Clinical pharmacology

(Rheumatoid arthritis & Osteoarthritis)

5th year lecture

4 December 2017

Rheumatoid arthritis

Definition

- Chronic multisystem disease of unknown aetiology
- Characterized by synovitis
- Involves peripheral joints
- Not spine (Except C1) C1-C2 atlanto axial joint
- Symmetrical
- Leads to cartilage damage and bone erosions and subsequent joint damage

Pathogenesis

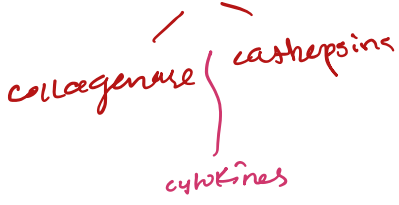
1. hyperplasia and hypertrophy of the synovial lining cells
- vascular changes:
2. – microvascular injury
   – Thrombosis
   – Neovascularization
3. Oedema
4. infiltration with mononuclear cells

Cells

- mononuclear cell collections are predominantly T lymphocyte.
- CD4+ T cells > CD8+ T cells
- autoantibodis (RF & CCP) are produced within the synovial tissue lead to the formation of immune complexes
- synovial fibroblasts produce enzymes such as collagenase and cathepsins that degrade components of the articular matrix
- Osteoclasts are also prominent at sites of bone erosion.

Cytokines

- secreted by activated lymphocytes, macrophages, and fibroblasts.



Treatment of RA

The goals of therapy are

- (1) relief of pain
- (2) reduction of inflammation
- (3) protection of articular structures
- (4) maintenance of function
- (5) control of systemic involvement

- None of the therapeutic interventions is curative
- The various therapies employed are directed at nonspecific suppression of the inflammatory or immunologic process

TREATMENT STRATEGIES

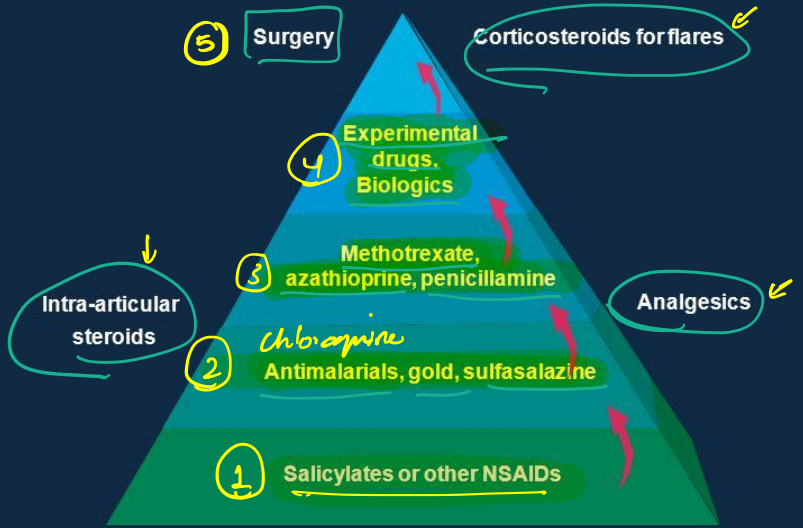
- **There are three general strategies for DMARD treatment of RA:**
- 1. sequential monotherapy
- 2. step-up combination therapy
- 3. initial combination (induction) therapy

- 1st approach has been abandoned in light of extensive data showing the superiority of step-up and induction approaches.

- Evidence suggests that ‘aggressive” treatment to rapidly achieve a low level of disease activity, which often necessitates a combination of agents, has superior efficacy to conservative approaches that involve sequential, low-dose monotherapy

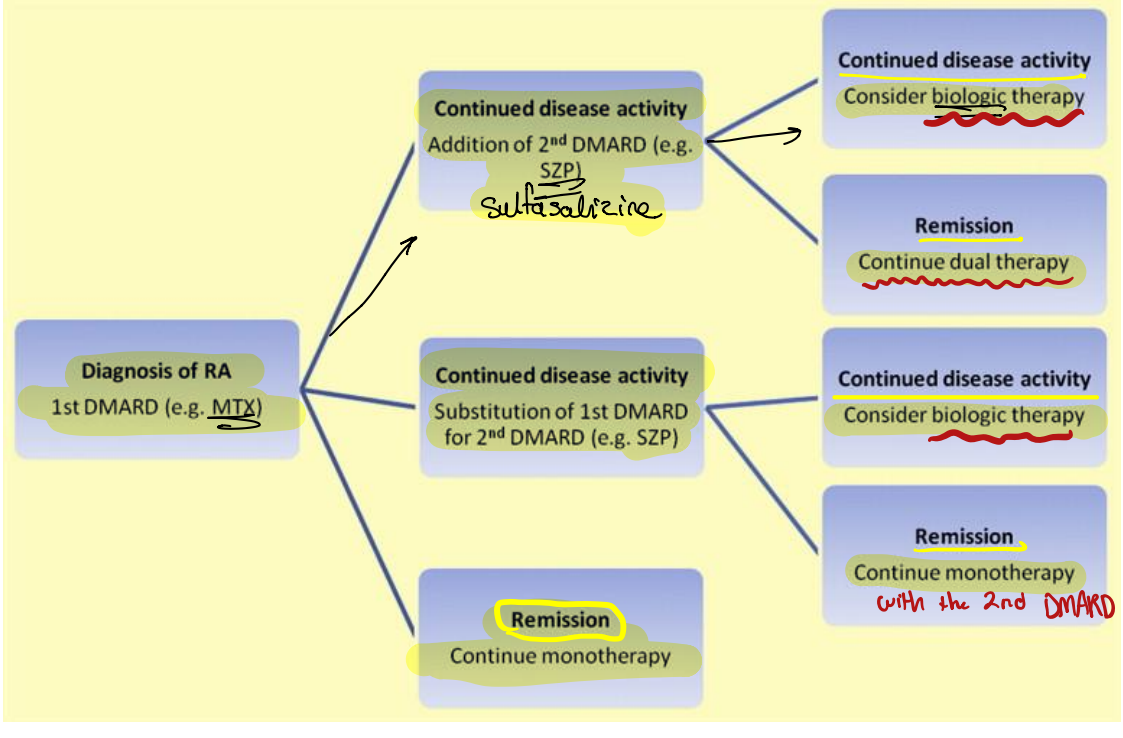
- Given the expense of combination therapy, especially with the biologic DMARDs the step-up combination approach remains the most common in clinical practice

The Traditional Treatment Pyramid for RA: Sequential Drug Therapy

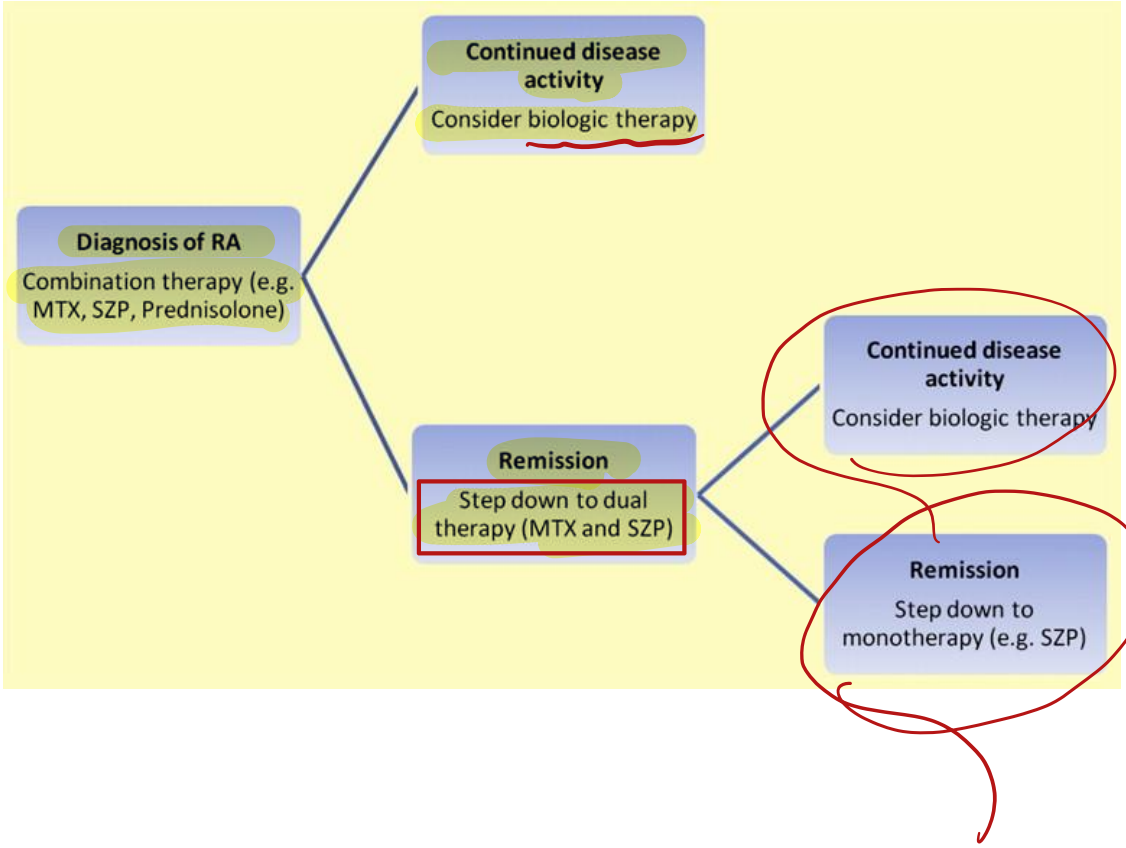


Adapted from *Primer on Rheumatic Diseases*. 10th ed. The Arthritis Foundation; 1993.

Step-up combination therapy



Initial combination (induction) therapy



- **Advantage of induction therapy**
  - more rapid control of synovitis and thus accumulation of joint damage

- **Disadvantages of induction approach:**
  1. potential overtreatment
  2. exposure to unnecessary toxicities in patients in whom disease may have been controlled by a single DMARD
  3. difficulty in attribution of an adverse event to a specific drug.

Conventional DMARDs

TABLE 94.1 DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

DMARD	Mechanism of action
Conventional DMARDs	
Methotrexate	Inhibition of purine biosynthesis/cytokine expression. Induction of monocyte apoptosis
Sulfasalazine	Inhibition of cytokine expression/neutrophil migration
Leflunomide	Inhibition of pyrimidine biosynthesis/cytokine expression/neutrophil migration
Hydroxychloroquine	Unknown
Azathioprine	Active metabolite, 6-mercaptopurine, interferes with adenine and guanidine biosynthesis
Cyclosporine	Inhibition of T-cell response via calcineurin inhibition
Cyclophosphamide	Lymphocyte cytotoxicity

Biologic DMARDs

1- TNF-α inhibitors
2- T-costimulation inhibition → Abatacept CTLA4 analogue
3- B cell inhibition → Rituximab
4- IL-6 inhibition → Tocilizumab
5- Anakinra → IL1 agonist

Biologic DMARDs	
Etanercept	Soluble 75kDa TNF receptor: inhibits biologic effects of TNF-α
Infliximab	Chimeric anti-TNF-α antibody: inhibits biologic effects of TNF-α. Cell lysis of TNF-α expressing cells
Adalimumab	Human anti-TNF-α antibody: inhibits biologic effects of TNF-α
Anakinra	Recombinant IL-1 receptor agonist: inhibits biologic effects of IL-1
Rituximab	Anti-CD20 monoclonal antibody: depletes B cells
Abatacept (CTLA4Ig)	Inhibits T-cell co-stimulation

TNF

B ab T

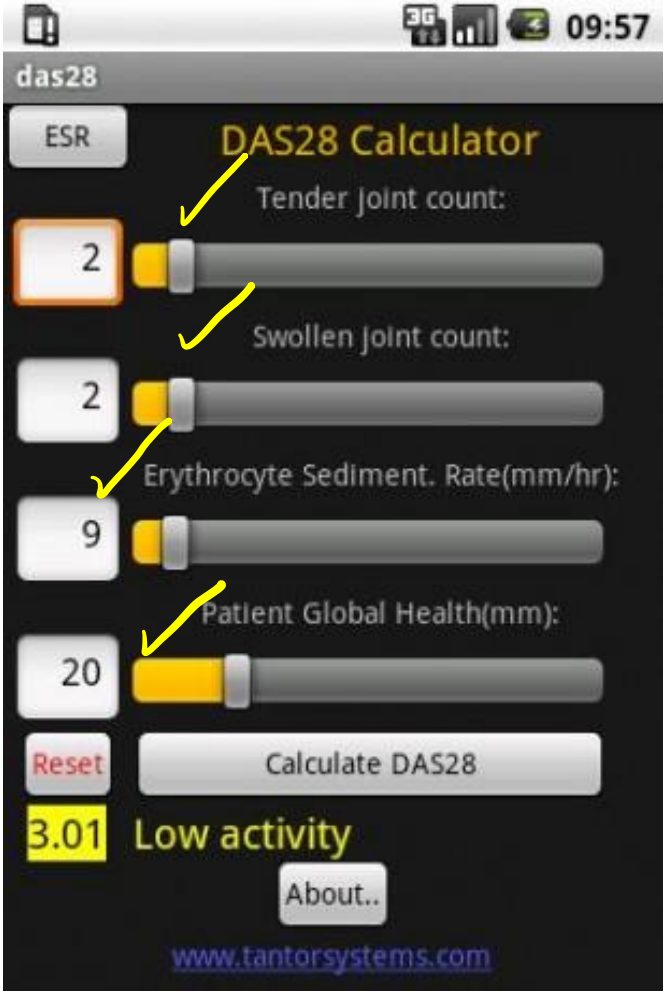
- Tocilizumab → monoclonal Ab competitively inhibits binding of IL6+R

Disease monitoring

- **When assessing how active the disease is the doctor will take four factors into account:**

1. Number of tender joints
2. Number of swollen joints
3. PGA: How active you think your disease is on a scale of one to ten
4. ESR or CRP

Patient global assessment


09:57
das28
ESR
DAS28 Calculator
Tender joint count:
2
Swollen joint count:
2
Erythrocyte Sediment. Rate(mm/hr):
9
Patient Global Health(mm):
20
Reset
Calculate DAS28
3.01
Low activity
About..
www.tantorsystems.com

DAS-28 interpretation

< 2.6 → remission

2.6 - 3.2 → low disease activity

3.2 - 5.1 → moderate disease activity

> 5.1 → high disease activity.

Initial DMARD

- Methotrexate is the first-line DMARD of choice
- Aggressive dose escalation of methotrexate
- Start 10 mg/wk & ↑ by 5 mg every 4 wk
- Because of the slow onset of action of MTX, an interval of 4 to 6 weeks is required to determine whether a patient has responded to a dose increase
- an interval of 3 months is recommended to evaluate the initial response to methotrexate

- patients who have had an inadequate response to 20 to 25/week of oral methotrexate ➔ change to SC or IM
  methotrexate may be more efficacious

Alternative initial therapy

- Leflunomide
- Sulfasalazine
- Hydroxychloroquine

- Leflunomide & sulfasalazine have equivalent efficacy to MTX
- Sulfasalazine given to patients with contra-indications to MTX

- Hydroxychloroquine:
  - low toxicity profile
  - low cost
  - safe in pregnancy

- less potent than other DMARDs, especially in its ability to slow radiographic progression.

Screening prior to starting DMARDs

- All need LFT, KFT, CBC
- MTX: CXR → it can cause lung fibrosis
- Biologics: CXR, hepatitis B &C, PPD
- HCQ: ophthalmology

purified protein derivative screening for TB

BC +
TB +
CXR d

Treatment monitoring

- NSAIDs: regular KFT
- Steroids: annual DEXA
- DMARDs: CBC, KFT, LFT
  - After 2 weeks
  - 1 month
  - 3 monthly

1/ 3months

The drugs

1 NSAIDs

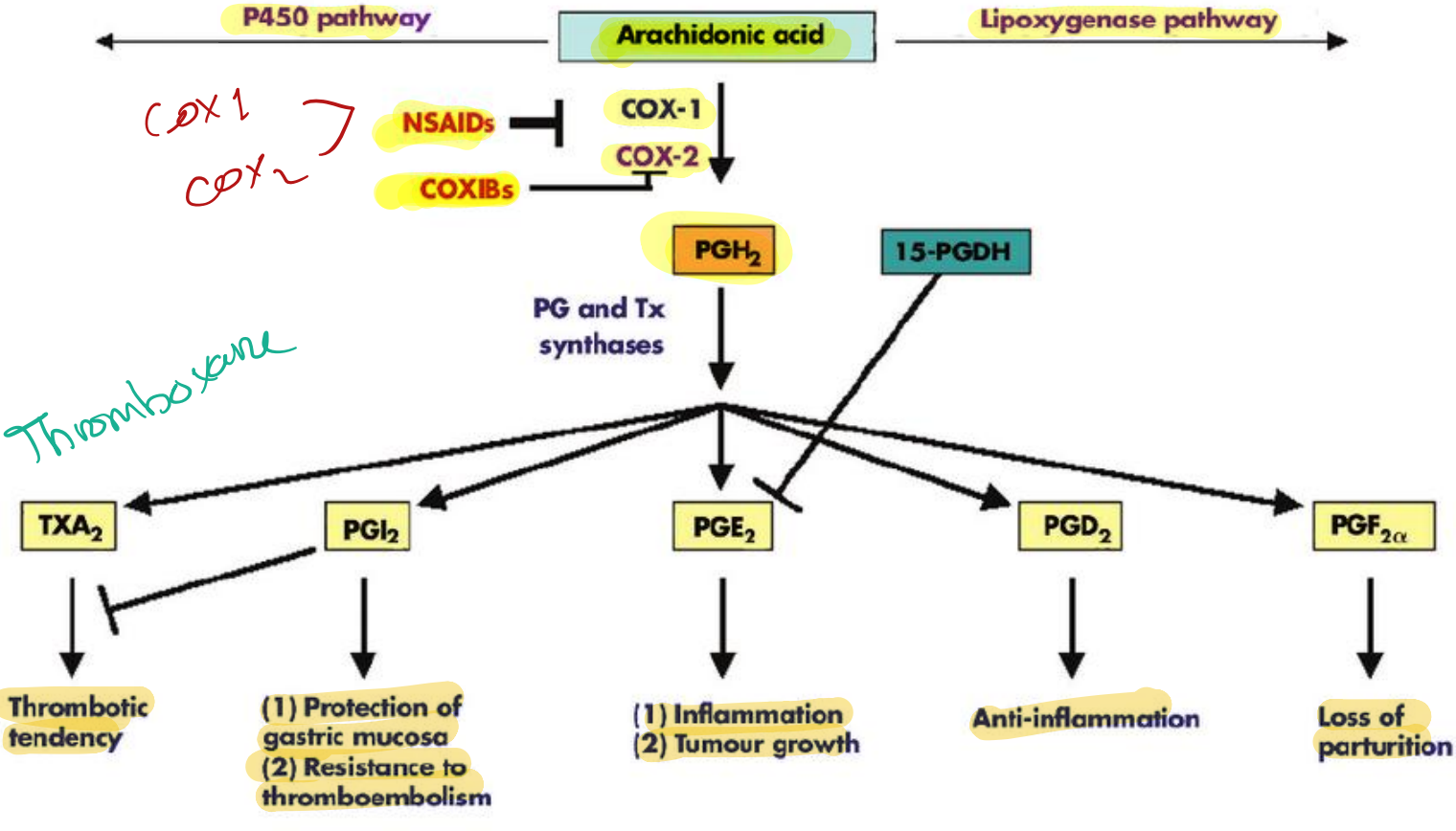
- Chemically heterogeneous group of compounds that provide symptomatic relief of pain and inflammation
  - Analgesic
  - anti-inflammatory
  - antipyretic
- not disease modifying, so their use as monotherapy for a prolonged period of time should be avoided.

MECHANISM OF ACTION

- Inhibition of the cyclo-oxygenase (COX)
- prostanoids reproduce the main signs and symptoms of the inflammatory response
  - PGE2 and PGI2 cause erythema, an increase in local blood flow,
  - PGE2 can produce fever.

- PG-synthase is found in two isoforms
  - COX-1, which is expressed constitutively in all cells but is inducible under appropriate conditions
  - COX-2, which is inducible in response to inflammatory, mitogenic or hemodynamic stimuli

Good for GI mucosa protection


P450 pathway
Arachidonic acid
Lipoxygenase pathway
COX-1
COX-2
NSAIDs
COXIBs
PGH2
15-PGDH
PG and Tx synthases
TXA2
PGI2
PGE2
PGD2
PGF2α
Thrombotic tendency
(1) Protection of gastric mucosa
(2) Resistance to thromboembolism
(1) Inflammation
(2) Tumour growth
Anti-inflammation
Loss of parturition

Side effects of NSAIDs

- GI: erosions, ulcers, GI haemorrhage
- Renal: salt & water retenstion, ARF
- Hypersensitivity
- Ductus arteriosus
- Liver: raised LFTs *
- Skin: EM, TEN, urticaria

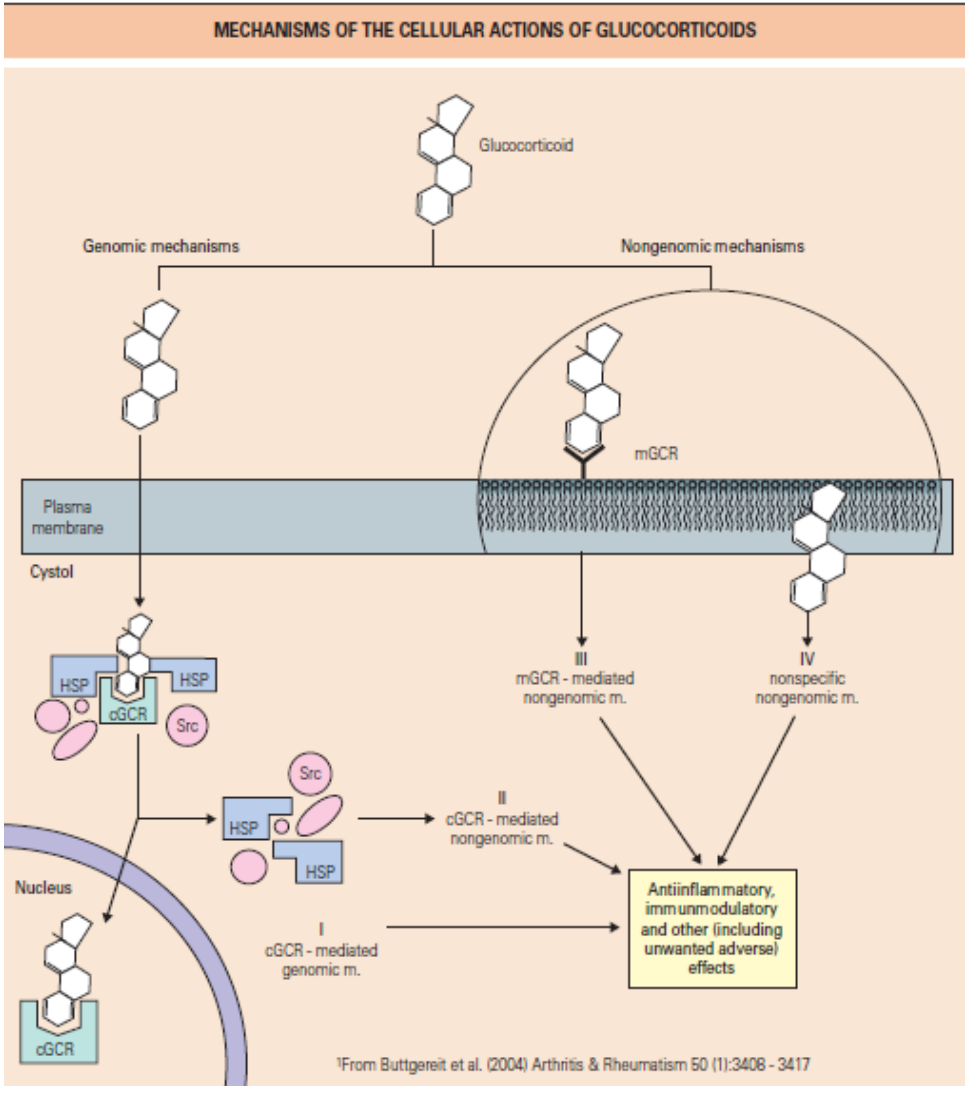
Closes

Like endomethacin (NSAID)

erythema multiforme

Toxic epidermal necrolysis

Corticosteroids


MECHANISMS OF THE CELLULAR ACTIONS OF GLUCOCORTICOIDS
Glucocorticoid
Genomic mechanisms
Nongenomic mechanisms
mGCR
Plasma membrane
Cystol
HSP
HSP
cGCR
Src
III
mGCR - mediated nongenomic m.
IV
nonspecific nongenomic m.
Src
HSP
HSP
II
cGCR - mediated nongenomic m.
Nucleus
I
cGCR - mediated genomic m.
Antiinflammatory, immunmodulatory and other (including unwanted adverse) effects
cGCR
[1]From Buttgereit et al. (2004) Arthritis & Rheumatism 50 (1):3408 - 3417

Corticosteroids

- The glucocorticoid/glucocorticoid receptor complex inhibits transcription factors NF-κB and AP-1.
- result in the decreased synthesis of proinflammatory cytokines such as IL-1, IL-2, IL-2 receptor, IFN-α, IL-6, and TNF-α.

Efficacy of steroids in rheumatoid arthritis

- Short- to moderate-term glucocorticoid studies reveal improved disease activity and functional status
- low dose glucocorticoids prevent radiographic joint destruction in RA.

Route of administration

- Oral
- IM
- IV
- Intra-articular

no SC

Adverse effects

- long-term, relatively low-dose glucocorticoid use is a significant cause of numerous potentially serious adverse

Adverse effects

1. Bone and muscle — annual DEXA
2. Cardiovascular
3. Gastrointestinal
4. Infections
5. Metabolic and endocrine
6. Dermatologic
7. Neuropsychiatric
8. Ophthalmologic

1 Muscle and bone

1. • Osteoporosis leading to fracture.
   – cumulative dose
2. • Osteonecrosis of bone
3. • Myopathy
   – peak dose of glucocorticoid rather than cumulative dose

myopathy

* فجأة بتحس بوجع العضلات عشان عاخدة جرعة كبيرة peak
* هشاشة العظام مع مرور الزمن. cumulative

Cardiovascular

- Hypertension
- Hyperlipidaemia
- atherosclerotic vascular disease.

3 Dermatologic

- skin thinning
- Ecchymoses
- cushingoid appearance
- Acne
- Hirsutism
- impaired wound healing

GI

- Gastritis
- Ulcers
- GI bleeding.
- Pancreatitis

5 Endocrine & metabolic

1. Hyperglycemia
2. adrenal suppression

Neuropsychiatric

- Insomnia
- depression
- Memory impairment

7 Ophthalmologic

- Cataracts
- Glaucoma

Corticosteroids

3 Hydroxychloroquine

conventional DMARD

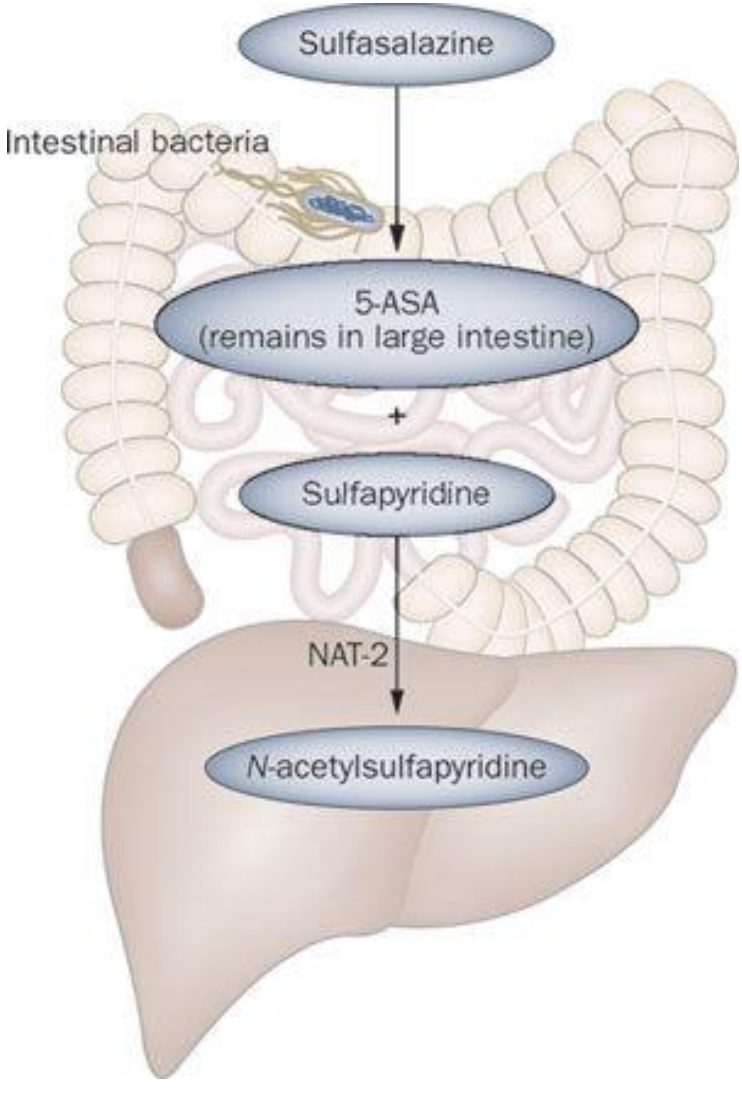
- limited efficacy when used alone
- more effective when used in combination with MTX or sulfasalazine
- Retinopathy

Ophthalmologic monitoring

  - can lead to blindness
  - extremely rare
  - Depends on cumulative dose (max 5 mg/kg)

4 Sulfasalazine (SSP)

- Sulfapyridine + 5-ASA (Aspirin)
- After ingestion it is split in the large intestine by bacterial enzymes into sulfapyridine (SP), which is then absorbed, and 5-ASA, which is excreted (amino salicylic acid.)
- decreases the progression of radiologic damage (+ steroids + MTX ≠ Hydrochloroquine.)


Sulfasalazine
Intestinal bacteria
5-ASA
(remains in large intestine)
+
Sulfapyridine
NAT-2
N-acetylsulfapyridine

Adverse effects of SSP

- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Leucopenia
- Rashes
- Hepatotoxicity

+ MTX

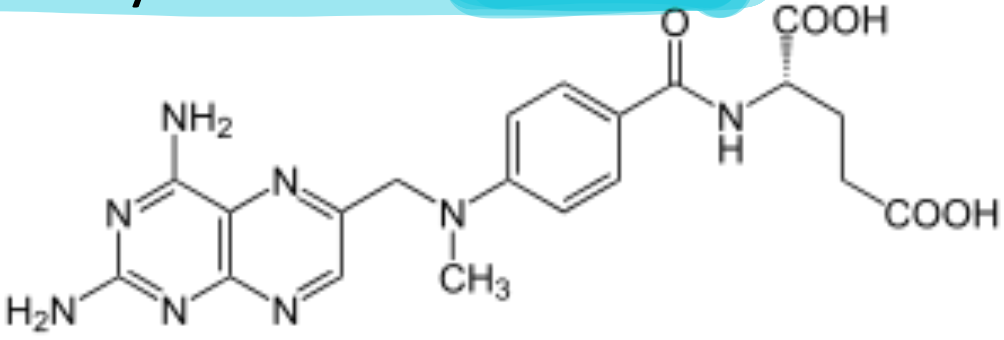
neutrophil migration.

- NSAIDs → liver enzymes
- SSP → hepatotoxic
- MTX → severe liver disease

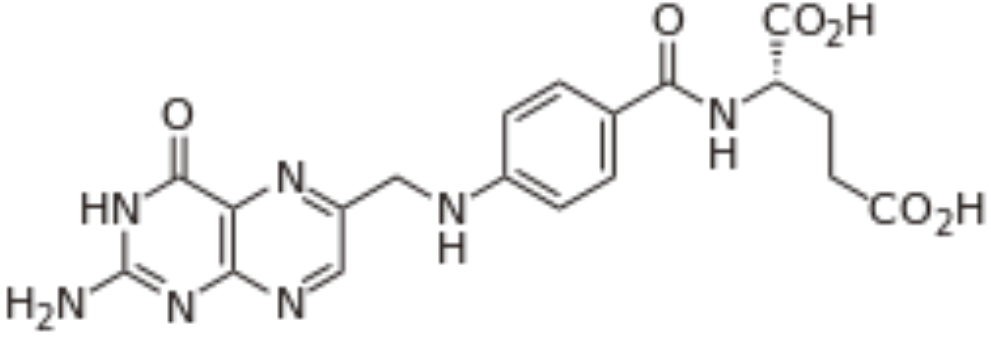
5 Methotrexate (MTX)

- first-line agent in the treatment of RA
- structurally similar to folic acid

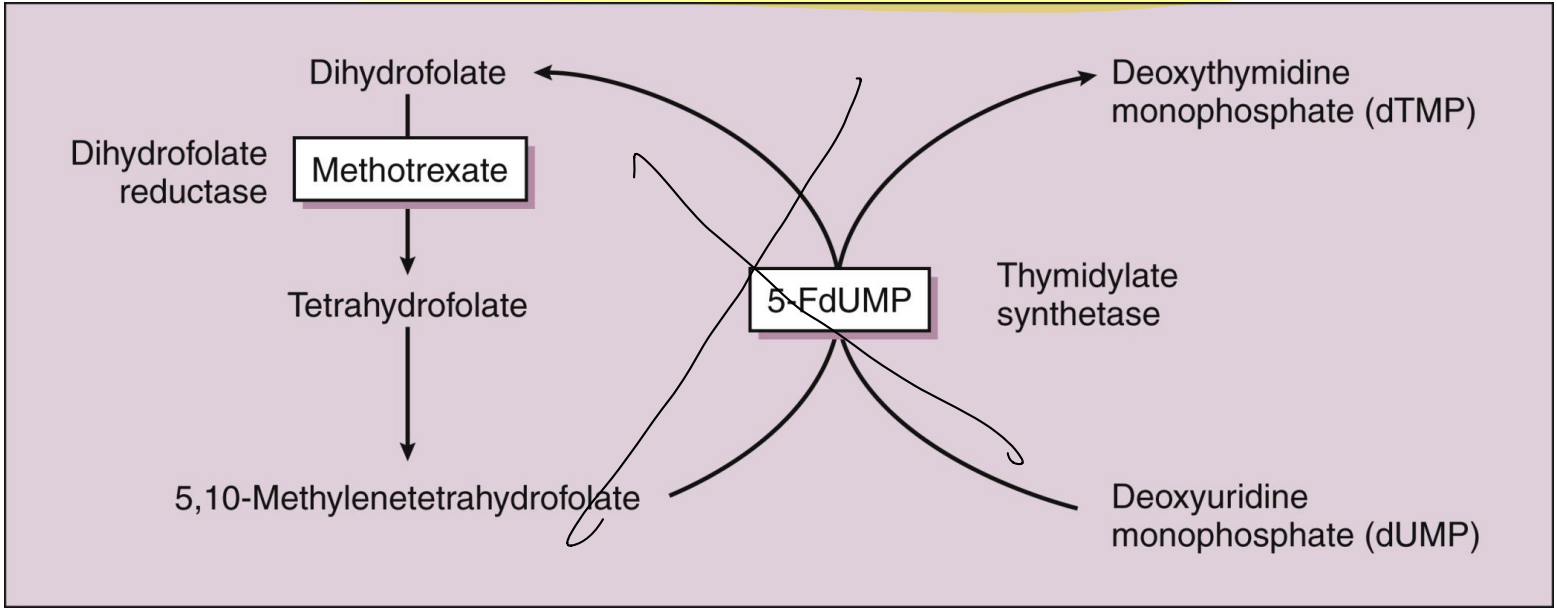
MTX



Folic acid



- Inhibits dihydrofolate reductase (DHFR) thereby deprives the cell of tetrahydrofolate
- slows radiographic progression of RA.



- monitoring of methotrexate therapy is required
- Serious liver disease and idiosyncratic pulmonary hypersensitivity are rare potential adverse effects.
- Methotrexate is a known teratogen and effective contraception should be considered in women with the potential for pregnancy.
- Men also

Adverse effects of MTX

- most common:
  - anorexia
  - Nausea
  - Vomiting
  - diarrhea

  vs SSP
- Hematologic abnormalities: Bone marrow suppression
  1. leukopenia (most common)
  2. Anemia
  3. thrombocytopenia.

- hepatic toxicity
- lung toxicity:
  - acute interstitial pneumonitis
  - Pulmonary fibrosis

Idiosynchratic pulmonary hypersensitivity.

- To prevent adverse effects of MTX, folic acid or folinic acid (leucovorin) is given concomitantly.

MTX

- Small rheumatoid nodules may increase in size at start of MTX therapy
- Hepatic fibrosis & cirrhosis is rare with MTX & occurs in < 0.1% of patients
- Pulmonary toxicity may present as an unexplained cough or may present with fever, hypoxia, eosinophilia & interstitial infiltrates
- Avoid concomittant use of other antifolate drugs such as trimethoprim

Contraindications to MTX

- active liver disease (including chronic hepatitis B and C infection)
- alcohol abuse
- pregnancy
- breastfeeding.

Metronidazole ⊗ Alcohol.
MTX

6

Leflunomide

very teratogenic

- Leflunomide inhibits pyrimidine synthesis, resulting in blockade of T-cell proliferation
- as effective as methotrexate and sulfasalazine
- provides additional benefit in patients partially responsive to methotrexate.
- The most common side effects are gastrointestinal symptoms and hepatotoxicity.
  - GI
  - liver
- Combination of leflunomide with methotrexate results in a significant increase in liver enzyme abnormalities.
- Leflunomide is teratogenic and is therefore contraindicated in women who may become pregnant.

Leflunomide

- Has a long half life & should be stopped at least 4 months before attempting pregnancy
- If elimination of leflunomide is desired (toxicity or pregnancy) cholstyramine 8 g TDS should be given for 11 days

7 Azathioprine

- pro-drug (active metabolite 6-mercaptopurine)
- Purine analogue. inhibits purine synthesis
  ➔↓T&B cell proliferation
- azathioprine use in RA is generally reserved for those patients who are intolerant of other agents

A G
CU T

Biologic DMARDs

1 Anti-TNF

- BIOLOGIC EFFECTS OF TNF-α
  1. – Adhesion molecule expression (E selectin, ICAM-1)
  2. – Synthesis of other proinflammatory cytokines (IL-1, IL-6, GM-CSF)
  3. – Synthesis of chemokines (e.g., RANTES, IL-8, MIP-1)
  4. – Activation of numerous cell types (T cells, B cells, macrophages)
  5. – Inhibition of regulatory T cells
  6. – Matrix metalloproteinase induction
  7. – Upregulation of RANK ligand expression
  8. – Induction of apoptosis
  9. – Antiviral and antitumor effects

Anti-TNF

- TNF-α primarily mediates inflammation by promoting cellular activation and trafficking of leukocytes to inflammatory sites.

Anti-TNF

- Infliximab
- adalimumab
- Golimumab
- certolizumab
- etanercept

chimeric

Human

BOX 61.3 RELATIVE CONTRAINDICATIONS TO THE USE OF TUMOR NECROSIS FACTOR INHIBITORS

1. Systemic lupus erythematosus, lupus overlap syndrome
2. Multiple sclerosis, optic neuritis, demyelinating disorders
3. Current, active, serious infections
4. Recurrent or chronic infections
5. Untreated latent or active mycobacterial infection
6. Hepatitis B infection
7. Congestive heart failure
8. Pregnancy

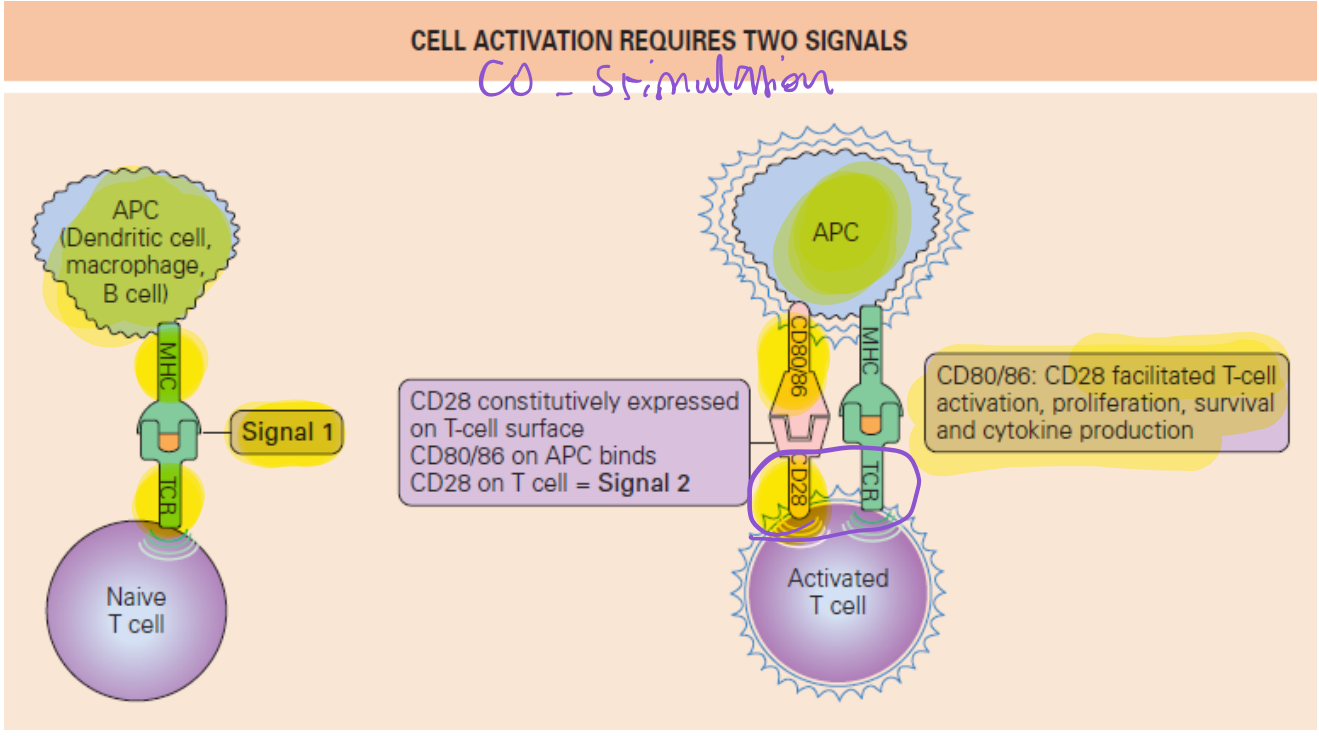
PPD

T-cell co-stimulation

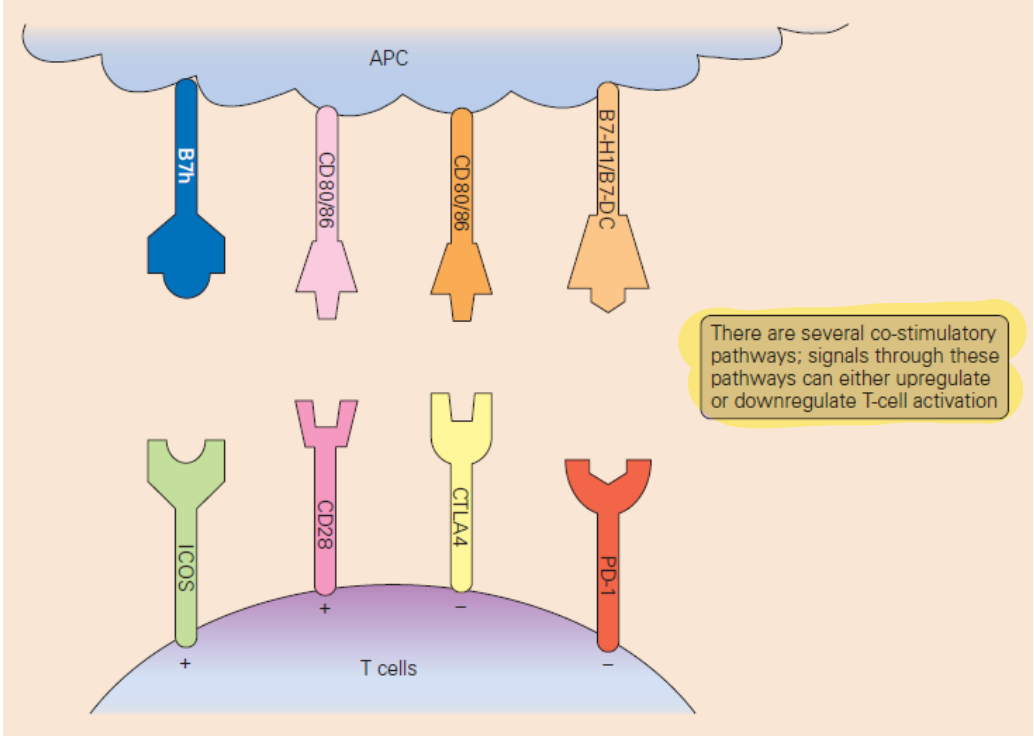
T-cell activation requires two signals:

1. First signal: engagement of the TCR with the MHC antigen complex

Second signal: transmitted by CD28 that interacts with either CD80 and CD86 ligands on APCs, leading to T-cell activation and proliferation

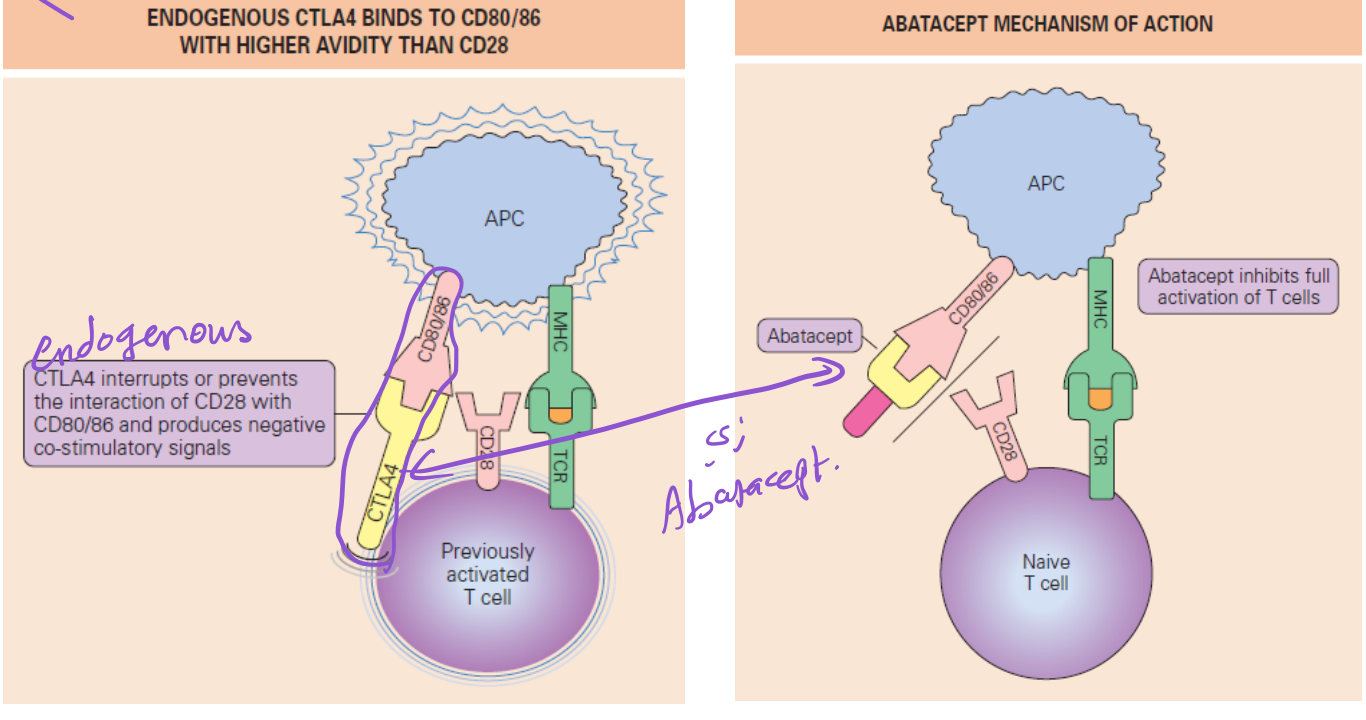


CO-STIMULATION IS REQUIRED FOR FULL T-CELL ACTIVATION



CTLA4 binds to CD80/86 with higher avidity than CD28

Abatacept binds to CD80/86 and inhibits T-cell co-stimulation



3 Anti-B Cell (Rituximab)

- CD20 is expressed on mature naïve B cells that have exited the bone marrow to enter blood
- it is not expressed on stem cells or on plasma cells
- Rituximab is a high-affinity chimeric monoclonal antibody specific to CD20

* 28 Tall
* 20B cell

- Rituximab causes B-cell depletion by:
  1. antibody-dependent, cell-mediated cytotoxicity
  2. complement-dependent cytotoxicity
  3. apoptosis

- Rituximab is given intravenously

IL-6

- Actions interleukin-6 (IL-6) include:
  - stimulation of B cell proliferation
  - immunoglobulin production
  - initiation of the acute-phase response.

- Tocilizumab is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor (IL-6R).

5

Anakinra

IL-1 agonist

Osteoarthritis

- Osteoarthritis (OA) is the most common form of arthritis
- pain is the most common symptom.
- aims of treatment:
  - to reduce pain
  - improve function and quality of life.
- management requires a combination of non-pharmacologic and pharmacologic modalities

Non-pharmacologic therapies

- Patient education
- Self-management
- Aerobic exercise
- Strengthening exercise
- Water-based exercise
- Weight loss
- Insoles نعال
- Braces
- Cane/stick
- Local heat/ice
- Acupuncture
- Transcutaneous electrical nerve stimulation TENS
- Yoga
- Ultrasound

Pharmacologic therapies

- paracetamol
- Non-steroidal anti-inflammatory drugs
- COX-2 selective inhibitors
- Topical NSAIDs
- Topical capsaicin
- Opioid analgesics
- Glucosamine sulfate
- Chondroitin sulfate
- Intra-articular corticosteroids
- Intra-articular hyaluronic acid preparations

Surgical intervention

- Joint lavage
- Arthroscopic debridement
- Osteotomy
- Joint replacement
- Joint fusion

Thank you