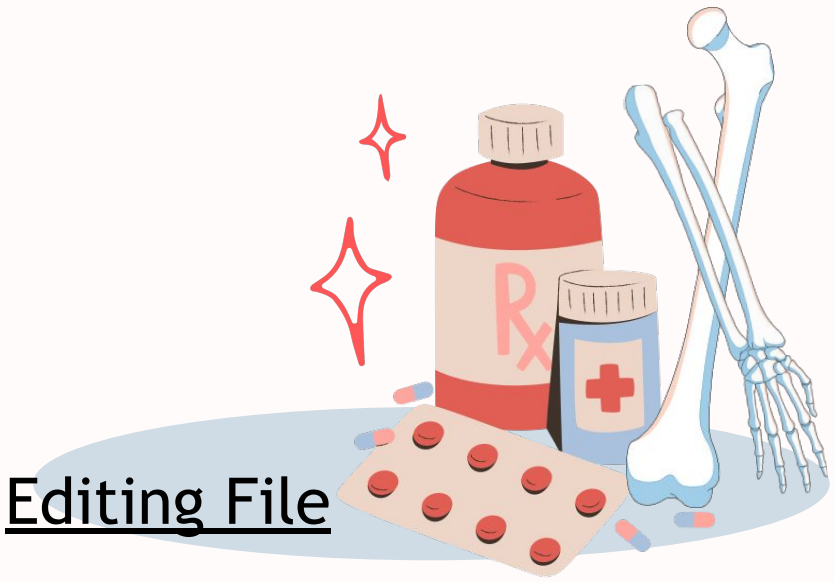
Disease Modifying Anti-Rheumatic Drugs

Lecture no.6

Color Index:

- Main Text
- Important
- Females' Slides
- Males' Slides
- Drs' Notes
- Extra info.



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Objectives

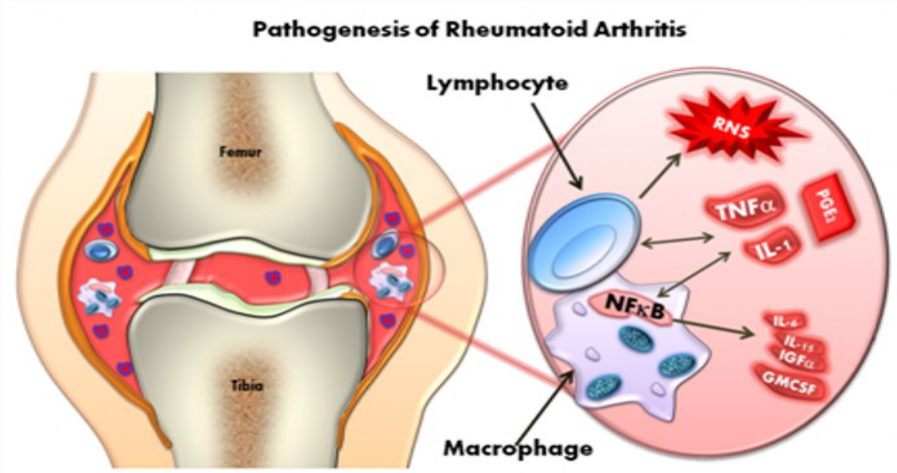
- Define DMARDs & emphasize the rationale for early treatment of rheumatoid arthritis.
- Classify drugs used for treatment of RA.
- Compare and contrast the advantages and disadvantages of NSAIDs, Steroids and DMARDs in treatment of RA.
- Explore the pharmacokinetics aspect and pharmacodynamic effects of selected DMARDs.

Rheumatoid Arthritis

➔ 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.

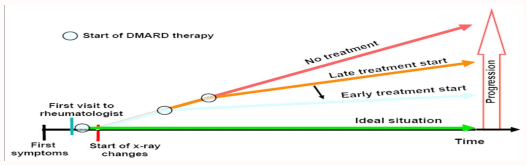
RA is a chronic autoimmune disorder in which the normal immune response is directed against an individual's own tissue leading to :

1. Decline in functional status
2. Work disability
3. Comorbidity
4. Increased mortality



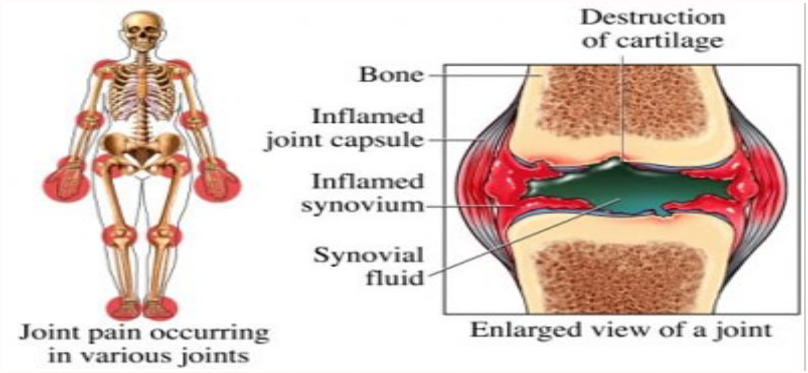
Rationale for early treatment:

- Joint damage is an early phenomenon of RA.
- 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 and aggressive treatment may have long- term benefits.

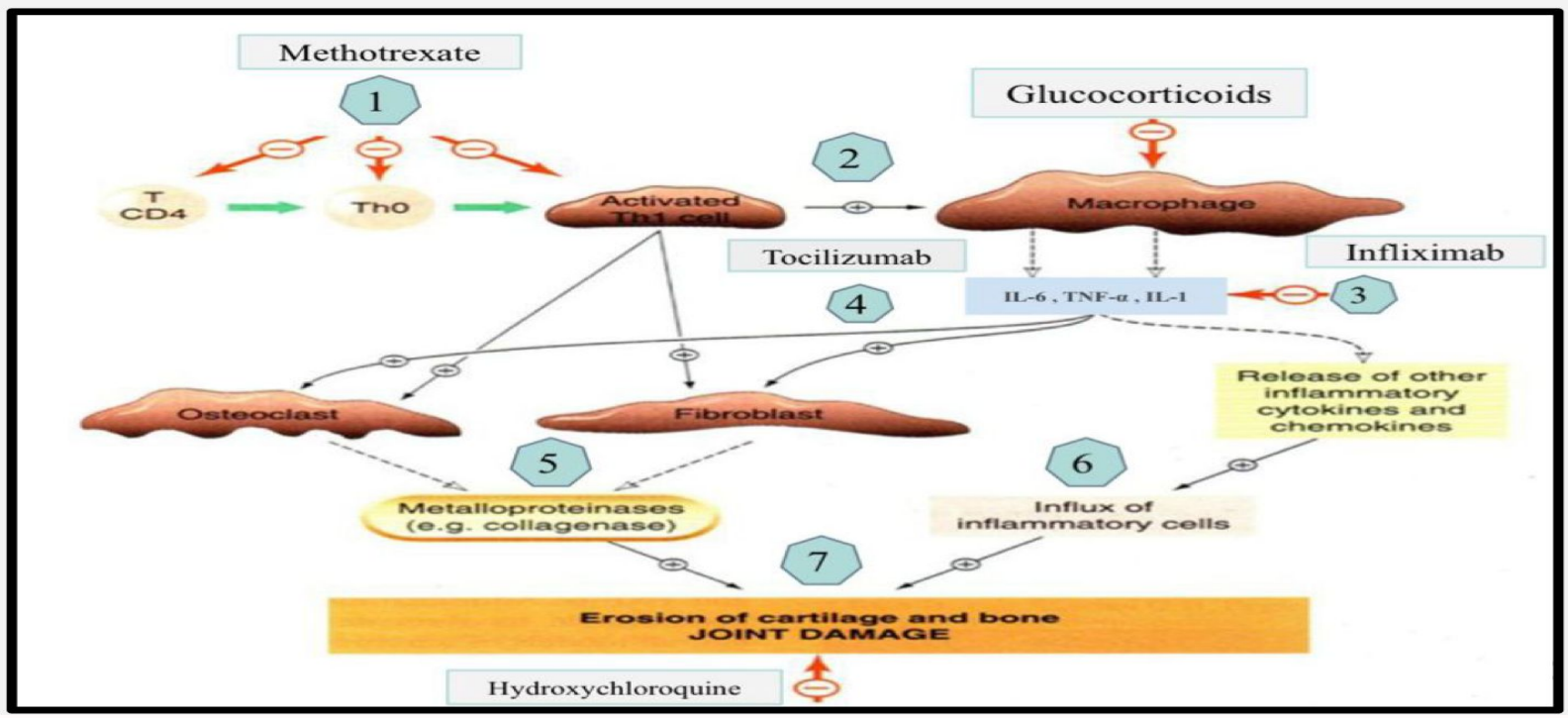


Epidemiology of rheumatoid arthritis:

-Affects 1-2% of the adult population
-Is more common among women than in men (2-3 times)
-Usually appears between age 25 and 40 years.
-The incidence also increases with age peaking between the 4th and 6th decades.
-Causes pain, disability and loss of function.



Pathogenesis of RA



1-Inflammation will stimulate T cells (T helper 1)
2-T-cells stimulate macrophages.
3-Macrophages produce cytokines. (TNF-alpha, IL-6).
4-Cytokines stimulate osteoclast and fibroblast.
5-Osteoclast and fibroblast lysis proteins (the proteins in the collagen by enzyme collagenase).
6-Other way cytokines (TNF-alpha, IL-6) stimulate more cytokines and more inflammatory cells which damage bone and cartilage.
7-The outcomes is erosion of cartilage and bone damage.

Drugs for Rheumatoid Arthritis

DMARDs: Disease Modifying Anti-Rheumatic Drugs

DMARDs

Biologic

-Infliximab
-Tocilizumab

Classical

-Methotrexate
-Hydroxychloroquine

- Used when the disease is progressing and 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. (that's why we use other drugs with them until they give effect)

NSAIDs

-Celecoxib

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

Glucocorticoids

-Prednisone

- 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.
  - Might develop muscle atrophy
  - NSAIDs>Glucocorticoid>DMARDs
  - Therapeutic action involves their anti-inflammatory and immunosuppressant effect.

Methotrexate (Classical DMARD)

- 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 therapy.

M.O.A ★

- **Inhibits dihydrofolate reductase**
- Reduces thymidine and purine synthesis (anti-cancer)
- But at the dosages used for the treatment of RA, methotrexate has been shown to:

1. Stimulate adenosine release from cells, producing anti-inflammatory effect (↓ILs & TNF,↓ metalloproteinases)
2. Inhibition of chemotaxis of polymorphonuclear leukocytes
3. Inhibition of T-cells (cell-mediated immune reactions).

Folic acid is essential for DNA synthesis. Methotrexate prevents folate to be converted to folic acid. Therefore, cell division stops and immune cells don't proliferate .

P.K

- 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 (orally)
- Given as monthly IV

ADRs

- Bone marrow suppression
- Dyspepsia, mucosal ulcers
- Hepatotoxicity
- Pneumonitis (inflammation of the alveoli of lungs)
- Teratogenicity (defects in a developing fetus)
- Leukopenia, anemia, stomatitis, GI ulcerations and alopecia are the result of inhibiting cellular proliferation
  - ★ Give folic acid to reduce GI and bone marrow effects
- Monitoring: full blood count, ALT, creatinine

HYDROXYCHLOROQUINE (Classical DMARD)

M.O.A ★

- Stabilization of lysosomal enzyme activity
- Trapping free radicals
- Suppression of T lymphocyte cells response to mitogens
- Inhibition of leukocyte chemotaxis
- Dampens (reduces) antigen-antibody reactions at sites of inflammation.

P.K

- Rapidly absorbed and 50% protein-bound
- Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes.
- Elimination: half-life is up to 45 days (because it's protein-bound so it takes time to be excreted)
- highly concentrated within cells -> increases intracellular pH (it stabilizes lysosomal enzyme)

٤٣٩: هذا الدواء قلوي، يدخل الحويصلة اللي وسطها حمضي، ويعادل PH فتصير الحويصلة اللي فيها cytokines ما تفرقع وما تطلع الإنزيمات اللي داخلها، وبالتالي مافي chemotaxis فيقل الالتهاب

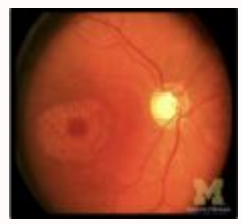
Clinical Uses ★

- 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 are required
- Nausea and vomiting
- Corneal deposits
- **Irreversible retinal damage**,rare
- **Ophthalmologic evaluation every 6 months**

أعراضه الجانبية تكون أكثر على العين، ممكن يعطى للحوامل



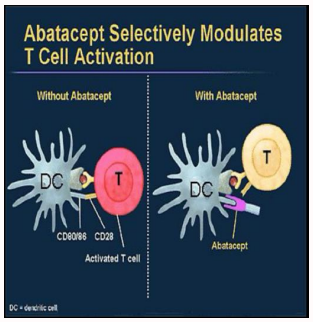
Biologic Disease Modifiers

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

They are expensive.
Last choice drugs

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

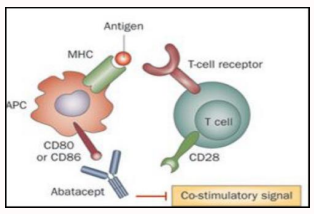
Others work by blocking cytokines,that send signals between those cells.



Classification★

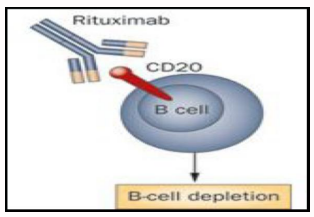
Abatacept

T-cell modulating drug



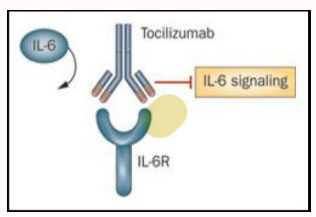
Rituximab

B-cell cytotoxic agent



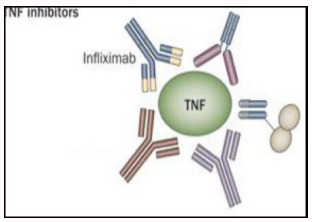
Tocilizumab

Anti-IL-6 receptor antibody



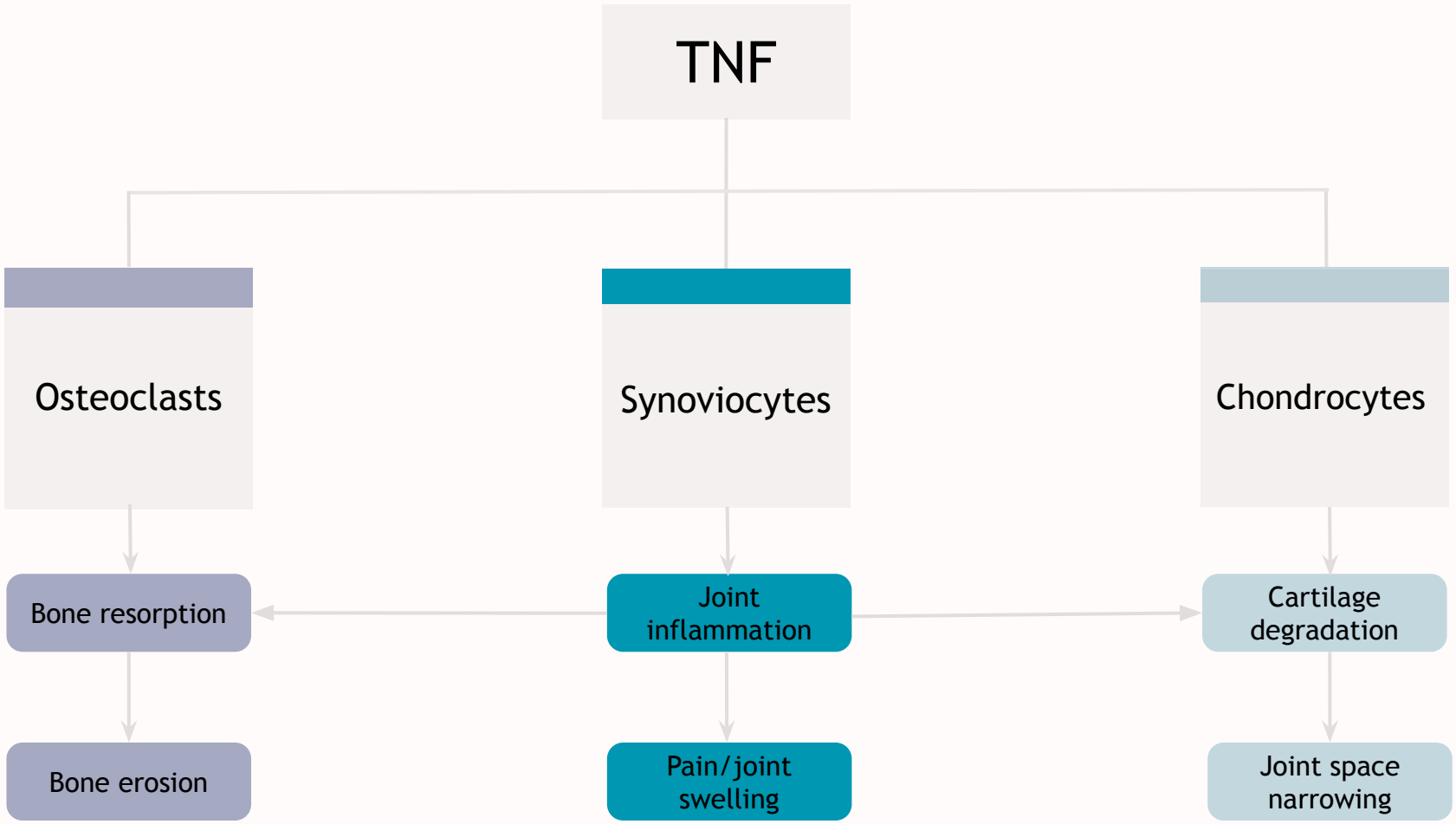
Infliximab

TNF-a blocking agents



TNF α Blocking Agents

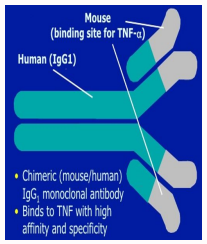
Role of TNF on Joint Destruction



Tumor necrosis factor-alpha (TNF-a) is a proinflammatory cytokine that plays a pivotal role in regulating the inflammatory response in rheumatoid arthritis (RA).We need to inhibit to stop the inflammation in joints.
(Team 442 note)

Infliximab

(TNF-a blocking agents)



- Infliximab is a chimeric **IgG1** monoclonal antibody (25% mouse,75% human).

★ Mechanism of Action

-It complexes with soluble TNF-a (and possibly membrane-bound TNF-a)and prevents its interaction with cell surface receptors.
-This results in down-regulation of macrophage and T-cell function.
Note : In infliximab , the suffix-mab is a short cut for (Monoclonal Antibody)

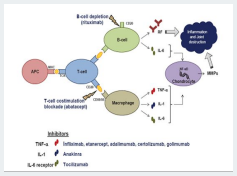
Pharmacokinetics

-Given as a IV infusion with "induction" at 0,2,and 6 weeks, then 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.

The body produce antibodies against this drug and becomes INACTIVE so we give methotrexate to reduce the antibodies against it.

★ ADRs

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



TNF function is to destroy cells including cancer cells so when we give INFLIXIMAB we decrease TNF SO it increase the risk of getting cancer.

★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.

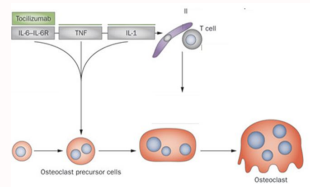
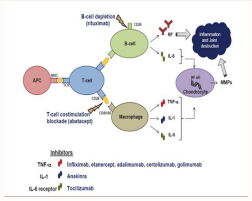
Monoclonal Antibody Directed Against TNF-a:

1) Infliximab (Remicade)- binds to free TNF-a
2)Adalimumab (Humira)- binds to free TNF-a
3)Etanercept(Enbrel)- engineered soluble TNF receptor

Explanation:
Usually,when TNF-a binds to its receptor it will trigger an inflammatory response. So Infliximab or Adalimumab bind to TNF-a preventing it from binding to its receptor. It was then found out that the TNF receptors themselves could also move and go bind to TNF and solubilize producing an inflammatory response . For this reason, Etanercept was made ; it will go to TNF-a and block it preventing it from binding to its receptor. So these are two ways where TNF can be blocked to prevent formation of inflammation.

Tocilizumab

(Anti-IL-6 receptor antibody)

P.K	• Half-life is dose dependent (increase dose, increase half life) • Given monthly as IV.
M.O.A	• IL-6 is a proinflammatory cytokine, involved 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.
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 Uses	• Used as monotherapy in adults with rheumatoid arthritis,or in children over 2 years with systemic juvenile arthritis. • Used in combination with methotrexate or other non-biologic anti-rheumatic in patients with active rheumatoid arthritis not responding to TNF blockers or other biologic drug
ADRs	 • Infusion reaction • Serious infections (bacterial,tuberculosis,fungal) • Increase in cholesterol level • Decrease in WBCs • Increase in liver enzymes • Blood tests will be used monthly for increase in cholesterol, liver, enzymes & decrease in WBCs. • Neutropenia and thrombocytopenia(reversible upon stopping the drug)

Males' Slides:

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.

MCQs

Q1.Which of the following drugs requires the patient to do ophthalmic evaluation every 6 months?			
a) Methotrexate	b) Infliximab	c) Hydroxychloroquine	d) Tocilizumab

Q2.Which of the following drugs inhibits T-cells (cell-mediated immune reactions)			
a) Methotrexate	b) Hydroxychloroquine	c)Infliximab	d) Tocilizumab

Q3.Which of the following DMARDs causes irreversible retinal damage?			
a) Tocilizumab	b) Methotrexate	c) Infliximab	d) Hydroxychloroquine

Q4.What can affect the metabolism of cyclosporine / warfarin ?			
a) Abatacept	b) Infliximab	c) Tocilizumab	d) Rituximab

Q5.Which of the following is a TNF-a blocking agent?			
a) Abatacept	b) Infliximab	c) Tocilizumab	d) Rituximab

Q6. What is contraindicated in latent TB or URT infections ?			
a) Infliximab	b) Methotrexate	c) Tocilizumab	d) Hydroxychloroquine

ANSWERS: 1) c 2) a 3) d 4) c 5) b 6) a

SAQs

1 **At dosages used for the treatment of RA, methotrexate has been shown to :**

1. stimulate adenosine release from cells, producing anti-inflammatory effect.
2. Inhibition of chemotaxis of polymorphonuclear leukocytes
3. Inhibiting of T-cells

2 **What is the mechanism of action of hydroxychloroquine ?**

- Dampens (reduces) antigen-antibody reactions at sites of inflammation.
- inhibition of leukocyte chemotaxis
- suppression of T lymphocytes cells response to mitogens
- trapping free radicals
- Stabilization of lysosomal enzyme activity

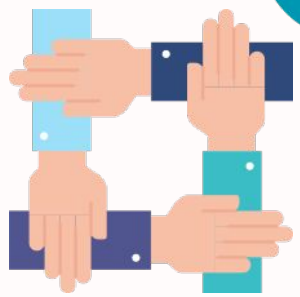
3 **What is the mechanism of action of Infliximab ?**

- This results in down-regulation of macrophage and T-cell function.
- It complexes with soluble TNF-a (and possibly membrane-bound) and prevents its interaction with cell surface receptors.

4 **What are the biological DMARDs?**

1-Abatacept
2-Rituximab
3-Tocilizumab
4-Infliximab

Team Leaders:



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