MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

Editing File

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LECTURE 6: DISEASE MODIFYING ANTI-RHEUMATIC DRUGS

NOTE:

In this lecture anything that's written in red or green is the female's Dr. notes
Anything written in purple is the male's Dr. notes

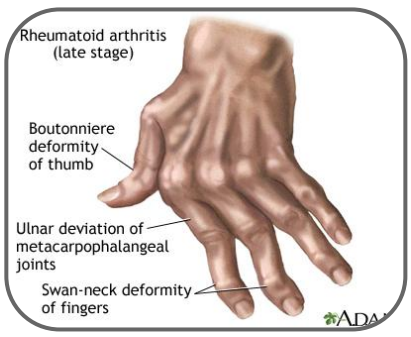
OBJECTIVES:

- ✓ Emphasize the rationale for early treatment of RA
- ✓ Classify drugs used for treatment of RA
- ✓ Compare and contrast the advantages and disadvantages of NSAIDs, Steroids and DMARDS in treatment of RA
- ✓ Explore the pharmacokinetic aspects and pharmacodynamic effects of selected DMARDs

Rheumatoid Arthritis (RA):

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 (affecting other tissues).
- Co-morbidity (is the presence of one or more additional disorders).
- Increased mortality



Epidemiology

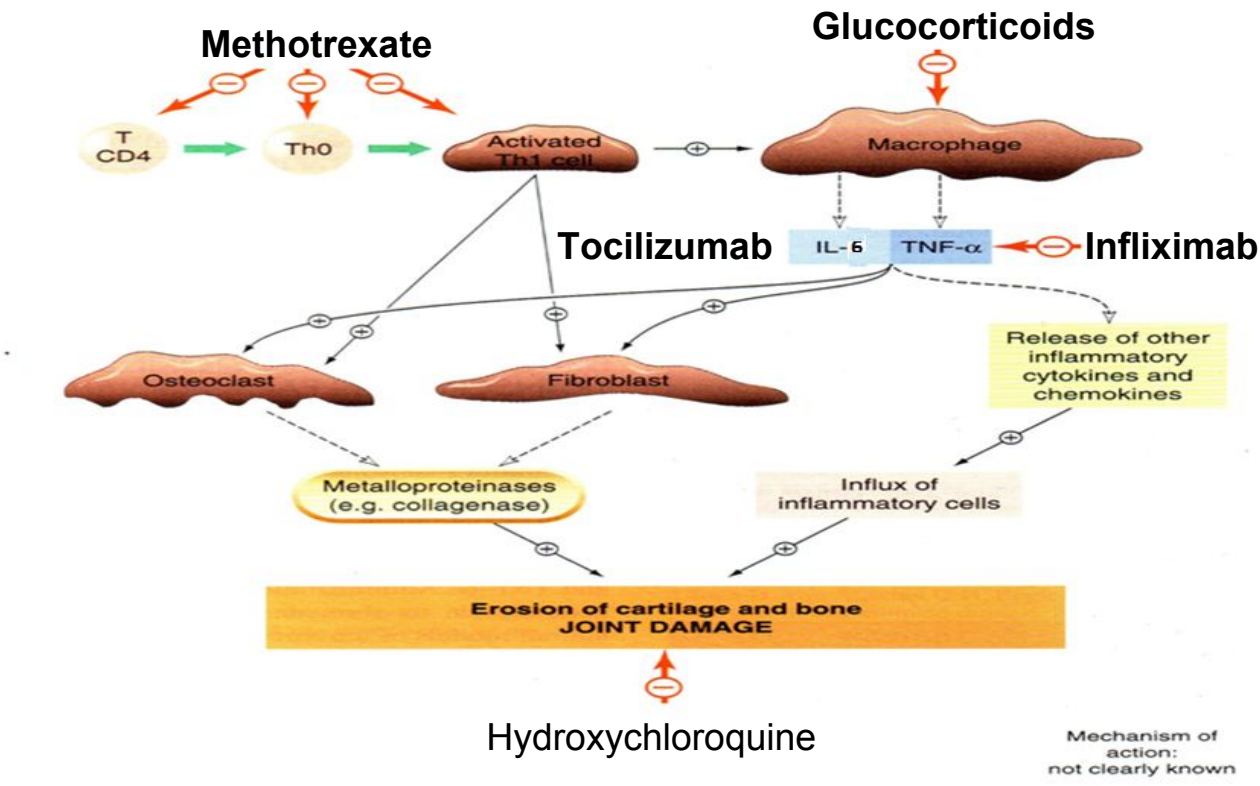
of Rheumatoid Arthritis:

- 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, stiffness, deformity and loss of function.

Pathogenesis of RA:

1-Synovial inflammation and hyperplasia (or swelling)	2-Autoantibody production (Rheumatoid factor)	3-Cartilage and bone destruction (Deformity)
First there will be an inflammation in the joint (especially in the synovial fluid) associated with hyperplasia (the place of the joint gets bigger).	The inflammation starts, so the T cells and B-cells will stimulate and that will produce antibodies.	the cytokines producing from the inflammatory cells will stimulate the osteoclast (TNF-α) and chondrocyte (which degrades the collagens "cartilage", via metalloproteinases such as collagenase.

❖ Targets for each drug:



Explanation from team 437:
Activated T helper cells leads to the activation of osteoclasts and fibroblasts which causes erosion of cartilage and bone destruction. Those activated cells stimulate macrophages that release certain cytokines or inflammatory cytokines which we target in treatment; TNF-alpha and Interleukins.

The drugs we use in the treatment act on:

✓ TNF-alpha

✓ IL-6

most important targets

❖ Rational for early treatment

- Severe disease is associated with increased mortality
- Early and aggressive treatment may have long-term benefits.

Early phenomenon	Less than 2 years of the disease activity	At 10 years of disease activity
• joint damage + disability.	• bone erosions in 93% of the patients.	• 50% of the patients will be work disabled.

Drugs for Rheumatoid Arthritis:

Drugs	NSAIDs	Glucocorticoids	DMARDs
Onset of Action	Rapid	Intermediate	Slow, Their effects take from 6 weeks up to 6 months to be evident
Effect on Disease	Does not slow the progression of the disease.	Reserved for temporary control of severe exacerbations and long-term use in patients with severe disease not controlled by other agents.	act on the immune system to slow (arrest) the progression of RA
symptomatic effects (therapeutic action)	Provides partial relief of pain and stiffness. (Relief the morning stiffness)	powerful Anti-inflammatory, Immunosuppressant	Have no analgesic effects
Formation of new deformity	Cannot stop formation of new deformity.	Cannot stop formation of new deformity	Cannot repair the existing damage, but prevents further deformity
Clinical use	Used in acute cases to relief inflammation & pain.	Administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy Because DMARDs take time to show the effect	Used in chronic cases when the disease is progressing & causing deformities
Chronic use	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.	Corticosteroids are too toxic for routine chronic use therefore used in resistant cases only Can cause atrophy of the adrenal cortex.	Types of DMARDs **Biologic** •Infliximab •Tocilizumab **Classical** •Methotrexate (anti-cancer) Adequate hydration is important in high dose of Methotrexate •Hydroxychloroquine

❖ DMARDs VS. NSAIDs

	DMARDs	NSAIDs
Onset	Slow الأبطأ بينهم	Rapid الأسرع بينهم
Effect of Rheumatoid arthritis	Arrest progression of the disease	No effect on the disease Only analgesic and anti-inflammatory
Deformity	Prevent new deformity	Can't stop the new deformity
Uses	In chronic cases if there is deformity	In acute cases to relief the pain and the inflammation

Any previous deformity CAN'T be fixed or cured, however The drugs can prevent new deformity.

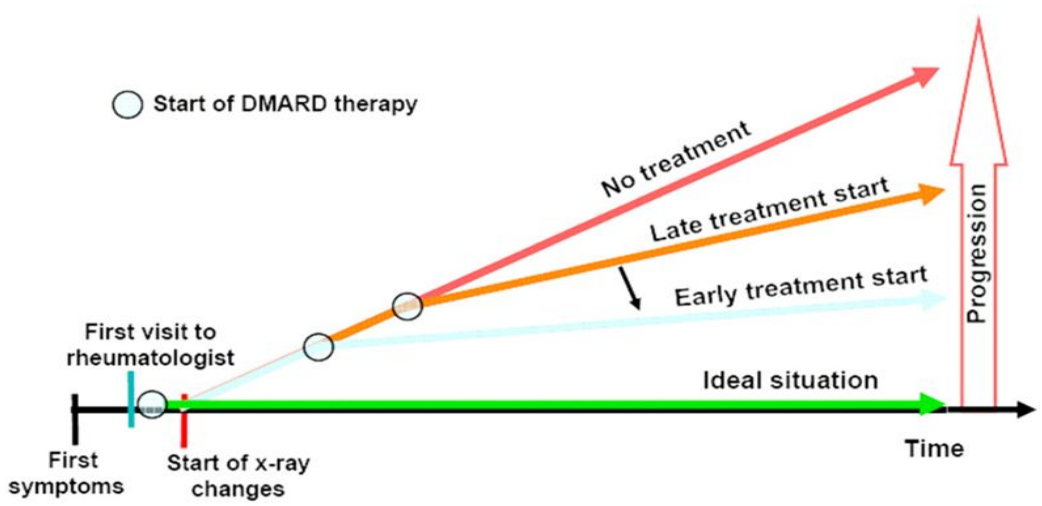
❖ clinical controversy:

found in male's slides

for patients with RA the order of DMARDs or biological agents choice isn't clearly defined. in addition, some advocate trials of combination DMARD therapy before courses of biological agents are tried.

Joint damage (is symmetrical) starts early in the disease so any delay in the treatment will lead to severe deformity of the joint.

Early diagnosis and aggressive treatment may have long-term benefits



Drug	Methotrexate
Special Features	•"**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.(high efficacy and less ADRs)
Mechanism of action	**At High Dose (Anti-cancer):** •Inhibits Dihydrofolate Reductase which inhibits the formation of folic acid. •Reduces Thymidine and purine synthesis which is important for DNA, no DNA means no proliferation of the cells. (for treatment for brain cancer the drug is administered intrathecally "into spinal cord") **At Low Dose (Anti-RA):** •Anti-inflammatory effect by stimulating adenosine release from cells •Inhibition of Polymorphonuclear chemotaxis •Inhibition of T-cells (Cell-mediated immune reactions) if they asked about the M.O.A for Methotrexate the answers is its M.O.A as an anti-RA (in red).
P.K	-Approximately 70% absorbed after oral administration. can be given by any rout -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. Enterohepatic circulation -Given 7.5-30 mg weekly.
ADRs	•Bone marrow suppression. due to inhibition of mitosis •Dyspepsia, mucosal ulcers. •Hepatotoxicity. •Pneumonitis (1) •Teratogenicity (2) •Leukopenia, anemia, stomatitis (3), GI ulcerations, & alopecia (4) are probably the result of inhibiting cellular proliferation. •Folic acid reduces GI & bone marrow effects.(reduces the side effects when administered with Methotrexate) •Monitoring: Full blood count (for anemia), ALT (for liver function),Creatinine (for renal function) (1): Inflammation of lung (2): malformation of embryo (3): inflammation of mucosal membrane of the mouth (4): hair loss

Drug	Hydroxychloroquine
Mechanism of action **Important**	(Anti-malarial drug, less effective.) 1.Stabilization of lysosomal enzyme activity. 2.Trapping free radicals. Those reactive substances are found in all inflammatory processes, has a free radical scavenging effect. 3.Suppression of T lymphocyte cells response to mitogens (substance that stimulates mitosis) 4.Inhibition of leukocyte chemotaxis. 5. Dampen antigen-antibody reactions at site of inflammation.
P.K	1-Rapidly absorbed and 50% protein-bound. 2-**Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes.** **accumulates in the eyes** ocular side effects 3-Elimination half-life up to 45 days. 4-Highly concentrated within cells → increases intracellular pH. Because it is a basic drug
ADRs	Doesn't have lots of ADRs unlike Methotrexate •Least toxic, no blood tests is required. •Nausea & vomiting. •**Corneal deposits. Because it has high affinity to melanin** •**Irreversible retinal damage.** •**Ophthalmologic evaluation** every 6 months.
Clinical uses	•Has not been shown to delay radiographic progression of disease. •Generally used for treatment of early, mild disease if administered alone or as adjunctive therapy in combination with other **DMARDs.** •Used in increasing methotrexate efficacy. •6 months response, mild anti-rheumatic effect.

Biologic Disease Modifier :

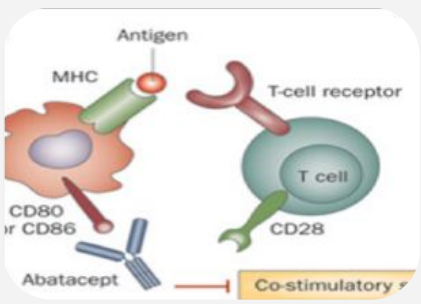
- **Biologic DMARDs** are genetically engineered drugs that are used to modify imbalances of the immune system in autoimmune diseases.
- They are expensive. because they are genetically synthesized.

- **The drug works by:**
  1. Work as agents block
  2. or modify the activity of selected cells in the immune system.
     Act on T-cells or B-cells or any immune system cells
  3. or by blocking cytokines, that send signals between those cells.

Classification of Biologic Disease Modifier

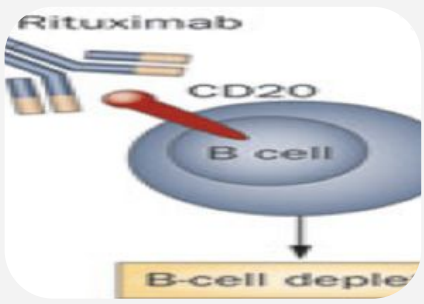
this part is important, you have to know the name of each drug and its target
anything that's written in grey is just for your understanding

T-cell modulating drug (Abatacept)



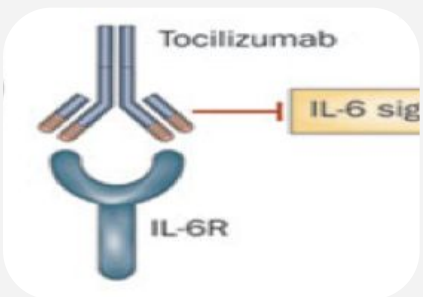
It modulates the immune response by binding to CD80/CD86 on an antigen presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding to CD28 on naïve T-cell and attenuating T-cell activation.

B-cell cytotoxic agent (Rituximab)



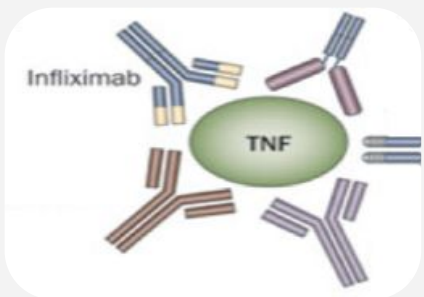
The drugs look like antibodies which will go to the B-cells and bind with the antigen on the surface of the B-cells, after the drug binds with the antigen it will destroy the B-cells

Anti-IL-6 receptor antibody (Tocilizumab)



The drug binds with the IL-6 receptors, so the IL-6 will not bind with the receptor, so no IL-6 effect

TNF- blocking agents (Infliximab) another example: Adalimumab



The drugs look like antibodies which will bind with the TNF-α and inhibit this cytokines from producing its action (inflammation)

Engineered soluble TNF Receptor (Etanercept) aka Enbrel

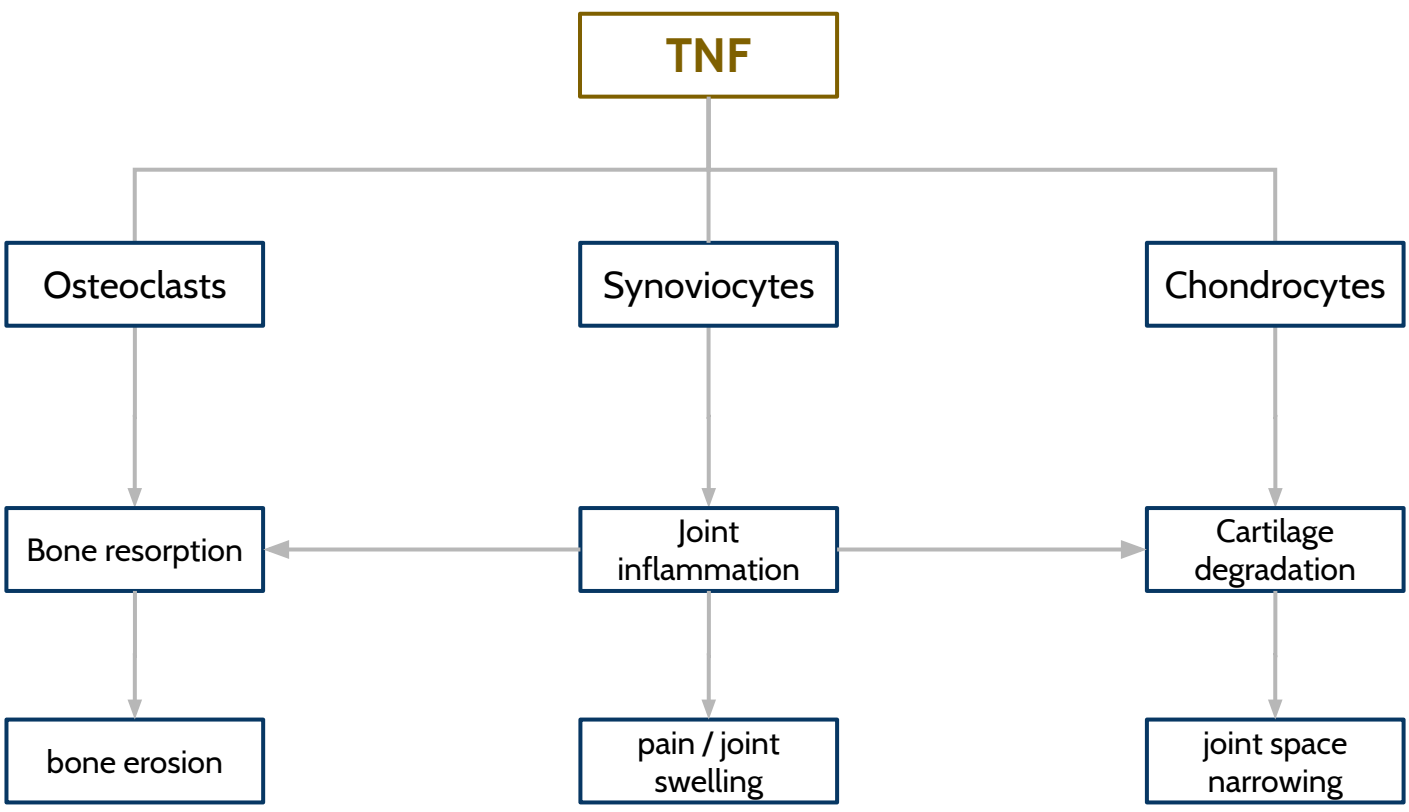
what is the role of TNF-receptors?

directed toward the soluble TNF

Functions as a decoy receptor to TNF-alpha inside the body and binds to it and remove it from the circulation.

Role of TNF on joint destruction

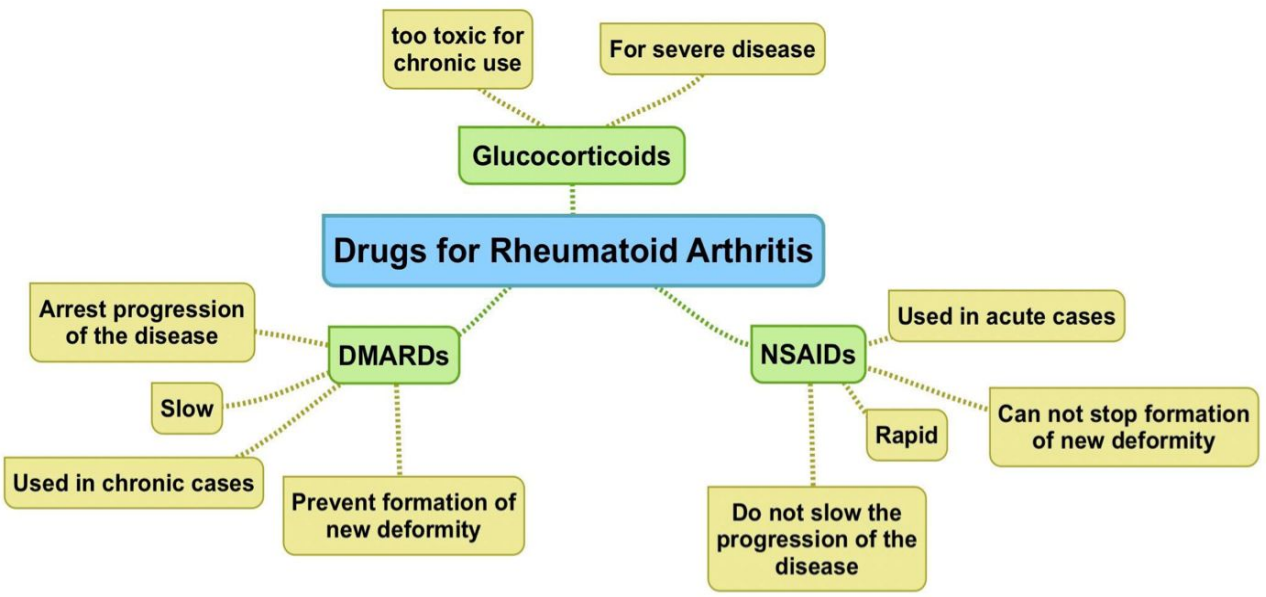
What is the role of TNF?

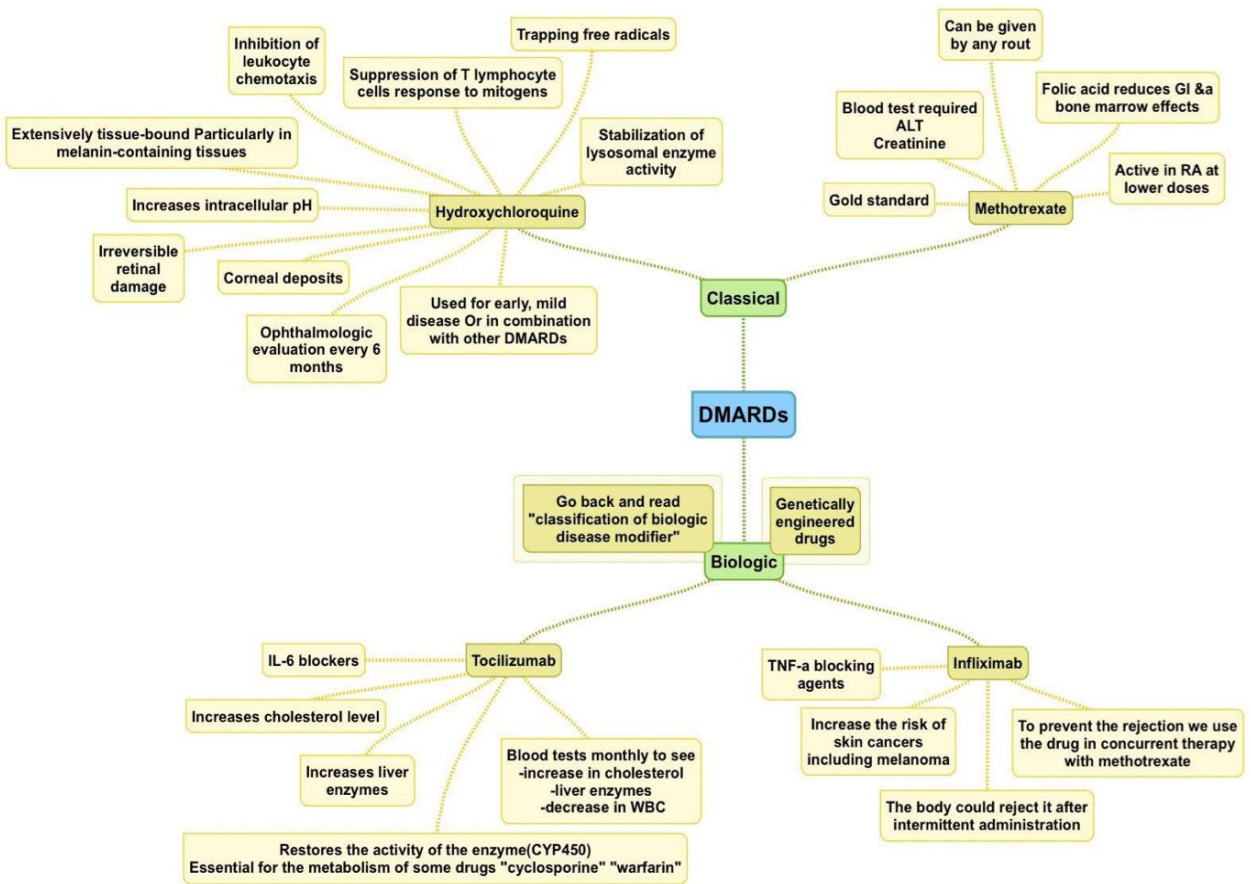


All of them Induce production of other cytokines, as IL-1, IL-6.

Drug	Infliximab (TNF-α blocking agents)	Tocilizumab (IL-6 blockers) used as last resort due to its serious ADRs
Definition	**A chimeric** (two sources; human+mouse) IgG1 monoclonal antibody (25% mouse, 75% human)	**IL-6 is a pro-inflammatory cytokine** implicated in the pathogenesis of RA With detrimental effects on both joint inflammation and cartilage damage
Mechanism of action	It complexes with soluble TNF-α (and possibly membrane-bound TNF-α) and prevents its interaction with the cell surface receptors (signaling). This results in down-regulation of macrophage and T-cell function. TNF has two forms free and bounded	binds to membrane IL-6 receptors, **blocking the activity of IL-6** (soluble form) in mediating signals that affect cytokine production, osteoclast activation
P.K	• **intravenous infusion** with "induction" at 0, 2, and 6 weeks and maintenance every 8 weeks thereafter • half-life 9–12 days	• Intravenous (IV) monthly • **Half-life:** dose-dependent
Clinical uses	• used in autoimmune disease like (RA, Ankylosing spondylitis, Crohn's disease, ulcerative colitis) • It could be combined with methotrexate, hydroxychloroquine and other non biological DMARDs	**As monotherapy:** • In adult with RA • In children over 2 years with systemic juvenile arthritis (more aggressive) **Combination With methotrexate or other non-biologic anti-Rheumatic drugs:** • Patients with active RA not responding to TNF blockers or other biologic drugs (Refractory cases)
Slide effects	• Upper respiratory tract infections • Activation of latent tuberculosis due to low immunity • Infusion site reaction can be acute • Headache • Cough • Increase the risk of skin cancers including melanoma rare	• Infusion reactions (allergic reaction) • Serious infections (bacterial, tuberculosis ,fungal) • Increase in cholesterol level • Neutropenia, and thrombocytopenia (reversible upon stopping the drug) • Decrease in WBCs (bone marrow depression) • Increase in liver enzymes
Special features	This drug has chimeric IgG1 monoclonal **antibodies** so the body could reject it After intermittent administration by producing human **antichimeric antibodies** in up to 62% of patients. **To prevent the rejection we use the drug in concurrent therapy with methotrexate.** **IMPORTANT Q: explain why methotrexate is used with infliximab ?**	**Drug interactions:** IL-6 inhibits CYP450, and as you now Tocilizumab inhibit IL-6, so the drug restores the activity of the enzyme CYP450 (essential for the metabolism of some drugs such as cyclosporine, warfarin). restoring the activity of CYP450 increases the toxicity and the effect of some drugs such as cyclosporine, warfarin by increasing their metabolism
Mentoring		• Blood tests monthly to see: • increase in cholesterol • liver enzymes • decrease in WBCs

SUMMARY
From team 437





QUIZ

1-What is the drug that block TNF alpha receptor?

A-Olokizumab
B-anakinra
C-Tocilizumab
D-infliximab

2-What is the Role of TNF on osteoclast?

A-joint space narrow
B-joint inflammation
C-bone erosion
D-joint pain

3-It is the first-line DMARD for treating RA

A-Hydroxychloroquine
B-Infliximab
C-Methotrexate
D-Tocilizumab

4-Which one of these is an T-cell modulating drug?

A-Infliximab
B- Abatacept
C-Methotrexate
D-Tocilizumab

5-What is an early phenomenon of Rheumatoid arthritis?

A-Joint damage
b-Joint erosion
C-Disability
D-Fracture

6-What is the anti-RA drug that has a rapid action?

A-Glucocorticoids
B-DMRDs
C-Methotrexate
D-NSAIDs

Answers:
1-D 2-C 3-C 4-B 5-A 6-D

pharmacology

Team 438

GOOD LUCK

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Sources:

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