Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Disease Modifying Anti-rheumatic Drugs

"DMARDs"

تحت المراجعة
غيداء ال معمم
&
عبدالرحمن الخيسواني

Objectives:

Editing File

- ✓ 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.

Important Notes Extra

Overview of Rheumatoid Arthritis

What is Rheumatoid Arthritis?

It is a chronic autoimmune) (Normally our immune system is directed towards invaders) disorder in which the normal immune response is directed against an individual's own tissue causing destruction to those tissue.

❖ This disorder leads to:

- Decline in functional status
- Work disability & socioeconomic costs.
- Systemic complications. Affects other tissues
- Co-morbidity & Increased mortality.

❖ Epidemiology of RA:

- Affects 1-2 % of the adult population.
- It's common in women than men (2 or 3 times) (It is an autoimmune disease so it is common in females than males) .
- Usually appears between ages 25 and 40 years(middle age).
- The incidence also increases with age, peaking between the 4th and 6th decades. Sometimes occurs within childhood, it is called (systemic juvenile arthritis)
- Causes pain,deformity,stiffness, disability* and loss of function. *For example patient can't hold a cup with her hand!

Cont.

❖ Characteristic of RA:

- Bone erosion
- Inflammation and hyperplasia of synovial membrane (Swelling)

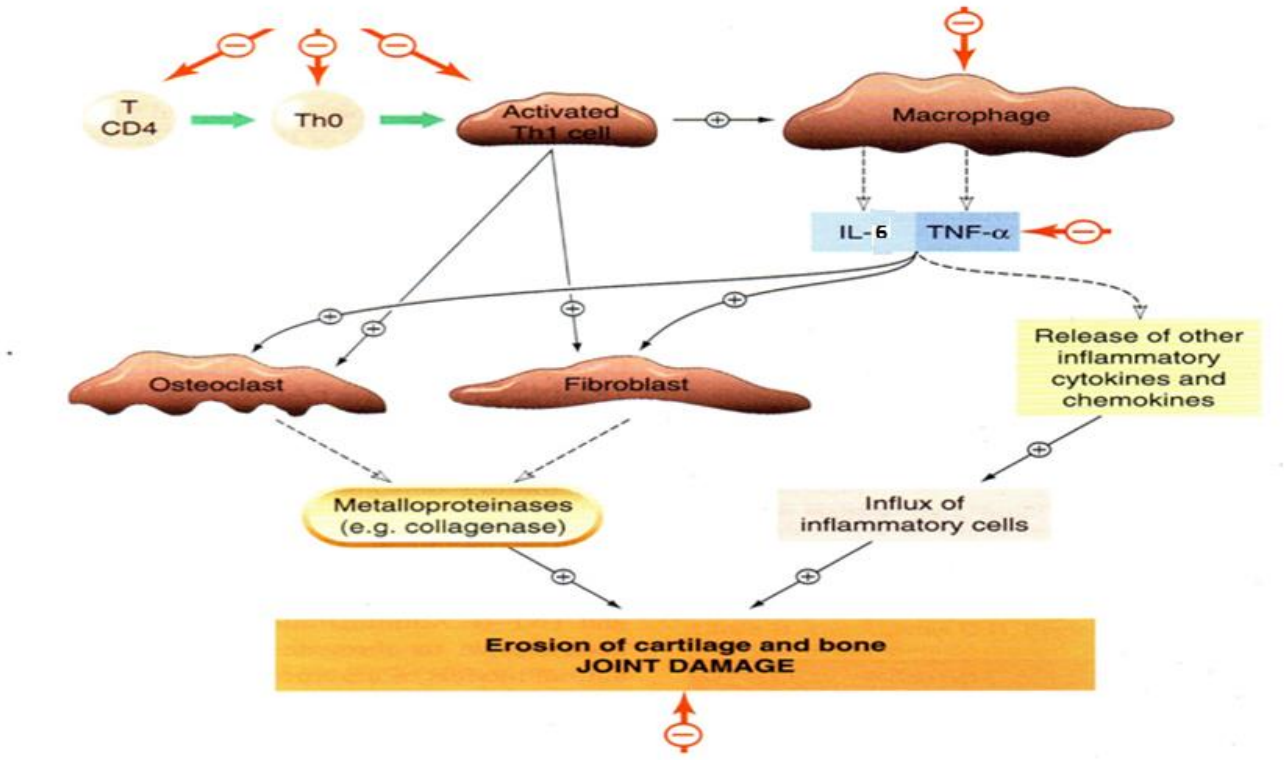
❖ Systemic complications of RA:

- Anemia
- Weight loss
- Osteoporosis
- Amyloidosis
- Renal, cardiovascular and neurological complications

❖ Pathogenesis of RA: Further explanations are in next slide!

1-Synovial inflammation and hyperplasia	2-Autoantibody production (Rheumatoid factor)	3-Cartilage and bone destruction (Deformity)
First there will be inflammation in the joint (especially in the synovial fluid) associated with hyperplasia (the place of the joint got bigger)	The inflammation started, so the T cells and B-cells will stimulate and that will produce antibodies in patient's serum.	the cytokines producing from the inflammatory cells will stimulate the osteoclast (TNF-α) and chondrocyte (which degrades the collagens "cartilage").

To Understand Better!



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:

- ✓ Th-cells
- ✓ B-lymphocytes
- ✓ TNF-alpha
- ✓ IL-6 → Both are inflammatory cytokines

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.

✓ More details are discussed in Pathology.

Drugs use for Rheumatoid Arthritis

Glucocorticoids

- Strong 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. Used in acute diseases with DMARDs just to relieve the pain until the DMARDs start to produce their action
- Reserved for temporary control of severe exacerbations and long-term use in patients with severe disease not controlled by other agents.
- too toxic for routine chronic use. that means we use glucocorticoids for short time, if we use it for long time it will be toxic. Worse than NSAIDS.

NSAIDs

- Rapid onset of action Used in acute cases to relief inflammation & pain
- Provide partial relief of pain and stiffness (Gives temporary relief and she/he can moves joint easily)
- Do not slow the progression of the disease hence can not stop formation of new deformity
- Chronic use (long use or high dose) should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.

NSAIDs and Glucocorticoids are both used in acute stage to reduce pain and inflammation so they don't give good prognosis since can't stop progression of the disease.

DMARDs

- Slow onset of action
- Arrest progression of the disease
- Prevent formation of new deformity

} Good prognosis but can't treat previous deformity.

- Used in chronic cases when deformity is existing

NSAIDs VS DMARDs:

	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

Cont. NSAIDs VS DMARDs:

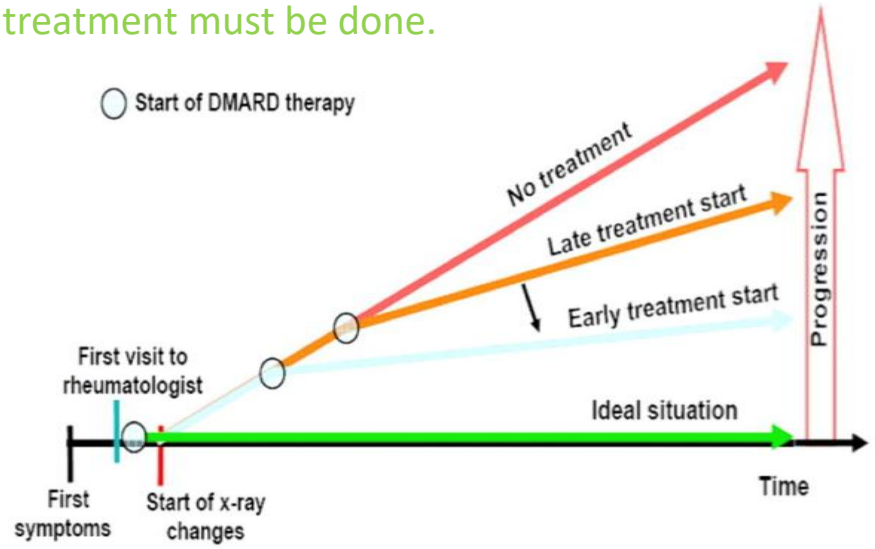
Deformity	Prevent new deformity	Can not stop the new deformity
Uses	In **chronic cases** if there is deformity	In **acute cases** to relief the pain and the inflammation

Rational for early treatment

❖ Stages of disease development:

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 patient will be work disabled.

✓ Joint damage (It is symmetrical) starts early in the disease so any delay in treatment will lead to severe deformity of the joint. Early diagnosis and aggressive treatment must be done.



Cont. Rational for early treatment

❖ Types of treatment:

Early Treatment	Late Treatment
•long-term benefits of the treatment The disease has not effect the whole joint or many joints in the body, and the drugs will slow the prognosis of the disease	•Sever disease + increasing in the mortality The disease effect manly so many joints in the body, so the prognosis of the disease is very sever, the drugs cannot treat anything

Classification of DMARDS

Class	DMARDs	
Sub-class	Biologic	Classical
Drugs	• Infliximab (famous) • Tocilizumab more important and more expensive subclass	• Methotrexate Anti-cancer • Hydroxychloroquine
M.O.A	Act on the immune system to slow the progression of Rheumatoid Arthritis.	
General features	❖ Used when the disease is progressing and causing deformities ❖ **Can not repair the existing damage but prevent further deformity** ❖ **Have no analgesic effect (no effect on Prostaglandins)**. That's why we use NSAIDs or Glucocorticoids with them ❖ Their effects take from 6 weeks up to 6 months to be evident.	

Classical DMARDs:

- ✓ Low molecular weight
- ✓ Adequate hydration (drinking a lot of water) is important in high dose of Methotrexate

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.**
Mechanism of action	**At High Dose (Anti-cancer):** تأثير الدواء و عمله يعتمد على مقدار الجرعة • Inhibits Dihydrofolate Reductase (to convert Folic acid into tetrahydrofolate) which is responsible for formation of **Thymidine** and **purine** which is important for DNA (No DNA means no proliferation of the cells) **At Low Dose (Treat RA):** • Anti-inflammatory effect by stimulating adenosine release from cells • Inhibition of Polymorphonuclear chemotaxis so don't migrate to inflammation site • Inhibition of T-cells (Cell-mediated immune reactions)
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 excrete in bile. Enterohepatic circulation ➢ Given 7.5-30 mg weekly.
ADRs	• Bone marrow suppression. due inhibition of mitosis • Dyspepsia, mucosal ulcers*. • Hepatotoxicity*. • Pneumonitis*. Inflammation of lung • Teratogenicity*. In pregnancy • Leukopenia, anemia, stomatitis, GI ulcerations, & alopecia are probably the result of **inhibiting cellular proliferation***. in rapidly dividing cells • **Folic acid reduces GI & bone marrow effects.** • **Monitoring**: Full blood count, ALT (liver enzyme),Creatinine. *Anti-cancer effect

Cont. of Classical drugs

Drug	**Hydroxychloroquine**
M.O.A	1. Stabilization of lysosomal enzyme activity. 2. Trapping free radicals. Those reactive substances are found in all inflammatory processes 3. Suppression of T lymphocyte cells response to mitogens. 4. Inhibition of leukocyte chemotaxis. It is a drug that acts on cells.
P.K	➢ Rapidly absorbed and 50% protein-bound. ➢ **Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes.** ocular side effects ➢ Elimination half-life up to 45 days. ➢ Highly concentrated within cells which increases intracellular pH.
ADRs	Doesn't have a lot of ADRs unlike Methotrexate. • Least toxic, no blood tests is required. • Nausea & vomiting. • **Corneal deposits*.** • **Irreversible retinal damage*.** • **Ophthalmologic evaluation every 6 months*.** *Ocular (eyes) side effects mainly!!!
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 months response, mild anti-rheumatic effect.

Biologic Disease Modifier:

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

Cont. of Biologic Disease Modifier:

- **The drugs work by:**

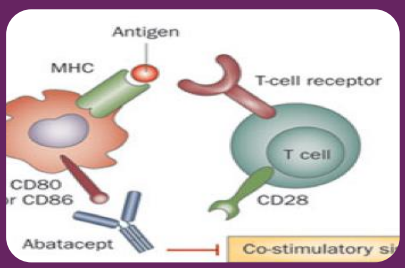
1. Work as agents block or
2. modify the activity of selected cells in the immune system. Act on T-cells or B-cells or any immune system cells
3. blocking cytokines, that send signals between those cells.

- The drugs are **expensive,** high molecular weight and genetically synthesized

❖ Classification of Biologic Disease Modifier

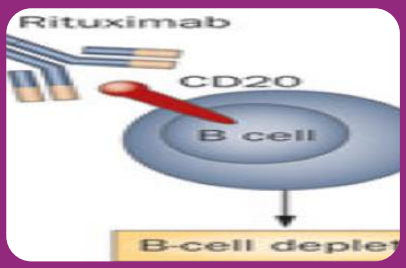
VERY IMPORTANT!

T-cell modulating drug (Abatacept)



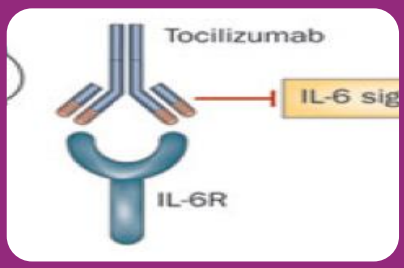
Its modulates the immune response by binding to CD80/CD86 on an antigen presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding to CD28 on naïve T-cell and attenuating T-cell activation.

B-cell cytotoxic agent (Rituximab)



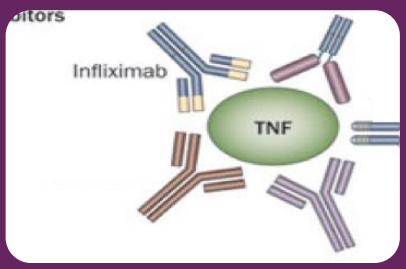
The drugs are look like antibodies which will go to the B-cells and bind with the antigen on the surface of the B-cells, after the drug binds with the antigen it will destroy the B-cells

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)



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

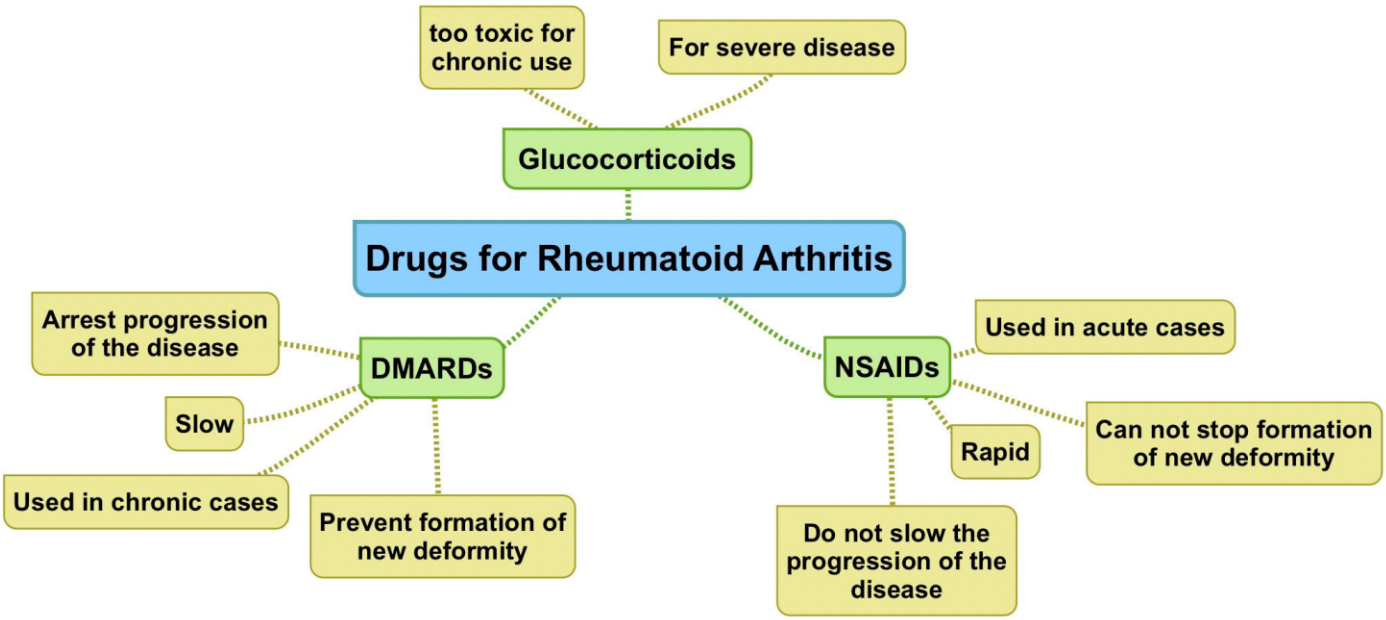
VERY IMPORTANT!

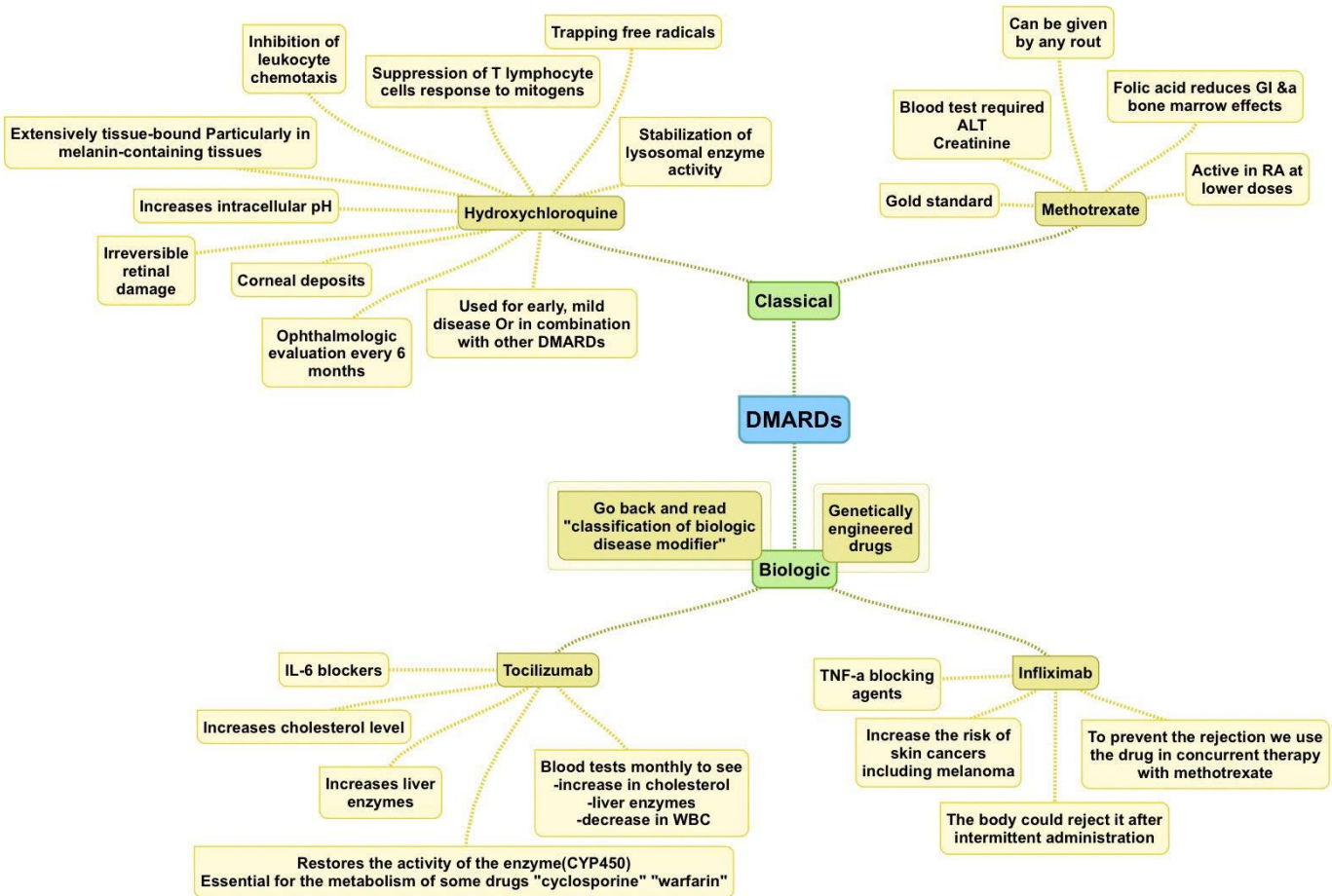
VERY IMPORTANT!

VERY IMPORTANT!

Drug	Infliximab (TNF-α blocking agents)	Tocilizumab (IL-6 blockers) VERY IMPORTANT!	
Definition	**A chimeric** (two sources; human+mouse) IgG_1 monoclonal antibody (25% mouse, 75% human)	**IL-6 is a proinflammatory 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 • 9–12 days	• Intravenous (IV) monthly • **Half life:** dose-dependent	
Clinical uses	• use in autoimmune disease like (RA, Ankylosing spondylitis, Crohn's disease, ulcerative colitis) not only RA • It may combined with methotrexate, hydroxychloroquine and other non biological DMARDs	As monotherapy: • In adult has rheumatoid arthritis • **In children over 2 years with systemic juvenile arthritis** (more aggressive)	Combination with methotrexate or other non-biologic DMARDs: Patients with active rheumatoid arthritis not responding to TNF blockers or other biologic drugs (Refractory cases)
Side effects	• Upper respiratory tract infections • **Activation of latent tuberculosis** • Infusion site reaction • Headache • Cough • **Increase the risk of skin cancers including melanoma**	• 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 morrow) • Increase in liver enzymes	
Special features	This drug has **chimeric** IgG_1 monoclonal antibody so the body could reject it After intermittent administration by elicits human antichimeric antibodies in up to 62% of patients. To prevent the rejection we use the drug in Concurrent therapy with **methotrexate**	**Drug interactions:** ***IL-6 inhibits CYP450, and as you now Tocilizumab inhibit IL-6, so the drug restores the activity of the enzyme (essential for the metabolism of some drugs such as cyclosporine, warfarin).** *no drug interaction.	
TNF-alpha Destructive role	• Acts on osteoclasts leading to bone erosion • Acts on synoviocytes leading to pain and swelling • Acts on chondrocytes leading to joint space narrowing	Mentoring	Blood tests monthly to see • increase in cholesterol • liver enzymes • decrease in WBCs

Summary


too toxic for chronic use
For severe disease
Glucocorticoids
Drugs for Rheumatoid Arthritis
Arrest progression of the disease
DMARDs
Slow
Used in chronic cases
Prevent formation of new deformity
NSAIDs
Used in acute cases
Can not stop formation of new deformity
Rapid
Do not slow the progression of the disease


Inhibition of leukocyte chemotaxis
Trapping free radicals
Suppression of T lymphocyte cells response to mitogens
Extensively tissue-bound Particularly in melanin-containing tissues
Stabilization of lysosomal enzyme activity
Increases intracellular pH
Hydroxychloroquine
Irreversible retinal damage
Corneal deposits
Ophthalmologic evaluation every 6 months
Used for early, mild disease Or in combination with other DMARDs
Can be given by any rout
Folic acid reduces GI &a bone marrow effects
Blood test required ALT Creatinine
Active in RA at lower doses
Gold standard
Methotrexate
Classical
DMARDs
Go back and read "classification of biologic disease modifier"
Genetically engineered drugs
Biologic
IL-6 blockers
Tocilizumab
Increases cholesterol level
Increases liver enzymes
Blood tests monthly to see -increase in cholesterol -liver enzymes -decrease in WBC
Restores the activity of the enzyme(CYP450) Essential for the metabolism of some drugs "cyclosporine" "warfarin"
TNF-a blocking agents
Infliximab
Increase the risk of skin cancers including melanoma
To prevent the rejection we use the drug in concurrent therapy with methotrexate
The body could reject it after intermittent administration

Questions

MCQs:

1-A 67 years man with history of Rheumatoid arthritis was referred to ER department after severe chest pain and collapsing. He was having heart attack and died at hospital after many tries of CPR. At autopsy , they found Atheroma (Fat plaque) obstructing his main coronary artery. Which drug he was on and that possibly caused atherosclerosis?

A)Tocilizumab
B)Infliximab
C)Ibuprofen

2-Could be used as antioxidant

A)Isoniazid
B)Hydroxychloroquine
C) Methotrexate

3-"Stimulating adenosine release from cells", it is the mechanism of action of which of the following DMARDs?

A)Methotrexate
B)Tocilizumab
C)Infliximab

4-Salma is a CEO at company and lately was diagnosed with Melanoma after 2 years of suffering from Rheumatoid arthritis. Which drug had caused this side effect to her?

A)Infliximab
B) Abatacept
C)Rituximab

5-To avoid deformities in RA, what should be done?

A)Starts with NSAIDs
B)Start treatment early with NSAIDs to relieve pain until DMARDs shows their effect
C)Surgery to wash out deposits and then start Steroids

1-A
2-B
3-A
4-A
5-B

Questions

SAQ:

- **Mention all biologic disease modifiers classes with their mechanism of action and give one example of each.**

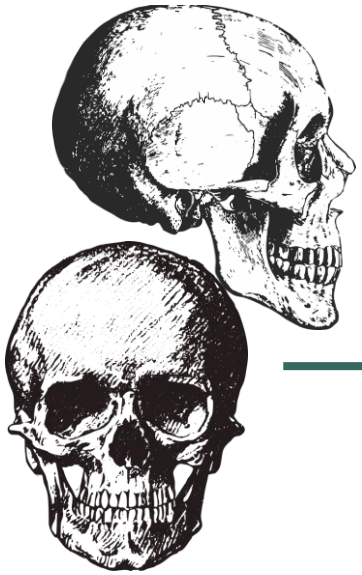
  Answer is in slide 10.
  Make sure to write drugs name correctly.

- **Why do we have to start treatment early with RA? Also, talk about one drug that's used to treat RA.**

  1. To avoid progressive deformities and disability.
  2. You can mention any drug you want with its MOA and ADRs and uses.

- **DMARDs act on what?**

  Acts on immune system by affecting:
  - ✓ Th-cells
  - ✓ B-lymphocytes
  - ✓ TNF-alpha
  - ✓ IL-6



"It is not hard, you just made it to the end!"

Team Leaders:

Yazeed Al-Harbi & Aseel Ba Dukhon

Thanks for those who worked on this lecture:

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Noura Al-Othaim

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References:

- ✓ Team436
- ✓ Doctors' notes and slides

@Pharma4370 pharmacology437@gmail.com