PHARMACOLOGY
TEAM 439

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MED439
KING SAUD UNIVERSITY

Editing file

DMARDS

OBJECTIVES:

- 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 pharmacokinetic aspects and pharmacodynamic effects of selected DMARDs

Important

In male and female slides

Only in male slides

Only in female slides

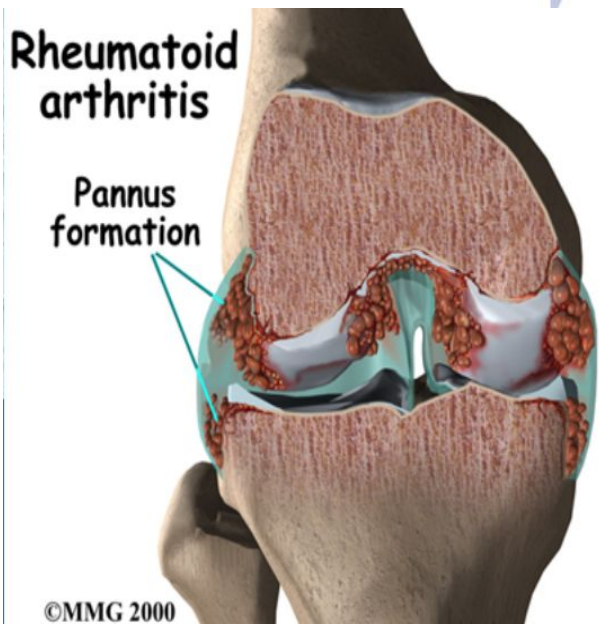
Extra information

Helpful video

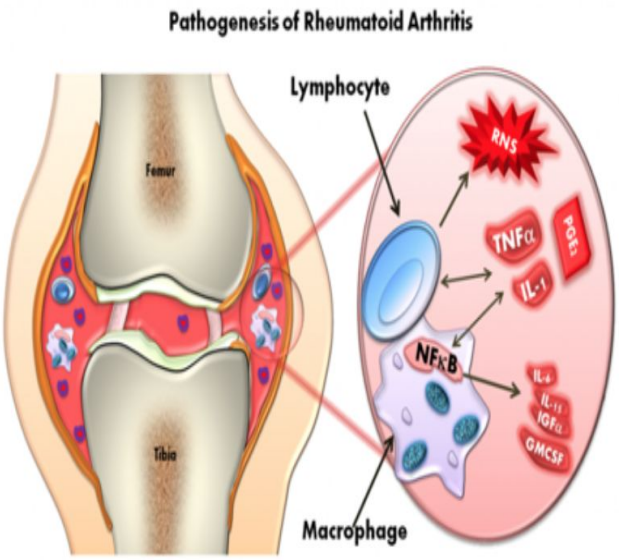
Rheumatoid Arthritis

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



- 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

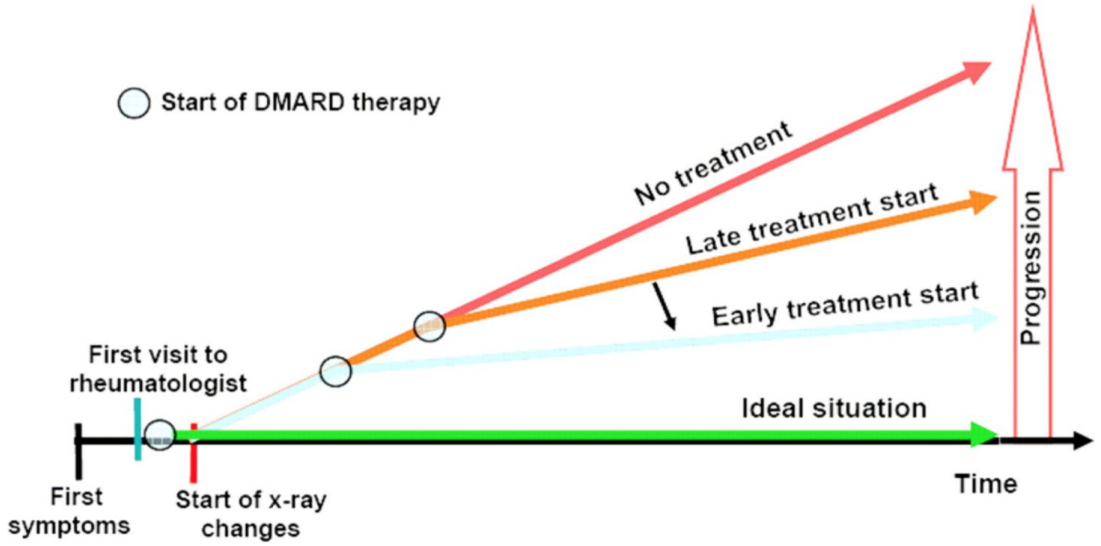


Rational for early treatment

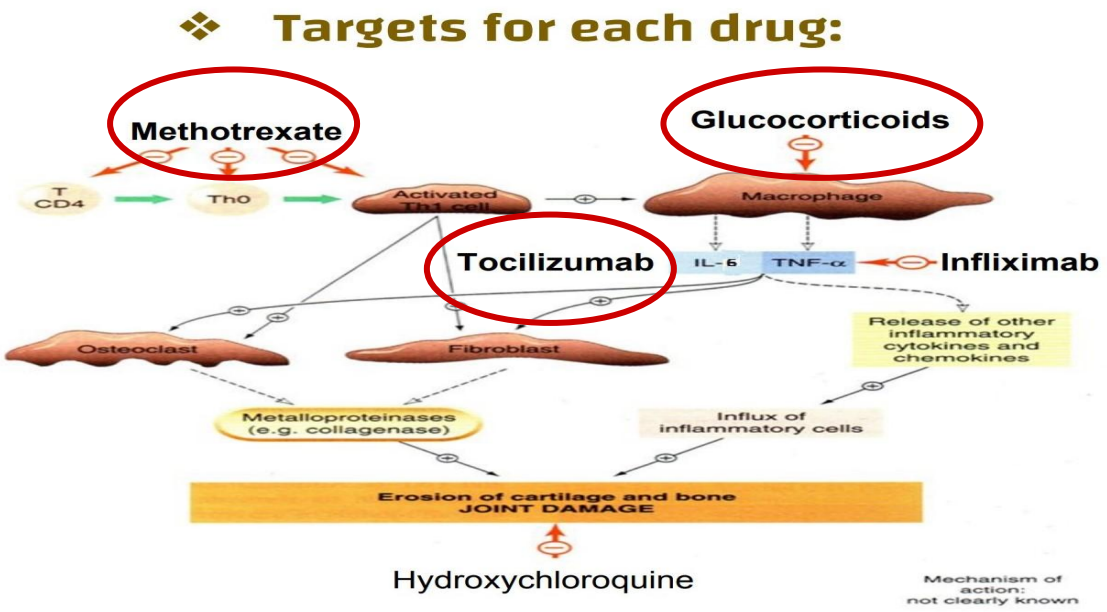
- Joint damage is an early phenomenon of rheumatoid arthritis
- Joint erosions occur in up to 93% of patients within less than 2 years of disease activity
- Disability occurs early – 50% of patients with RA will be work disabled at 10 years
- Severe disease is associated with increased mortality
- Early and aggressive treatment may have long-term benefits

Rational for early treatment

This diagram shows: The earlier the treatment when RA symptoms appears, the better the prognosis



Pathogenesis



Drugs for Rheumatoid Arthritis

- DMARDs
  - Classical
  - Biologic
- NSAIDs
- Glucocorticoids

Comparison between Rheumatoid arthritis drugs

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 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).
- 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

We give (glucocorticoid) until the DMARDs give its effect

DMRADs

Disease-**M**odifying **A**nti-**R**heumatic **D**rugs

- 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 (that's why we use other drugs with it)

Classical

- Methotrexate
- Hydroxychloroquine

Biologic

- Inflixi**mab**
- Tocilizu**mab**

Methotrexate

1.Gold standard"& is the first-line DMARD
2.Active in RA at (lower doses) and in cancers at (high Dose) chemotherapy

Mechanism

- Inhibits dihydrofolate reductase
- Reduces thymidine & purine synthesis (anticancer)
- 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)

  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

Pharmacokinetics

- Approximately 70% absorbed after oral administration
- Given as monthly IV
- 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)

ADRS

- Bone marrow suppression.
  There's bone depression because this drugs prevents cell division.
- Dyspepsia(عسر هضم), 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

MOA

- 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

Pharmacokinetics

- 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)

يعني هذا الدواء قلوي ، فيدخل الحويصلة اللي وسيطها حمضي ، ويعادل الPH، فتصير الحويصلة اللي فيها ال cytokines ما تفرقع وما تتطلع الإنزيمات اللي داخلها، وبالتالي مافي chemotatix، ويقل الإلتهاب

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 is required
- Nausea & vomiting
- Corneal deposits
- Irreversible retinal damage
- Ophthalmologic evaluation every 6 months

أعراضه الجانبية تكون أكثر على العين ،،،ممكن ينعطى للحوامل

Biologic disease modifier

- They are 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

Classification

غالبا يسون اختبار دم على حسب المرتفع من الانفلاميشن في الجسم ، يبدون بدواء معين فإذا ما أعطى فائدة ، يجربون غيره وهكذا

Infliximab

TNF-a blocking agents

Tocilizumab

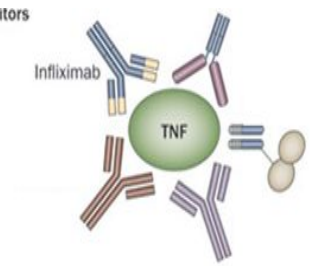
Anti-IL-6 receptor antibody

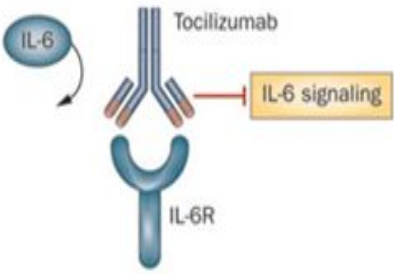
Rituximab

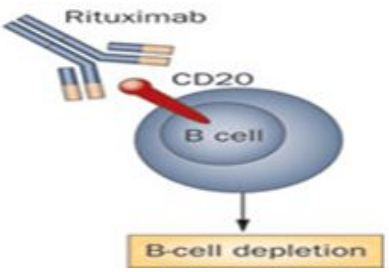
B-cell cytotoxic agent

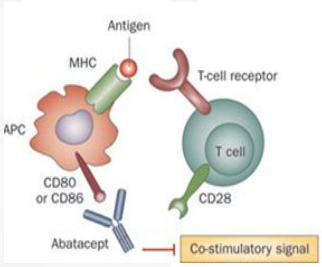
Abatacept

T-cell modulating drug

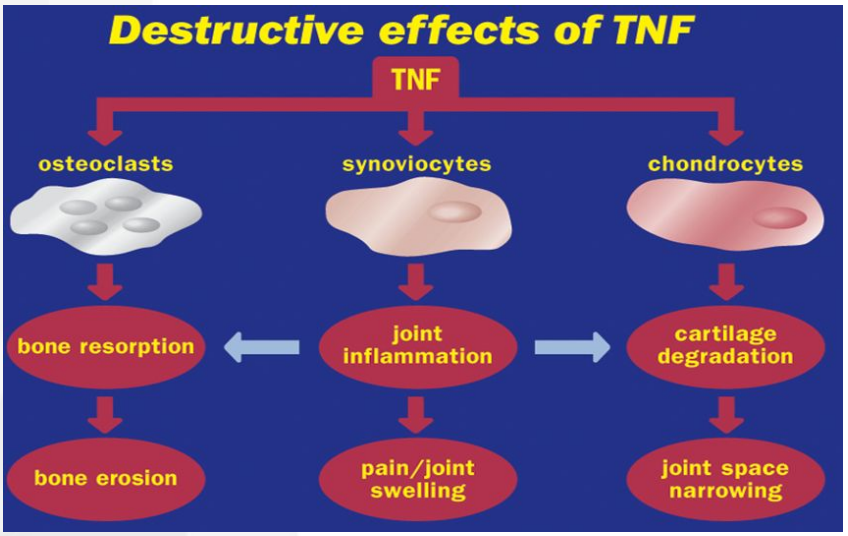








Role of TNF- α on joint destruction



TNF- α acts on osteoclasts to start bone destruction, stimulates chondrocytes to increase cartilage degradation. And it also causes synovium to swell when acting on synoviocytes.

Infliximab
(TNF- α blocking agents)

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

MOA

- 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.

Note : In inflixi**mab**, the suffix -MAb is a short cut for (Monoclonal Antibody). E.g: Adalimu**mab**

Pharmacokinetics

- Given as an intravenous infusion with "induction" at 0, 2, and 6 weeks, then maintenance every 8 weeks thereafter.

نعطي الدواء بالأسبوع الصفر ، يعني أول مرة كجرعة أولى ، ثم بالأسبوع الثاني ، ثم الأسبوع السادس ، ثم نحافظ على الجرعة كل ثمانية أسابيع

- 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

يعني أن الجسم يكون antibodies ضد هذا الدواء، ويصير غير فعال ، لذلك نعطي معه methotrexate حتى نقلل مهاجمة الجسم له و نقلل ال Antibodies

Clinical uses

- Infliximab is approved for use in RA, Ankylosing spondylitis (inflammation to bones of vertebrae), Crohn's disease, ulcerative colitis
- It could be combined with methotrexate, hydroxychloroquine and other non-biological DMARDs ما نعطيه لحاله حتى لا تقل فعاليته

ADRS

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

وظيفة الTNF-a أنه يدمر الخلايا وحتى الخلايا السرطانية ويحارب العدوى ، فإذا عطينا infliximab ، رح يقل مستوى الTNF وبالتالي يزيد خطر الإصابة بالأورام والعدوى والTb.

Tocilizumab

MOA

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

Pharmacokinetics

- Half-life is dose-dependent
  يعني كل ما زادت الجرعة ، كل ما زادت الhalf-life
- Given as monthly IV

Clinical uses

- Used as monotherapy in adult with rheumatoid arthritis, or in children over 2 years with systemic juvenile arthritis
- Used 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

ADRS

- Infusion reactions
- Serious infections (bacterial, tuberculosis ,fungal)
- 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

Drug interactions

- IL-6 inhibits CYP450
- Tocilizumab restores the activity of the enzyme (Because it inhibits IL-6. creating an increase in CYP450 which metabolises some drugs like warfarin and cyclosporine which leads to a reduced effect of these drugs).

MCQ

1- Usually Rheumatoid Arthritis affects:			
A- between ages 25 and 40 years	B- Old people and children	C- Women more than men	D- Both A & C

2- Which of these statements is incorrect about NSAIDs ?			
A-Provide partial relief of pain and stiffness	B- Rapid onset of action	C- slow the progression of the disease	D- Used in acute cases to relief inflammation

3- Hepatotoxicity is an ADR that happen when you take:			
A-Methotrexate	B-Hydroxychloroquine	C-Tocilizumab	D- Infliximab

4- One of these Drugs is not used to treat Rheumatoid Arthritis			
A- Hydroxychloroquine	B- Methotrexate	C- Atracurium	D- Tocilizumab

5-Which of the following drugs is a blocker for IL-6 receptor used to treat inflammation?			
A-Methotrexate	B-Hydroxychloroquine	C-Tocilizumab	Infliximab

ANSWERS

1	2	3	4	5
D	C	A	C	C

1)why infection may appear when infliximab or tocilizumab are prescribed ?

2)Which drug is an antibody against TNF-a, used to treat inflammation?

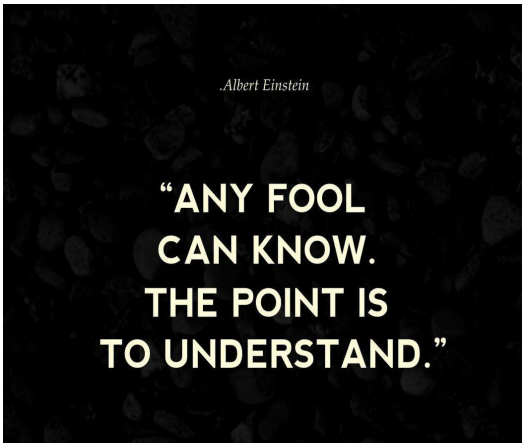
3)why does methotrexate have a side effect on bone marrow, WBC and hair follicles ?

A1) ~~Because they are immunosuppressant~~

A2) ~~Infliximab~~

A3 ~~because methotrexate prevents DNA replication, therefore, proliferation stops and the number of cells decreases.~~

GOOD LUCK!



Team leaders

طرفة الشريدي
حمود القاضب

Girls team members

منيرة السدحان
لينا المزيد
سديم الحازمي
نورة المسعد
وسام ال حويس
رانيا المطيري
الجوهرة البنيان
شادن العبيد
سديم آل زايد
روان باقادر
ميس العجمي
نورة السالم
نوف السبيعي
ندى بابللي
دانه نائب الحرم

Boys team members

بسام الاسمري
ماجد العسكر
باسل فقيها
عبدالرحمن الدويش
حمد الموسى
راكان الدوهان
محمد القهيدان

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