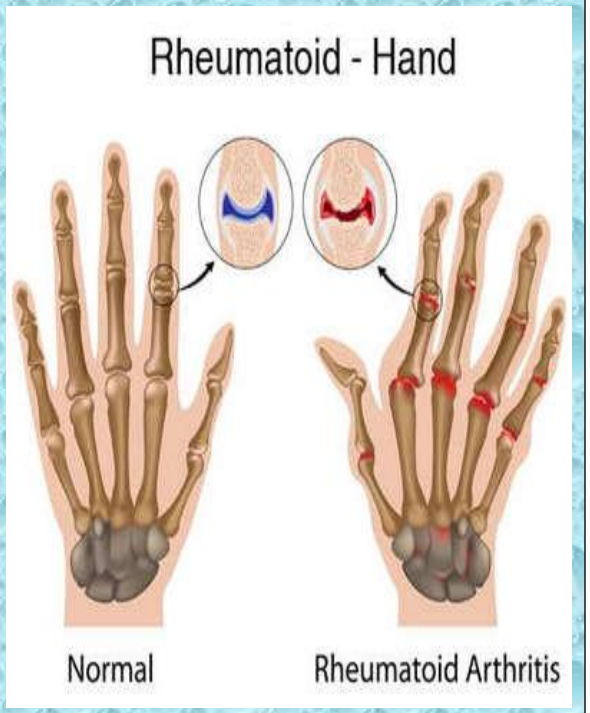
CLINICAL USES

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 to increase methotrexate efficacy

6 month response, mild antirheumatic effect.



ADRS

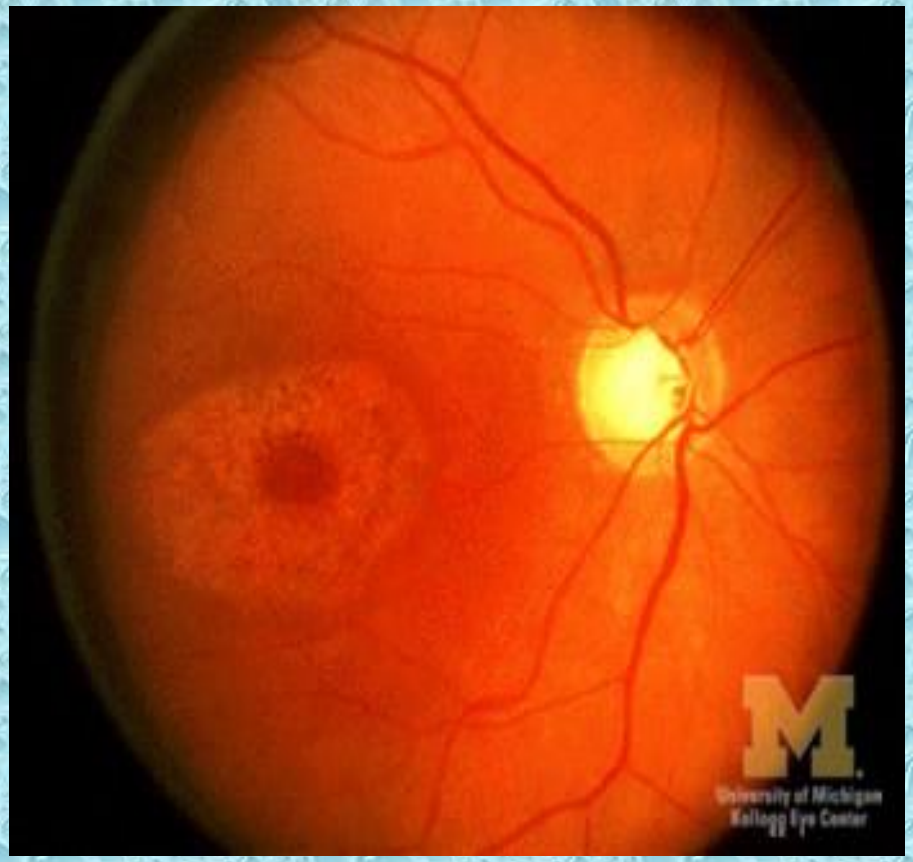
Least toxic, no blood tests is required

Nausea & vomiting

Corneal deposits

Irreversible retinal damage, rare

Ophthalmologic evaluation every 6 months



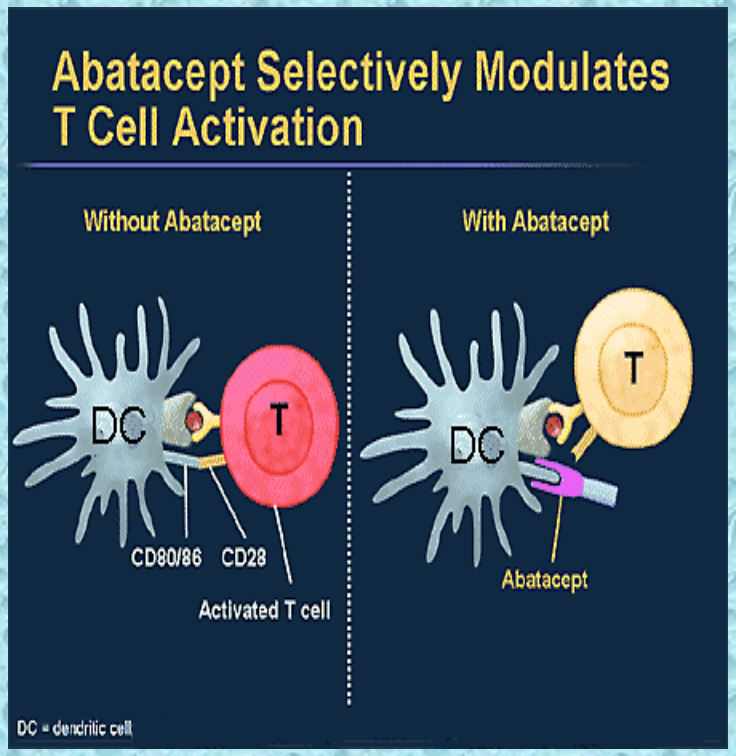
BIOLOGIC DISEASE MODIFIER

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

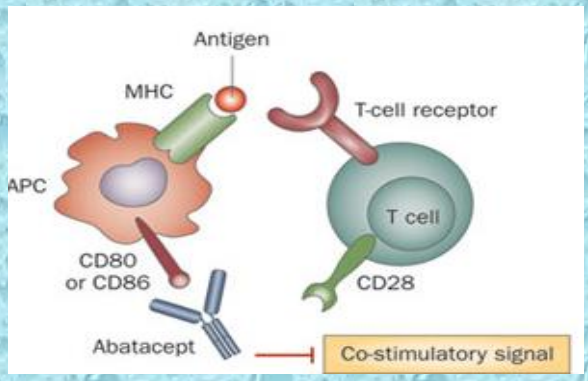
They are expensive

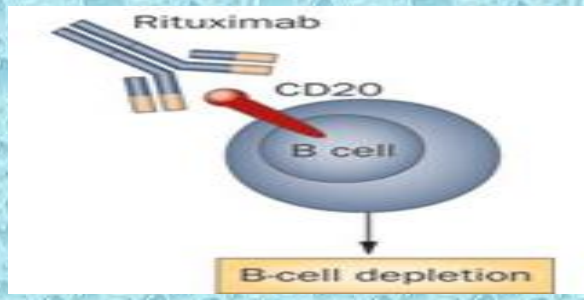


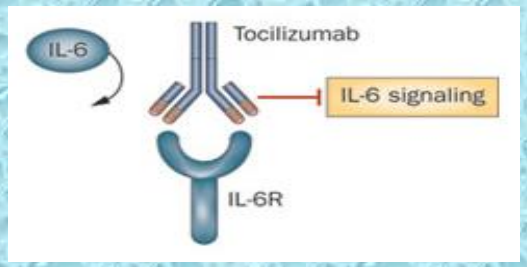
BIOLOGIC DISEASE MODIFIER

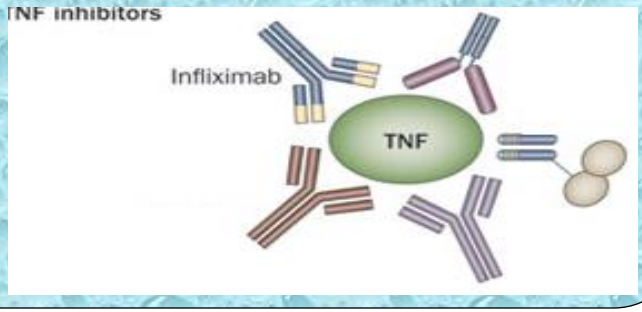
CLASSIFICATION

- ❖T-cell modulating drug (abatacept)
- ❖B-cell cytotoxic agent (rituximab)
- ❖Anti-IL-6 receptor antibody (tocilizumab)
- ❖TNF- blocking agent (infliximab)



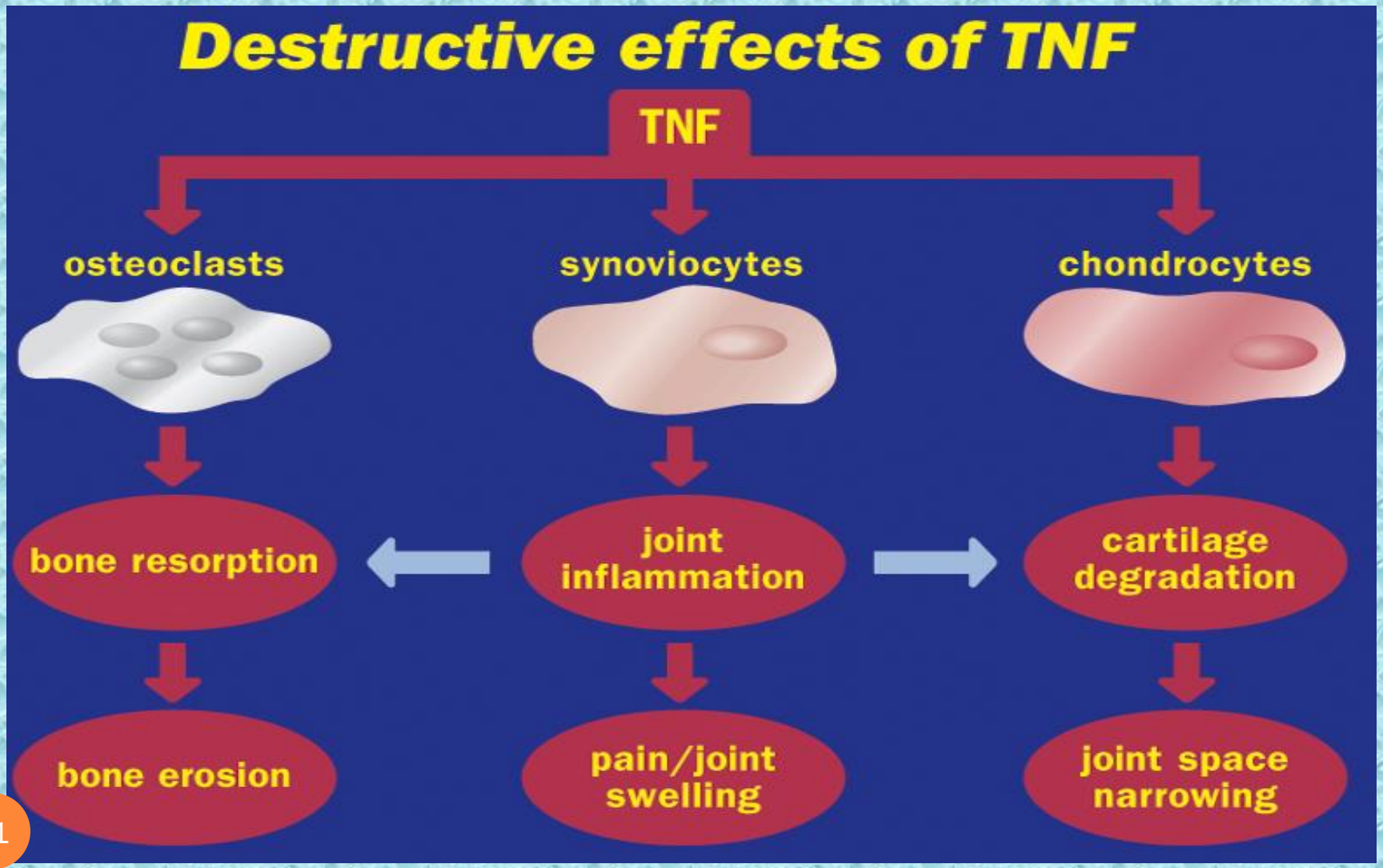






TNFα BLOCKING AGENTS

ROLE OF TNF ON JOINT DESTRUCTION



TNFα BLOCKING AGENTS

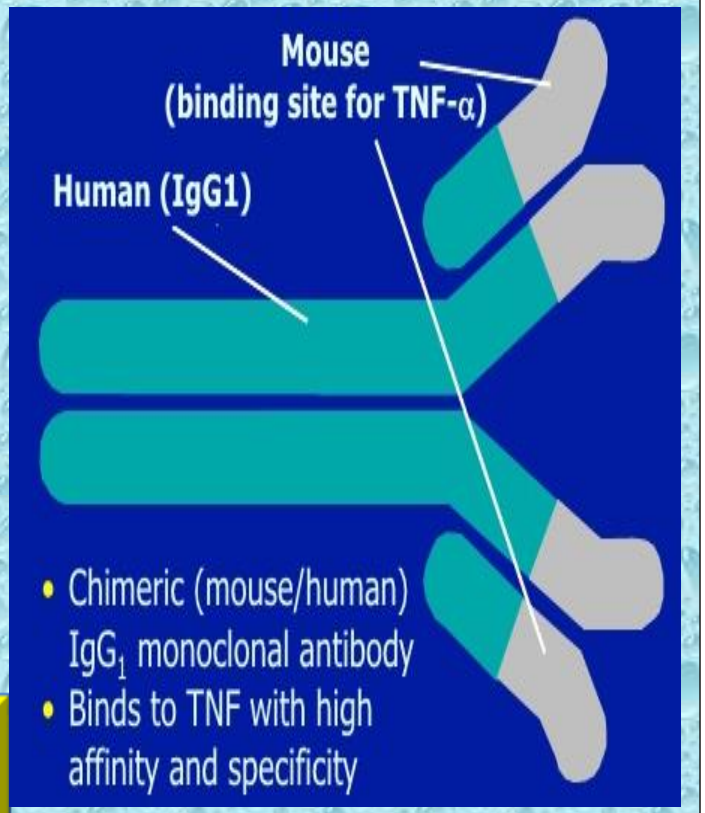
INFLIXIMAB

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 & T-cell function.

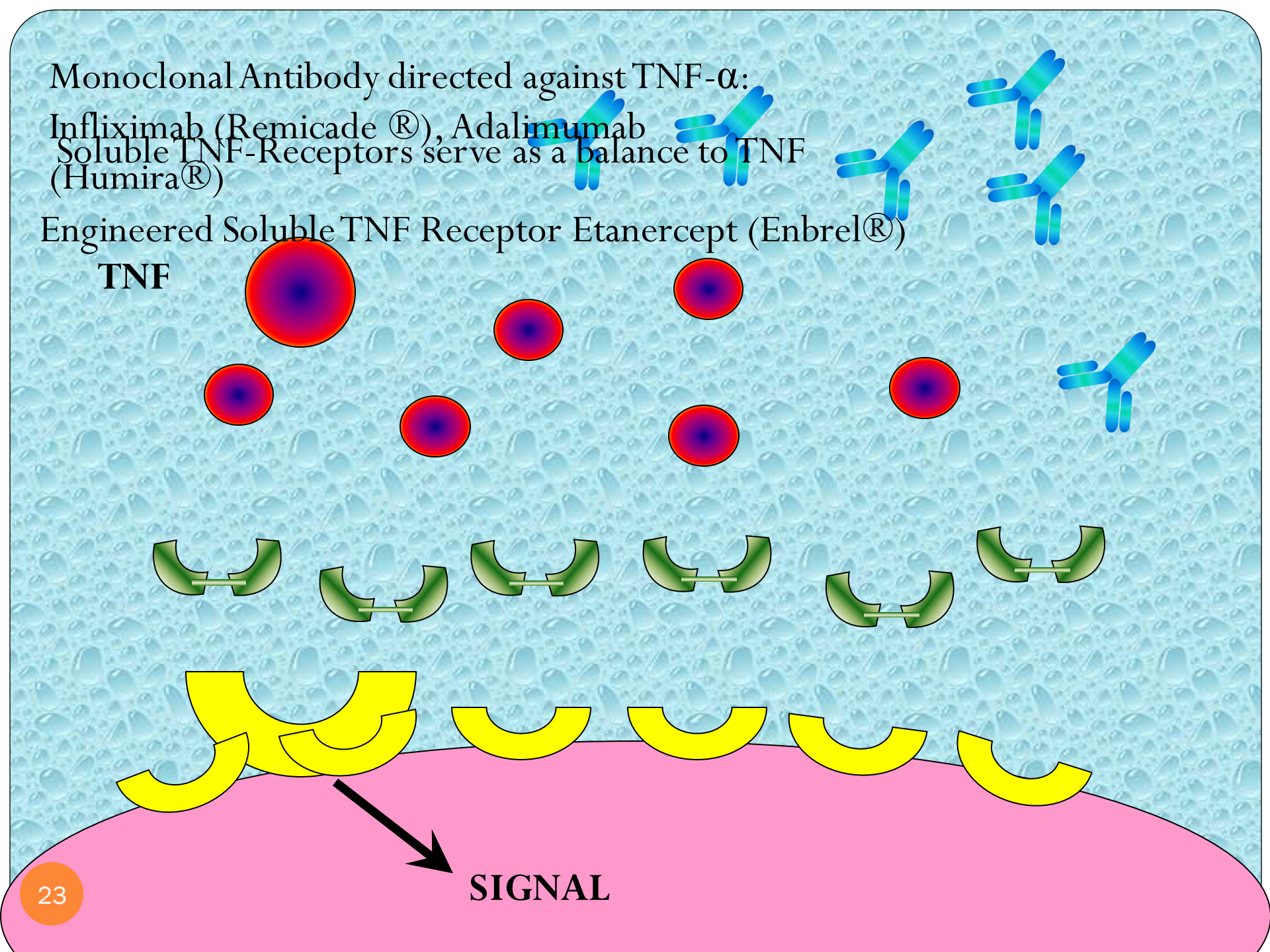


Monoclonal Antibody directed against TNF-α:

Infliximab (Remicade ®), Adalimumab (Humira®)

Soluble TNF-Receptors serve as a balance to TNF

Engineered Soluble TNF Receptor Etanercept (Enbrel®)



INFLIXIMAB

PHARMACOKINETICS

Given as an IV infusion with "induction" at 0, 2, and 6 weeks & 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

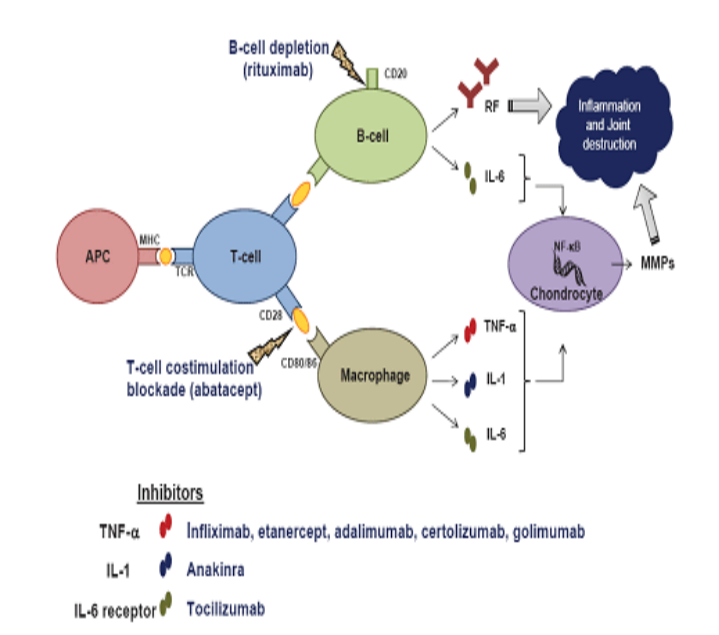
Infliximab is approved for use in RA, Ankylosing spnodilytis, Crohn's disease, ulcerative colitis

It could be combined with methotrexate, hydroxychloroquine & 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 & 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 RA 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 RA not responding to TNF blockers or other biologic drugs

TOCILIZUMAB

ADRS

Infusion reactions

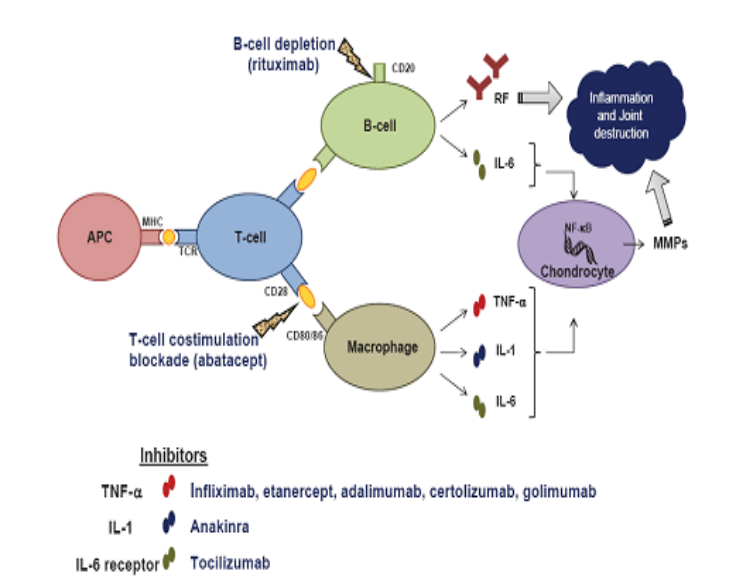
Serious infections (bacterial, tuberculosis, fungal)

Increase in cholesterol level

Neutropenia, & 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).