

DMARDS

EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

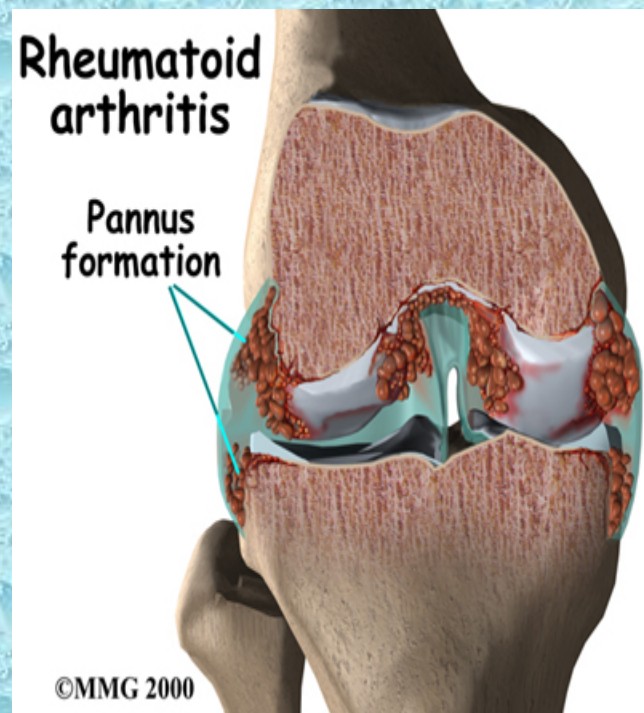
Affects 1-2% of the adult population

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

Usually appears between ages 25 and 40 years

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

Causes pain, disability and loss of function



DMARDs

ILOS

Emphasize the rationale for early treatment of RA

Classify drugs used for treatment of RA

Compare and contrast the advantages and disadvantages of NAISDs, Steroids and DMARDs in treatment of RA

Explore the pharmacokinetic aspects and pharmacodynamic effects of selected DMARDs



RHEUMATOID ARTHRITIS

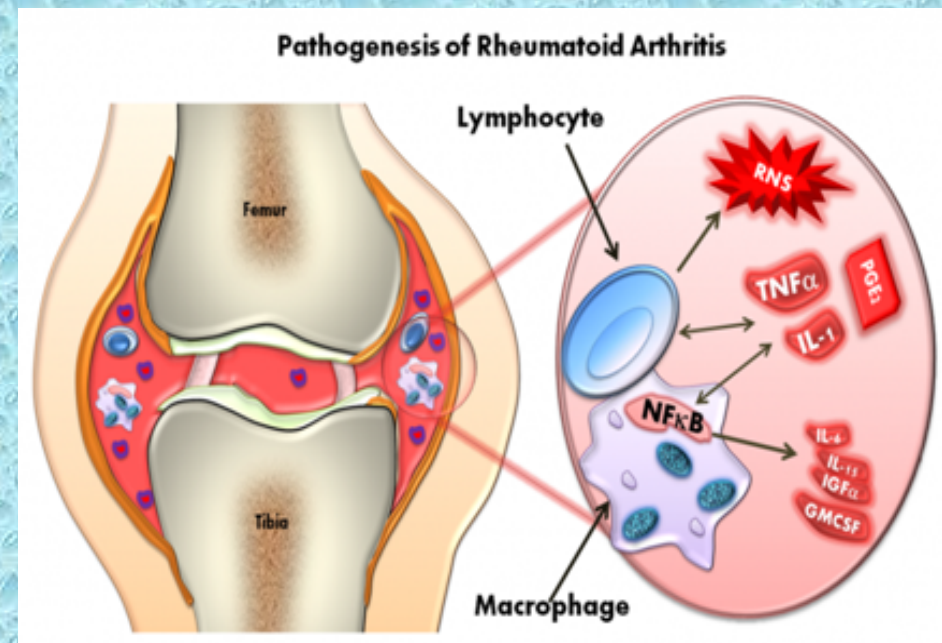
RA is a chronic **autoimmune** disorder in which the normal immune response is directed against an individual's own tissue leading to:-

Decline in functional status

Work disability

Co-morbidity

Increased mortality



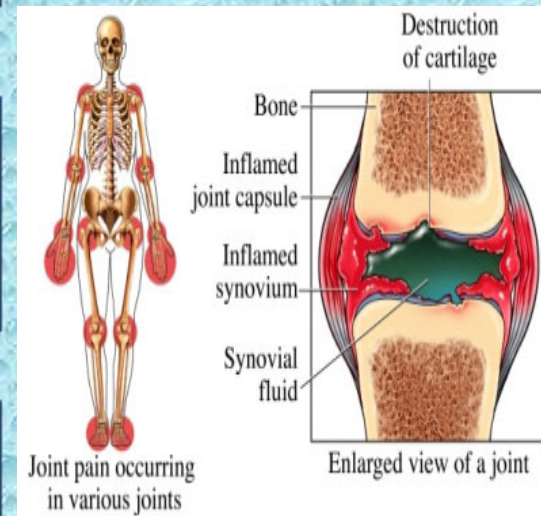
RATIONALE FOR EARLY TREATMENT

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

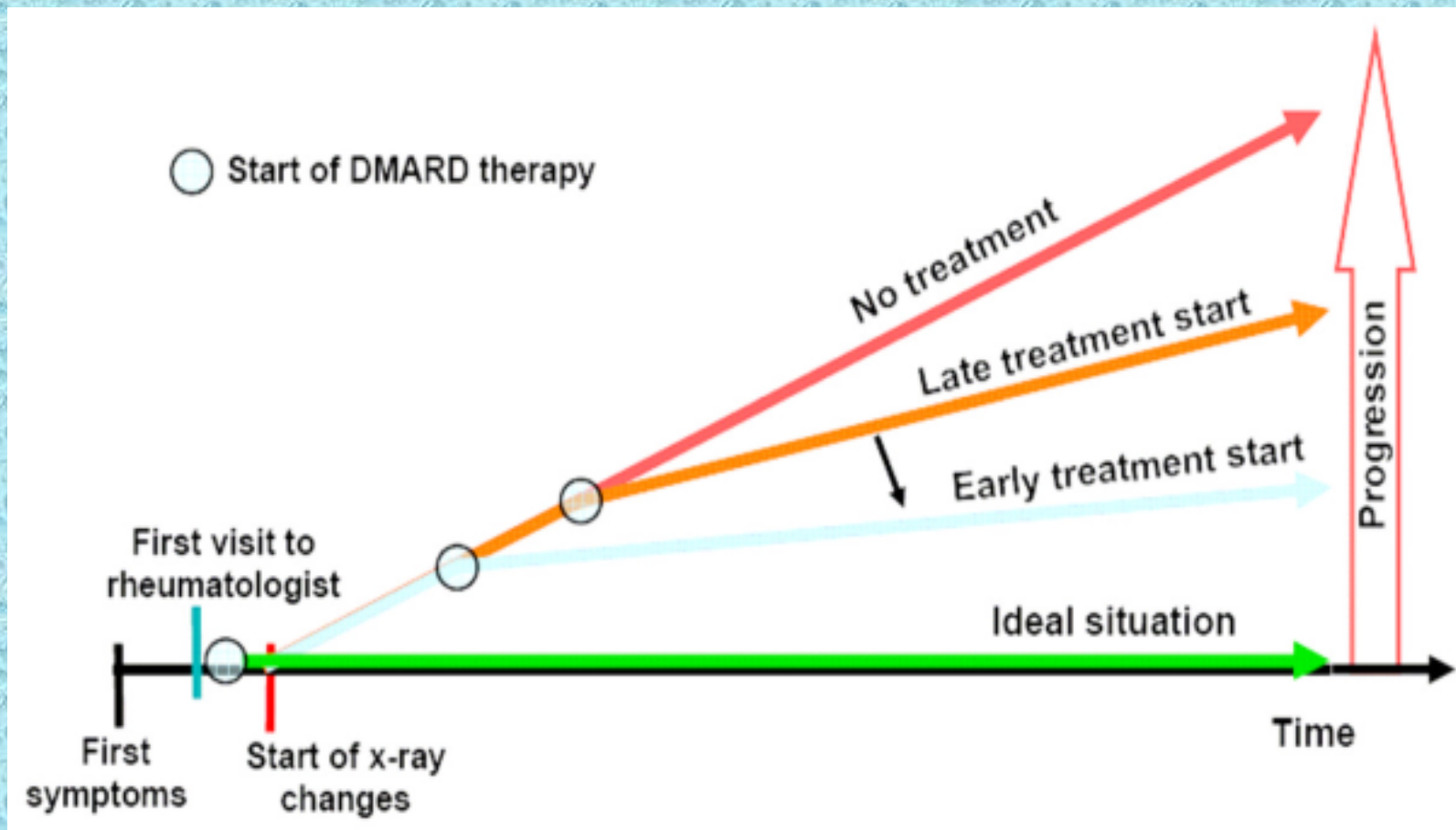
Disability occurs early – 50% of patients with RA will be work disabled at 10 years

Severe disease is associated with increased mortality

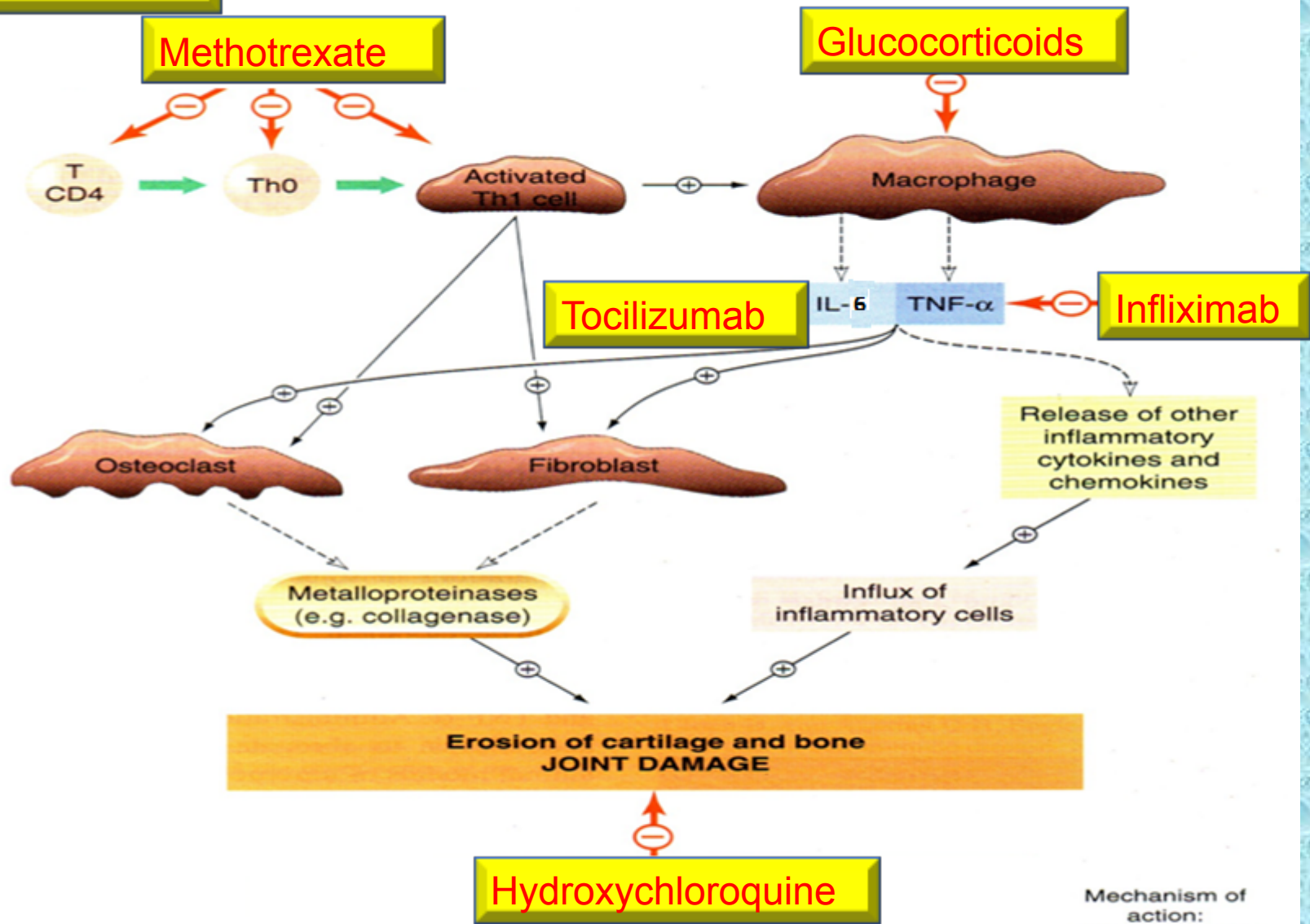


RATIONALE FOR EARLY TREATMENT

Early and aggressive treatment may have long-term benefits



PATHOGENESIS



Mechanism of action:
not clearly known

CLASSIFICATION

Drugs for Rheumatoid Arthritis

DMARDs

NSAIDs

Glucocorticoids

Classical

Biologic

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 relieve inflammation & pain

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)

Therapeutic action involves their anti-inflammatory & immunosuppressant effect

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



CLASSIFICATION OF DMARDs

DMARDs

Biologic

Infliximab

Tocilizumab

Classical

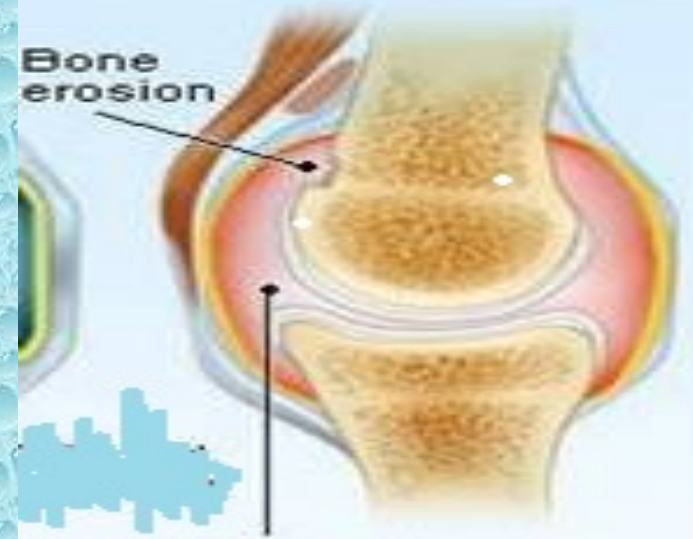
Methotrexate

Hydroxychloroquine

Rheumatoid Arthritis

Bone erosion

Swollen inflamed Synovial membrane



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



METHOTREXATE

MECHANISM

Inhibits dihydrofolate

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

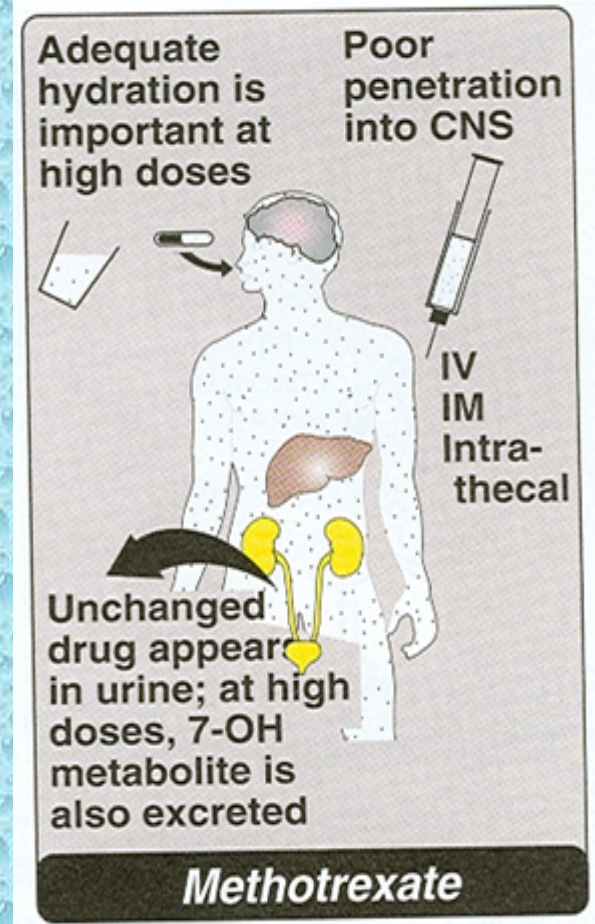
Approximately 70% absorbed after oral administration

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

Dampens antigen–antibody reactions at sites of inflammation



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 intracellular pH



It's funny: My joint pains seem to improve when fish are plentiful...

HYDROXYCHLOROQUINE

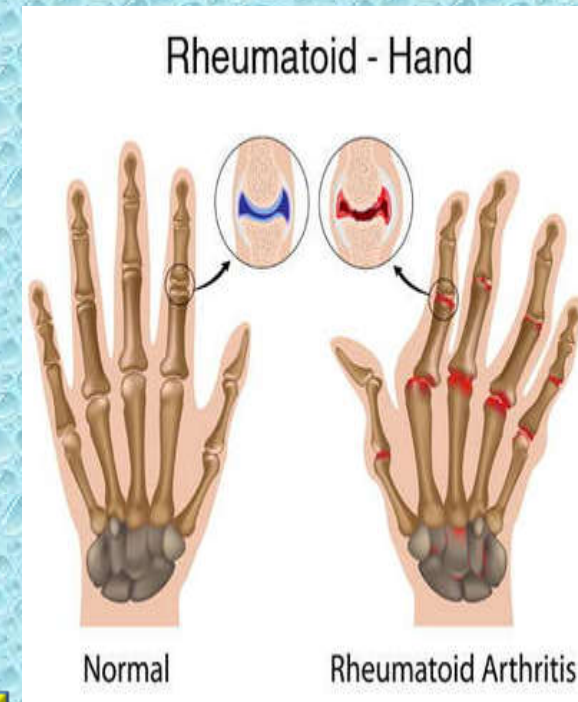
CLINICAL USES

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 methotrxate efficacy

6 month response, mild antirheumatic effect



ADRS

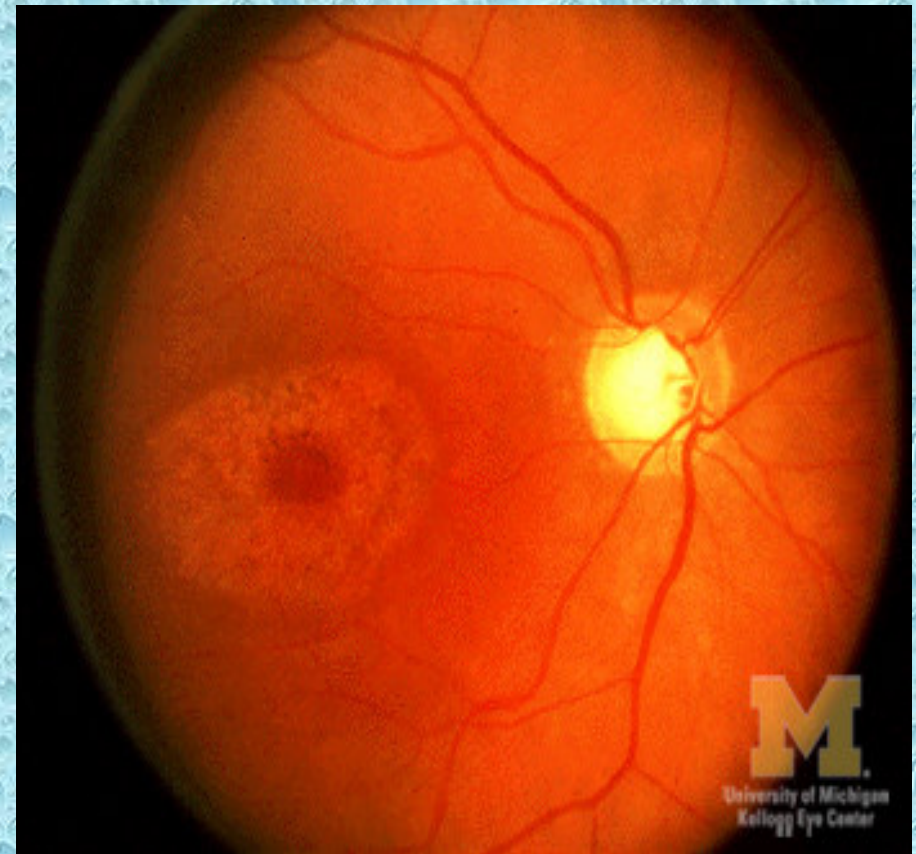
Least toxic, no blood tests is required

Nausea & vomiting

Corneal deposits

Irreversible retinal damage, rare

Ophthalmologic evaluation every 6 months



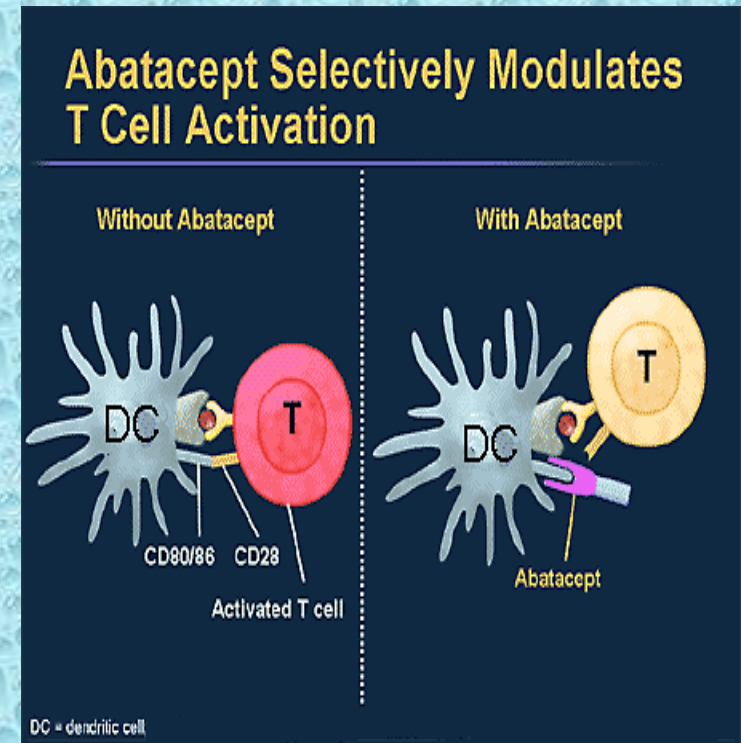
BIOLOGIC DISEASE MODIFIER

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

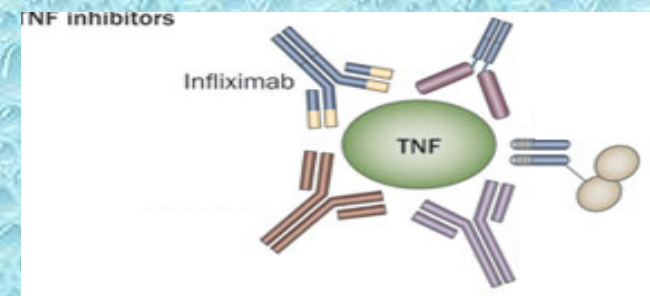
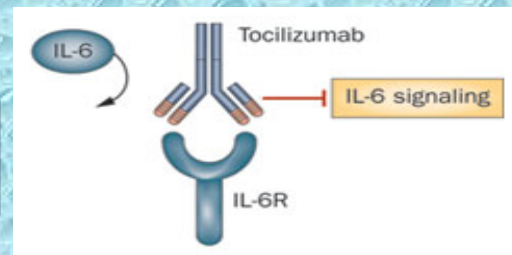
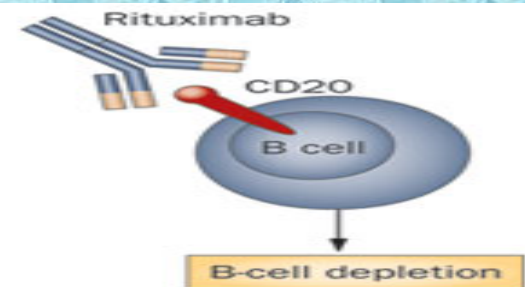
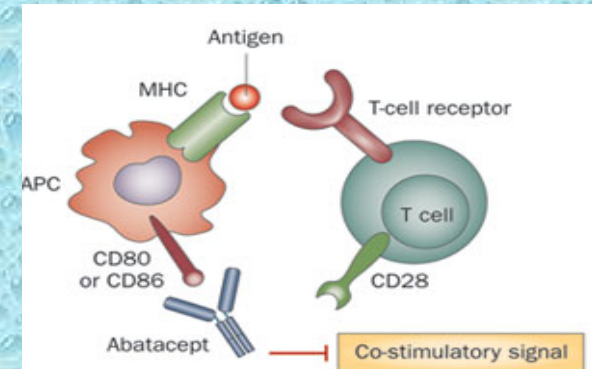
CLASSIFICATION

❖ T-cell modulating drug (abatacept)

❖ B-cell cytotoxic agent (rituximab)

❖ Anti-IL-6 receptor antibody (tocilizumab)

❖ TNF- blocking agents (infliximab)



TNF α BLOCKING AGENTS

ROLE OF TNF ON JOINT DESTRUCTION

Destructive effects of TNF

TNF

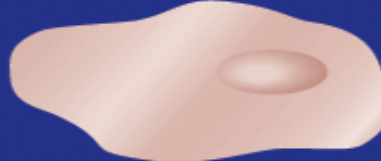
osteoclasts



bone resorption

bone erosion

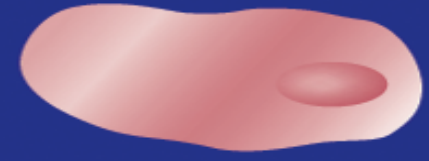
synoviocytes



joint inflammation

pain/joint swelling

chondrocytes



cartilage degradation

joint space narrowing



TNF α BLOCKING AGENTS

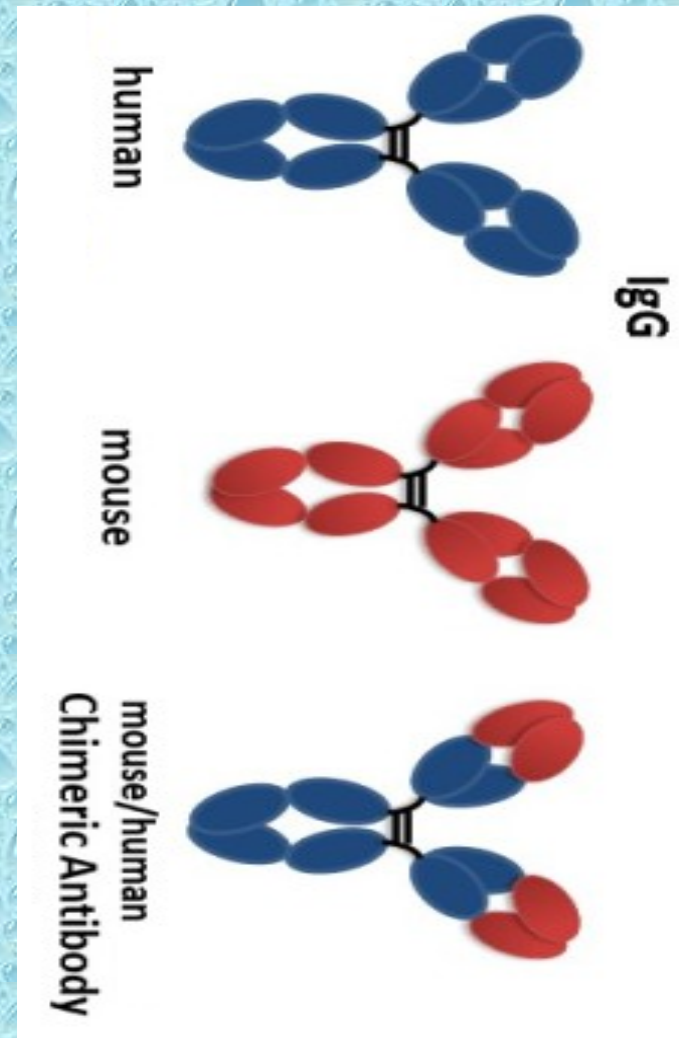
INFLIXIMAB

A chimeric IgG₁ monoclonal antibody (25% mouse, 75% human)

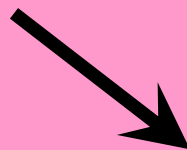
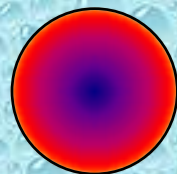
MECHANISM

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.

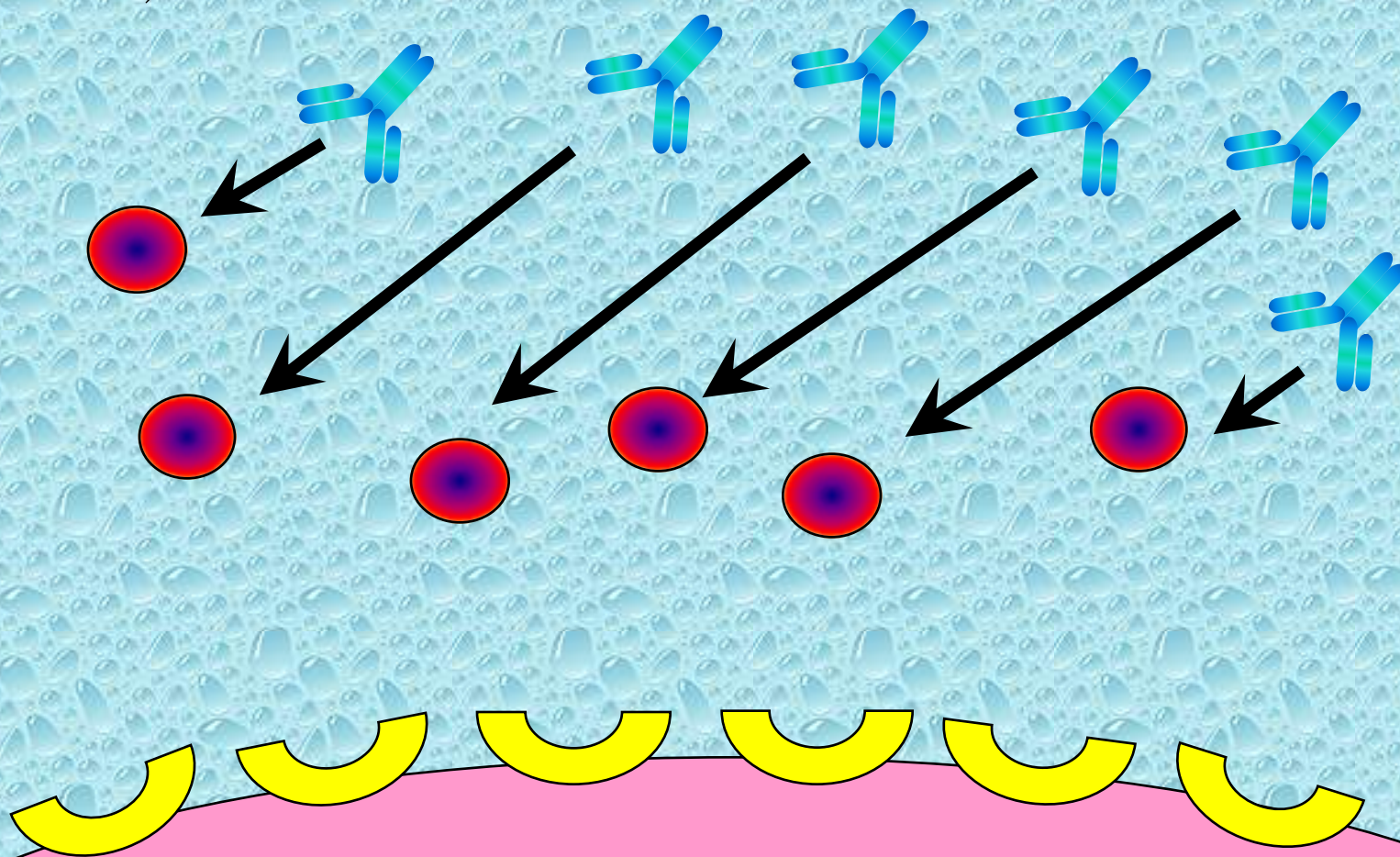


TNF

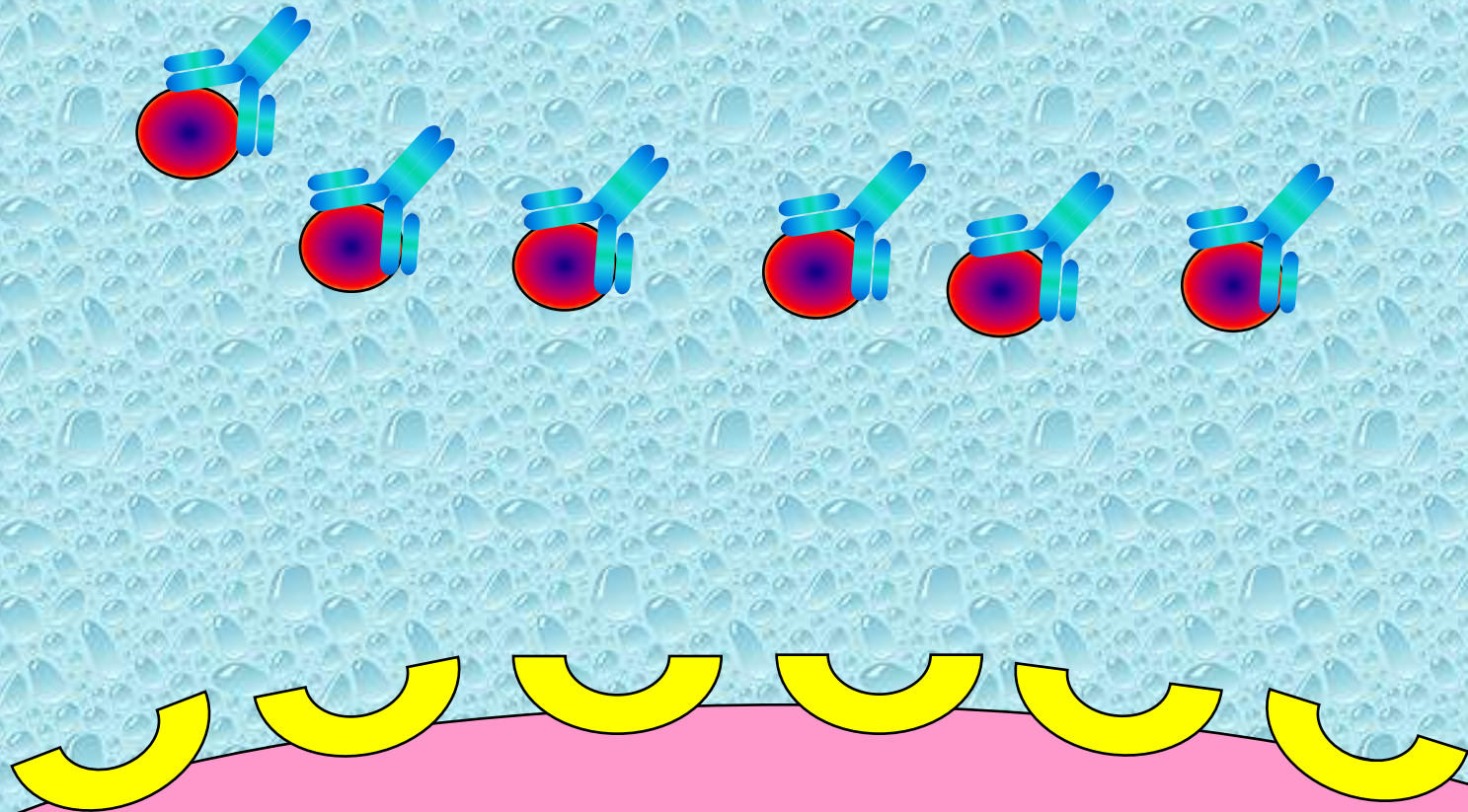


SIGNAL

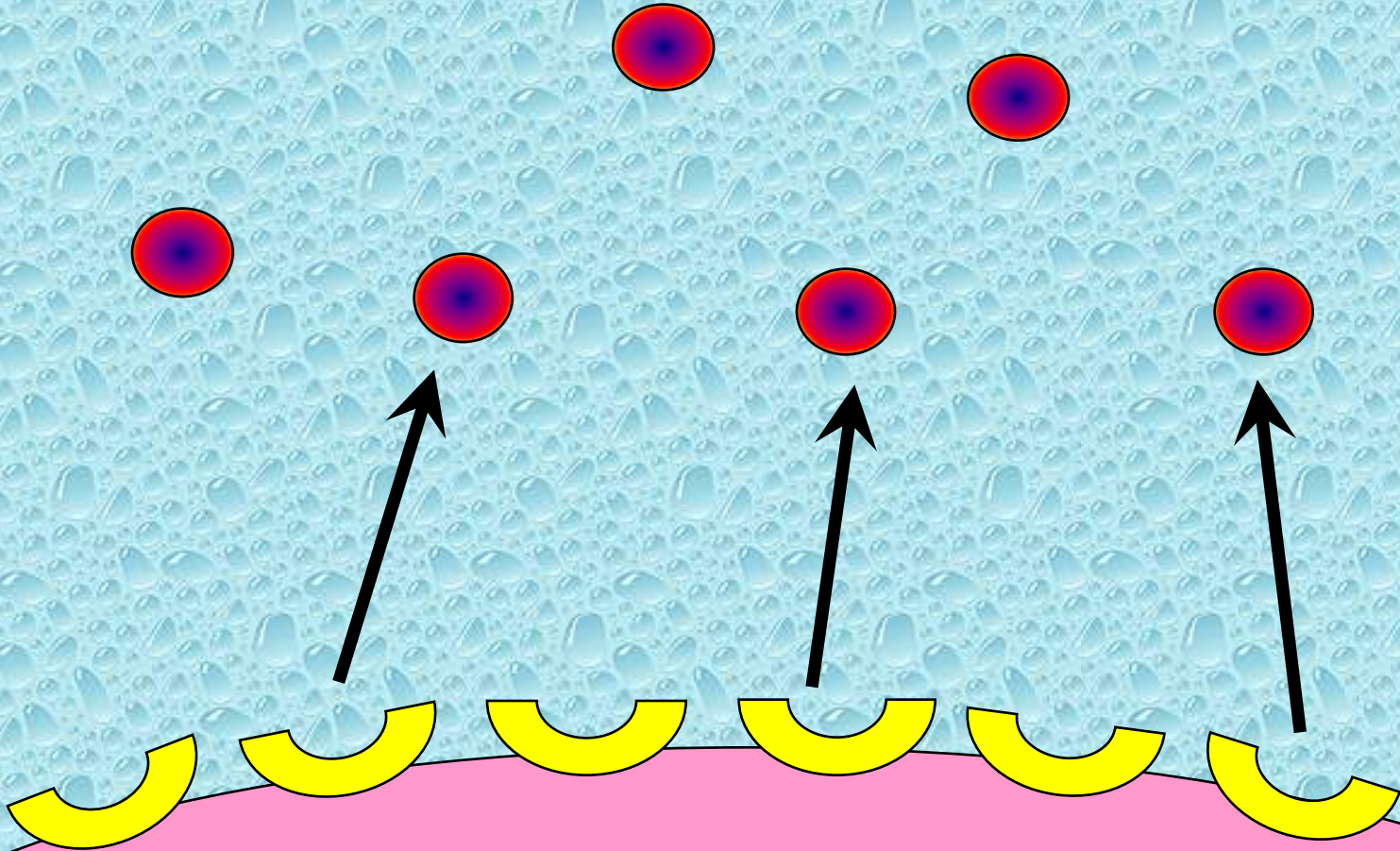
Monoclonal Antibody directed against TNF-
alpha: Infliximab (Remicade®), Adalimumab
(Humira®)



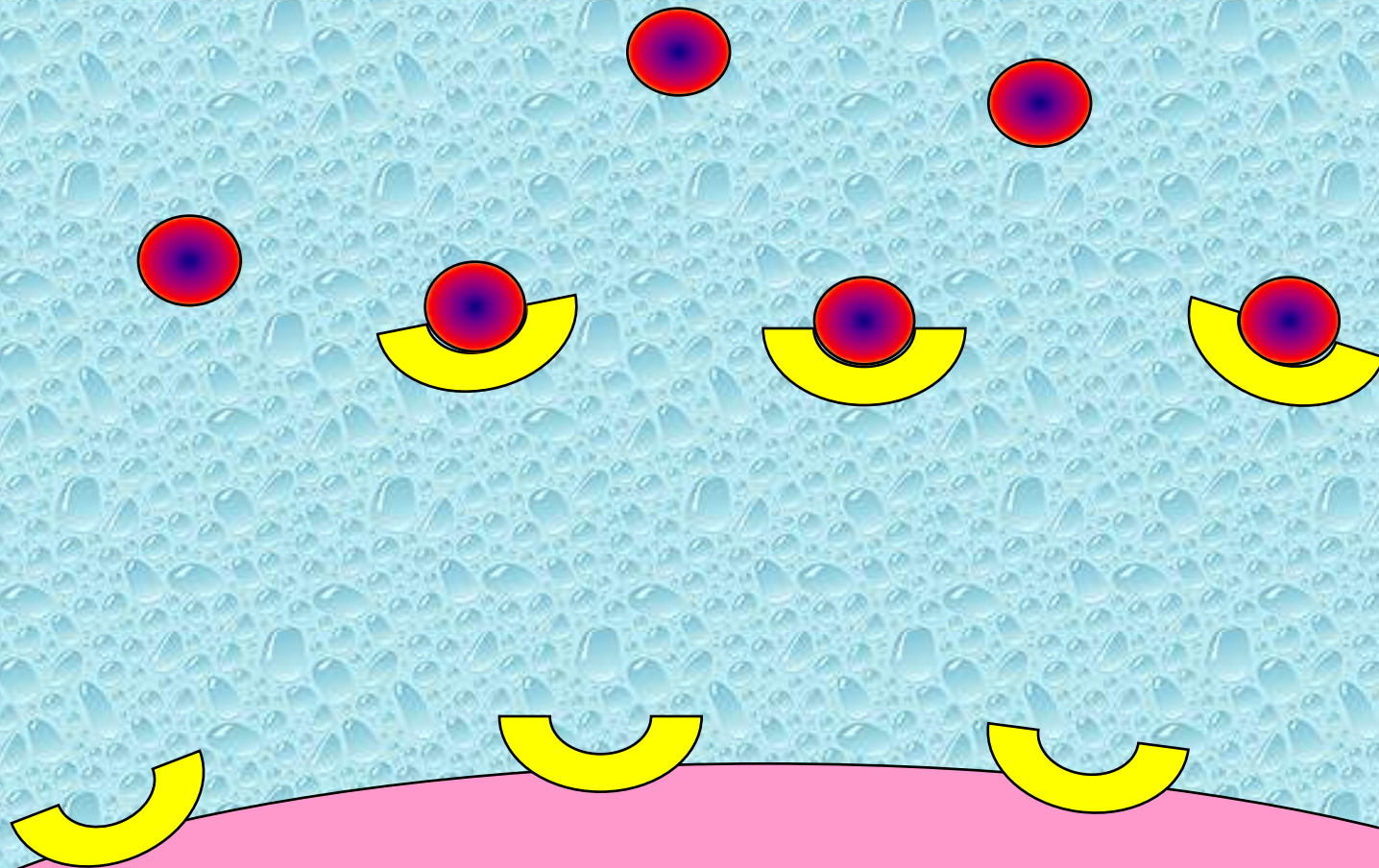
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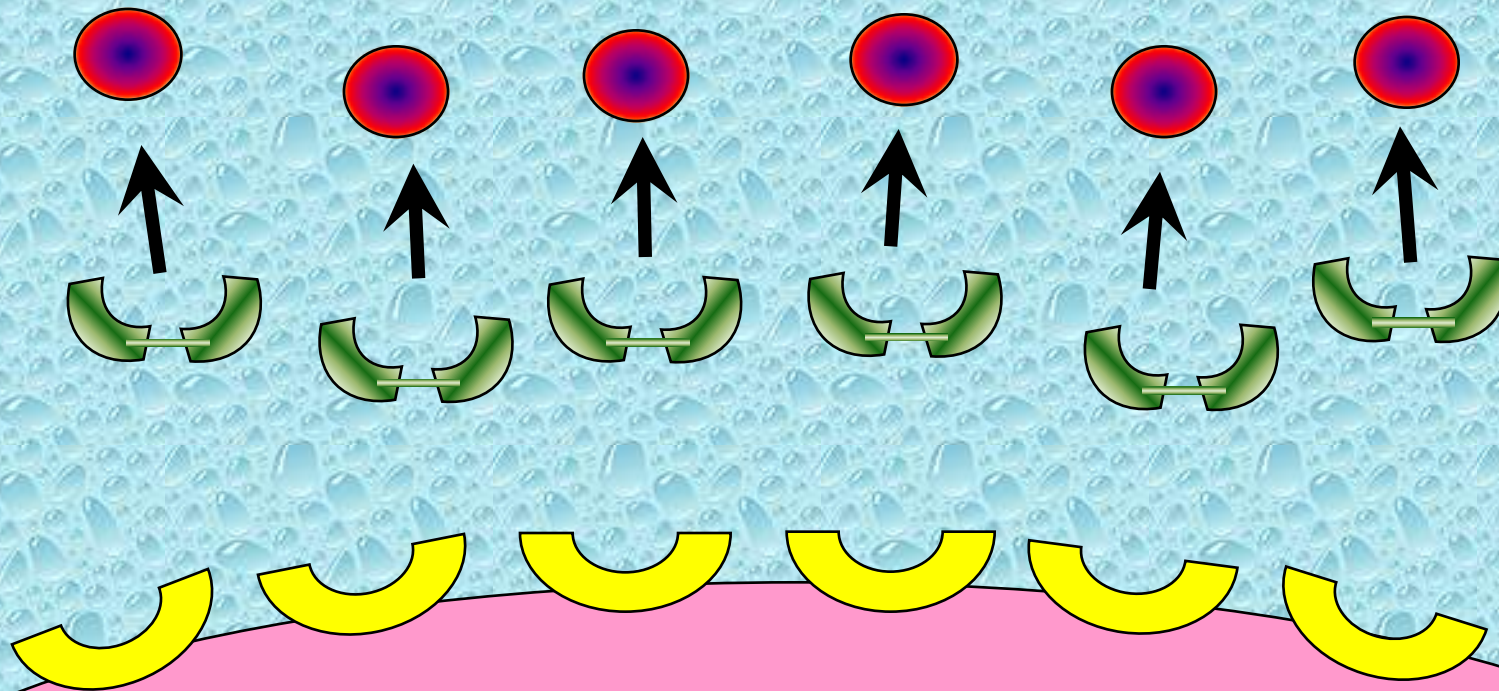
Soluble TNF-Receptors serve as a balance to
TNF



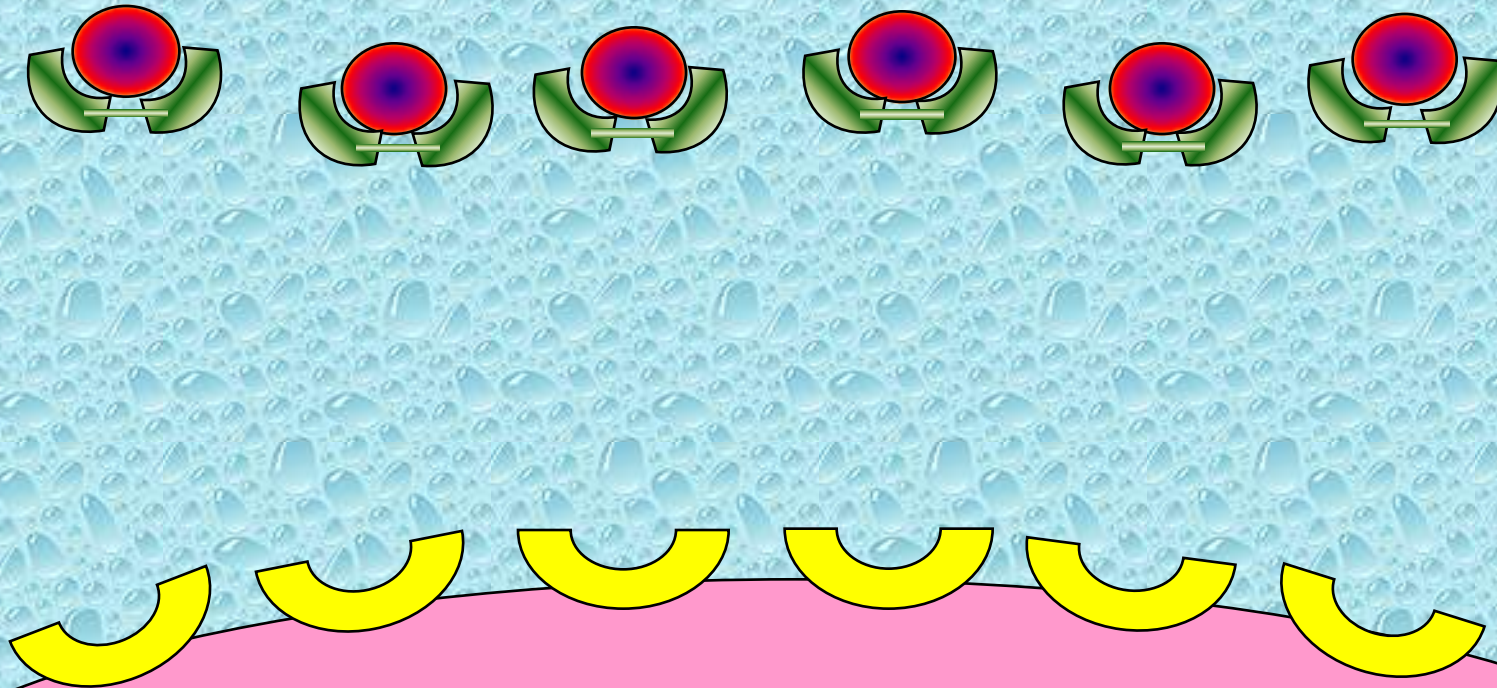
Soluble TNF-Receptors serve as a balance to
TNF



Engineered Soluble TNF Receptor Etanercept (Enbrel®)



Engineered Soluble TNF Receptor Etanercept (Enbrel®)



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

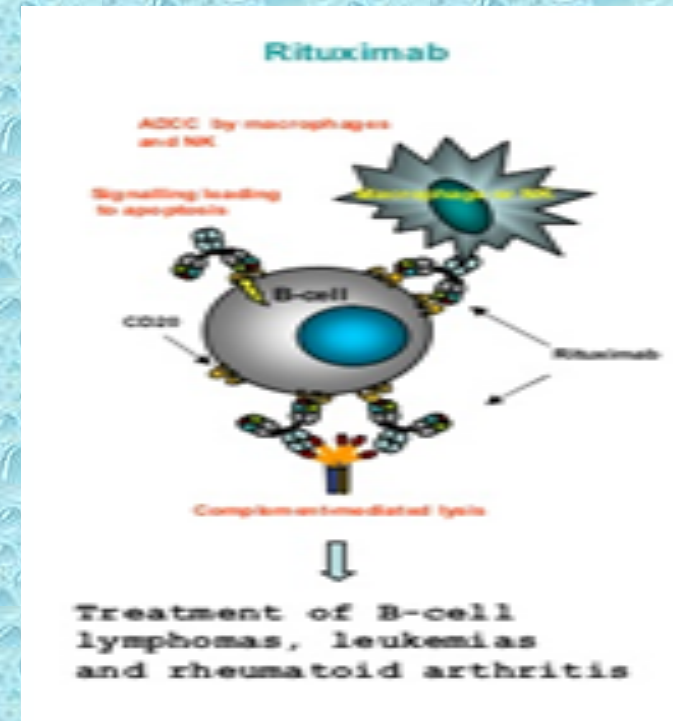


INFLIXIMAB

CLINICAL USES

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

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



INFLIXIMAB

ADRS

Upper respiratory tract infections

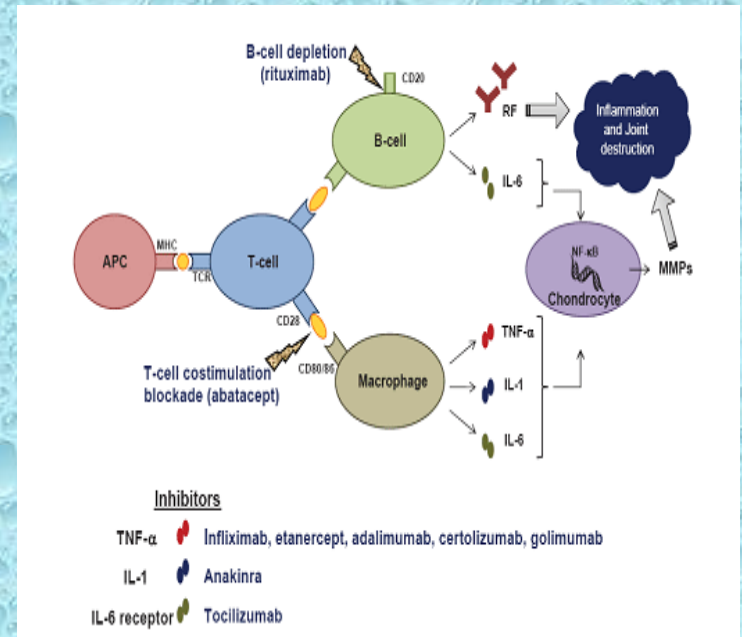
Activation of latent tuberculosis

Infusion site reaction

Headache

Cough

Increase the risk of skin cancers—
including melanoma



TOCILIZUMAB

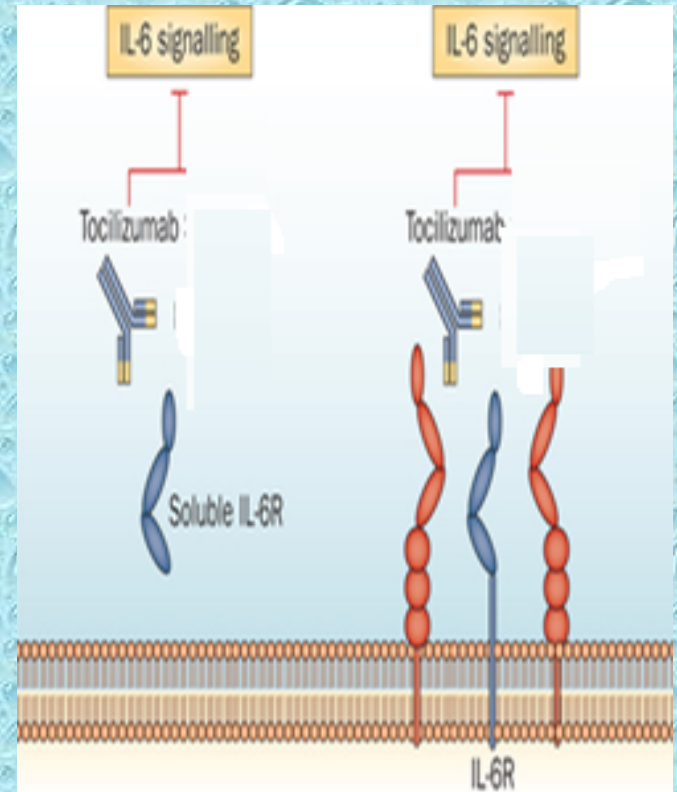
IL-6 is a proinflammatory cytokine implicated in the pathogenesis of RA,

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

Serious infections (bacterial, tuberculosis ,fungal)

Infusion reactions

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).



CLINICAL CONTROVERSY

For patients with rheumatoid arthritis, the order of DMARD or biological agent choice is not clearly defined. In addition, some advocate trials of combination DMARD therapy before courses of biological agents are tried.

Hypertension

Target BP

<140/90 mm Hg

Diabetes?

A1c levels

0 - 4

4-6

6 - 12+

Normal A1c

Pre-Diabetic

Diabetic

Treat -to -target strategy?

Disease Activity Score 28 (DAS28)