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)
- Symmetrical
- Leads to cartilage damage and bone erosions and subsequent joint damage

Pathogenesis

- Hyperplasia and hypertrophy of the synovial lining cells
- Vascular changes:
  - microvascular injury
  - Thrombosis
  - Neovascularization
- Oedema
- Infiltration with mononuclear cells

Cells

- Mononuclear cells 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 prominent at sites of bone erosion.

Cytokines

- Small proteins (~5–20 kDa) that are important in cell signaling
- Secreted by activated lymphocytes, macrophages, and fibroblasts on demand.

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

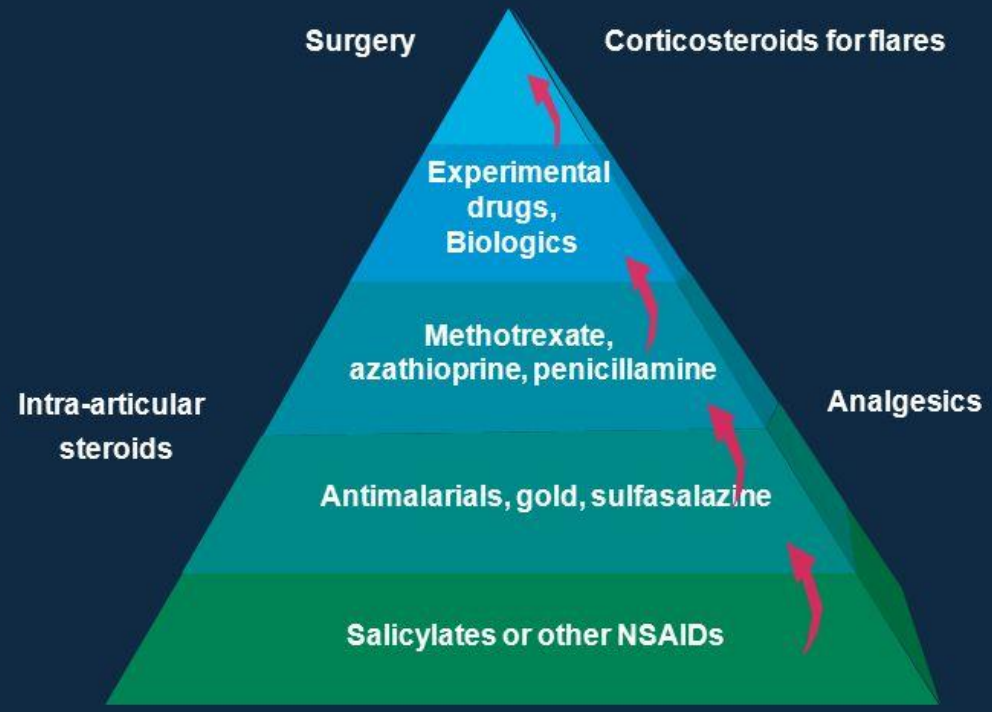
- **There are three general strategies for DMARD treatment of RA:**
- 1. Sequential monotherapy
- 2. Step-up combination therapy
- 3. Initial combination (induction) therapy

- 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

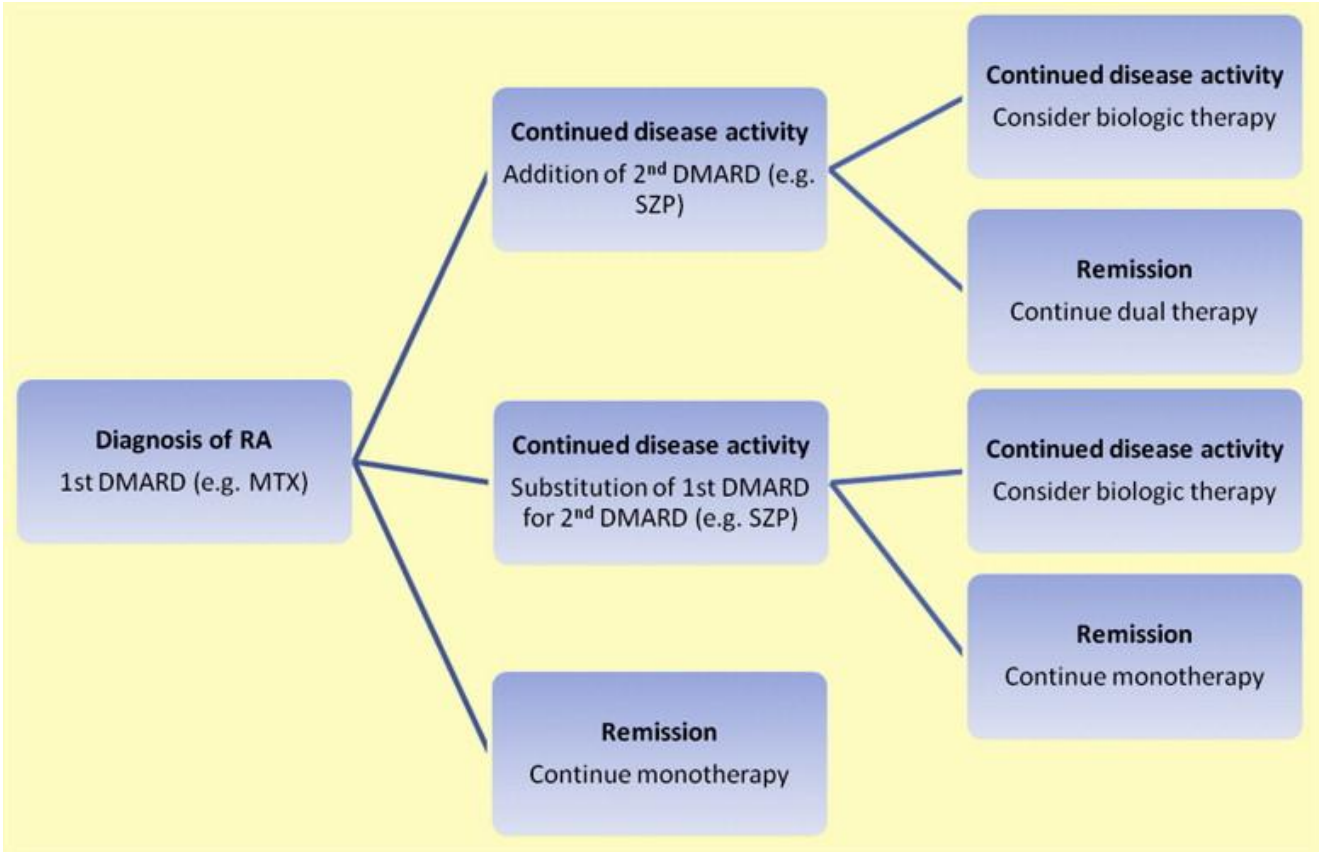
- Given the expense of combination therapy, especially with the biologic DMARDs the step-up combination approach remains the most common in clinical practice

The Traditional Treatment Pyramid for RA: Sequential Drug Therapy

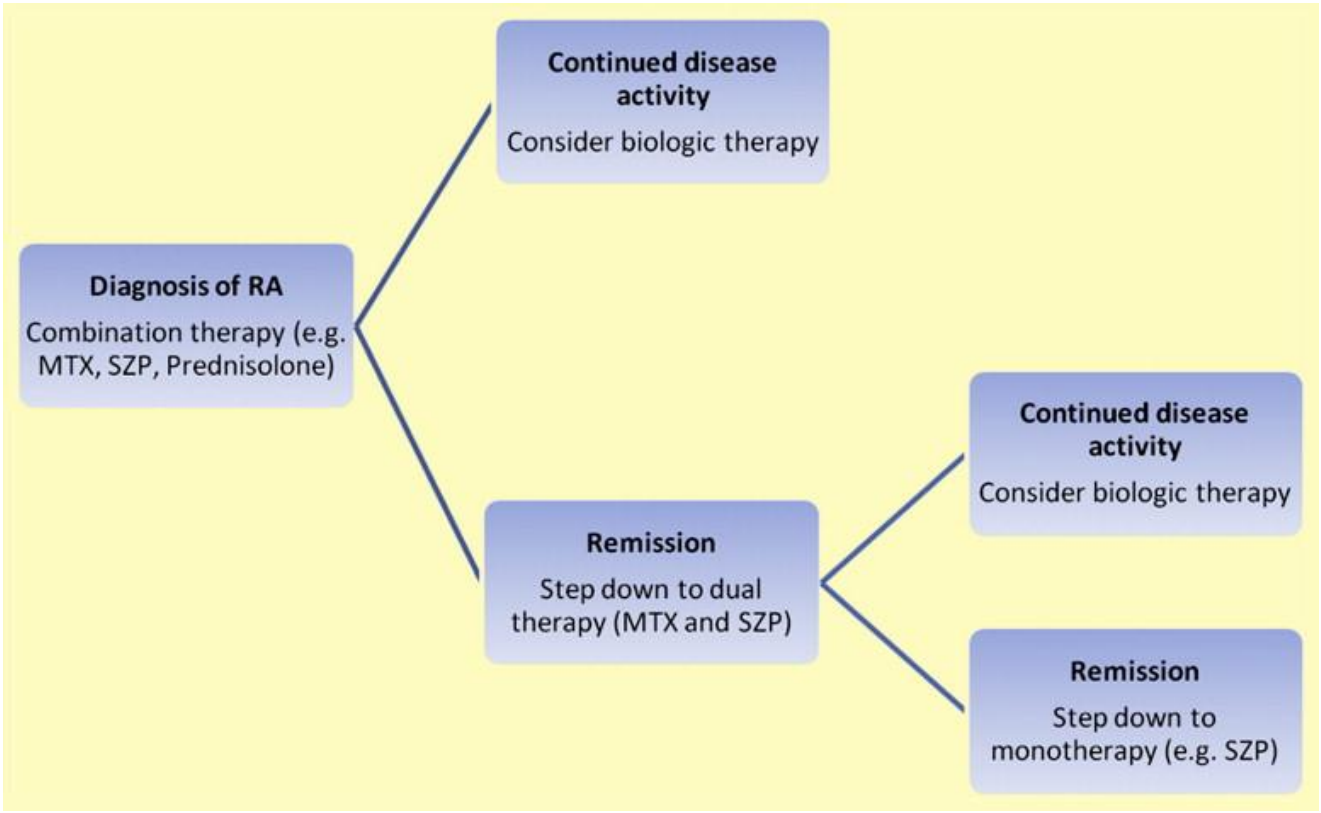


Adapted from *Primer on Rheumatic Diseases*. 10th ed. The Arthritis Foundation; 1993.

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:**
  - Potential overtreatment
  - Exposure to unnecessary toxicities in patients in whom disease may have been controlled by a single DMARD
  - 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

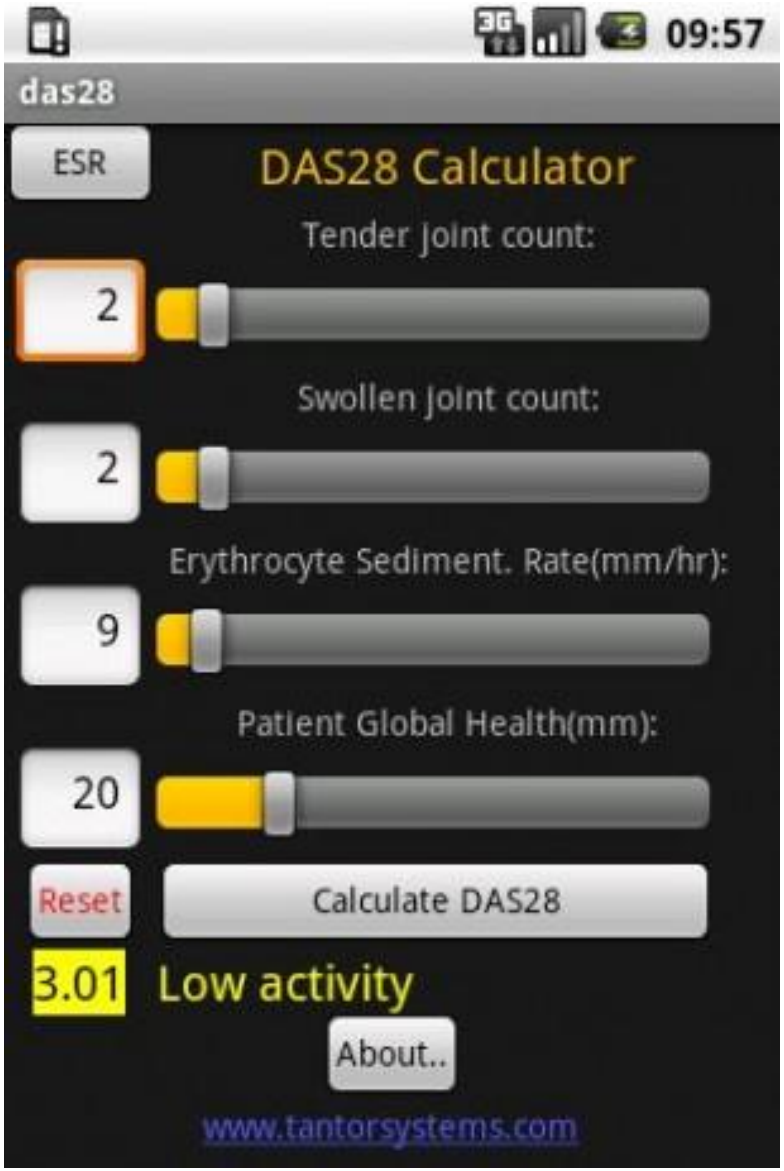
Biologic DMARDs

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

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


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
- Biologics: CXR, hepatitis B &C, PPD
- HCQ: ophthalmology review

Treatment monitoring

- NSAIDs: regular KFT
- Steroids: annual DEXA
- DMARDs: CBC, KFT, LFT
  - After 2 weeks
  - After 1 month
  - 3 monthly
  - If stable, 6 monthly

The drugs

NSAIDs

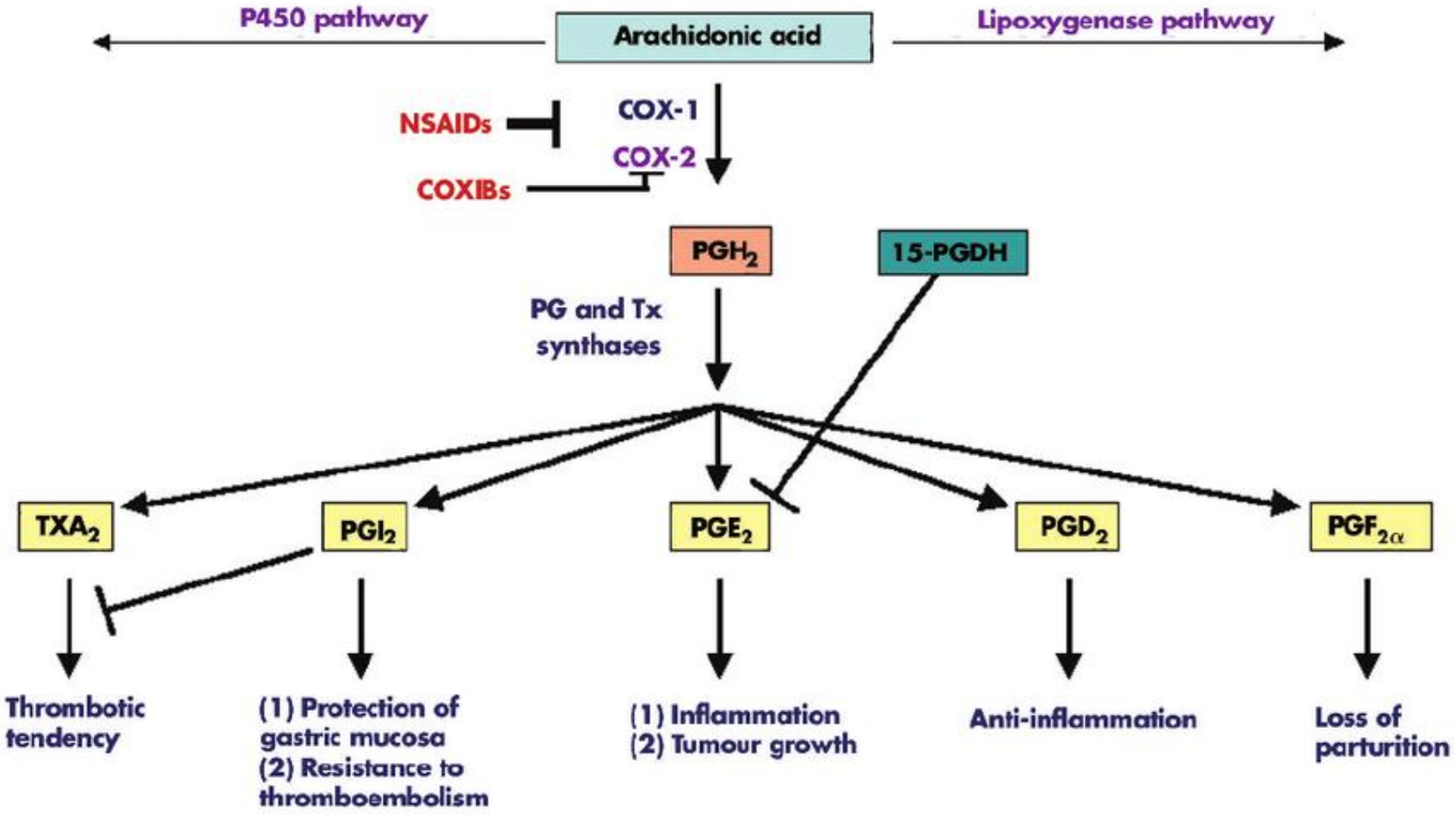
NSAIDs

- 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 (PGE2 and PGI2) reproduce the main signs and symptoms of the inflammatory response:
  - Erythema
  - Increase in local blood flow
  - Fever.

- PG-synthase (cyclo-oxygenase) 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

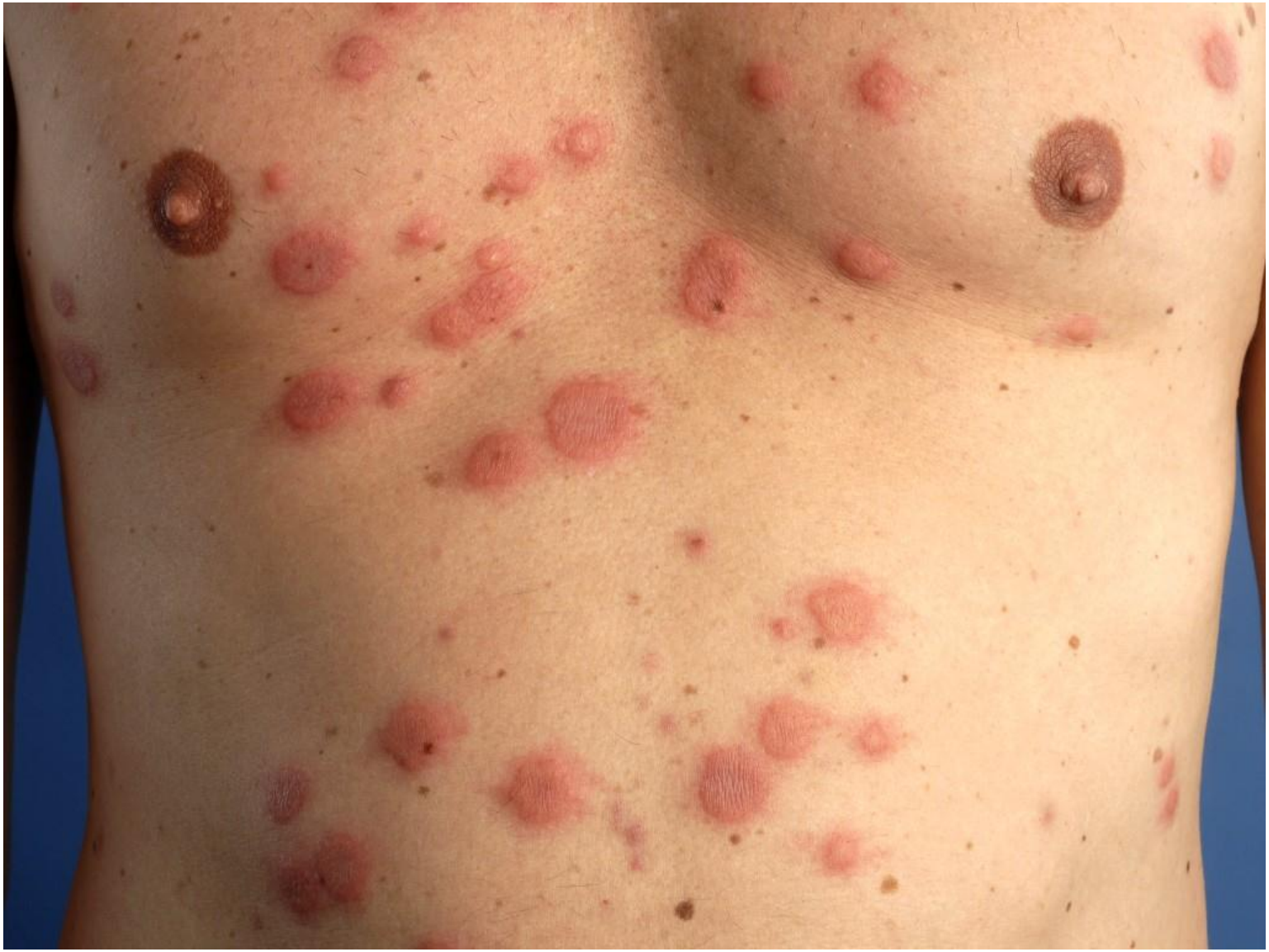

P450 pathway
Arachidonic acid
Lipoxygenase pathway
NSAIDs
COX-1
COX-2
COXIBs
PGH2
15-PGDH
PG and Tx synthases
TXA2
PGI2
PGE2
PGD2
PGF2α
Thrombotic tendency
(1) Protection of gastric mucosa
(2) Resistance to thromboembolism
(1) Inflammation
(2) Tumour growth
Anti-inflammation
Loss of parturition

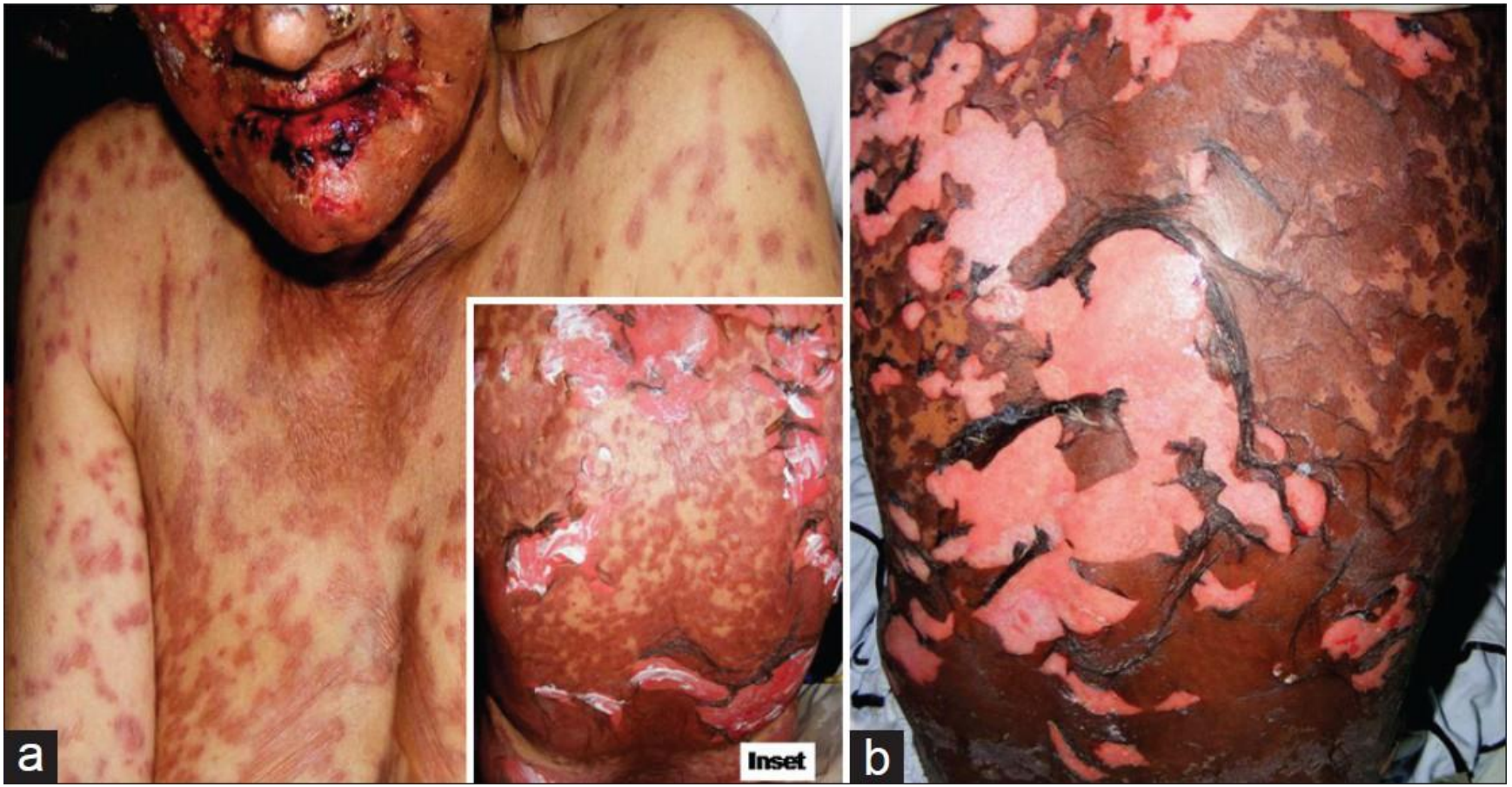
COX-2 inhibitors

- Selectivity for COX-2 reduces the risk of peptic ulceration
- Celecoxib, etoricoxib
- ? CV risk

Side effects of NSAIDs

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

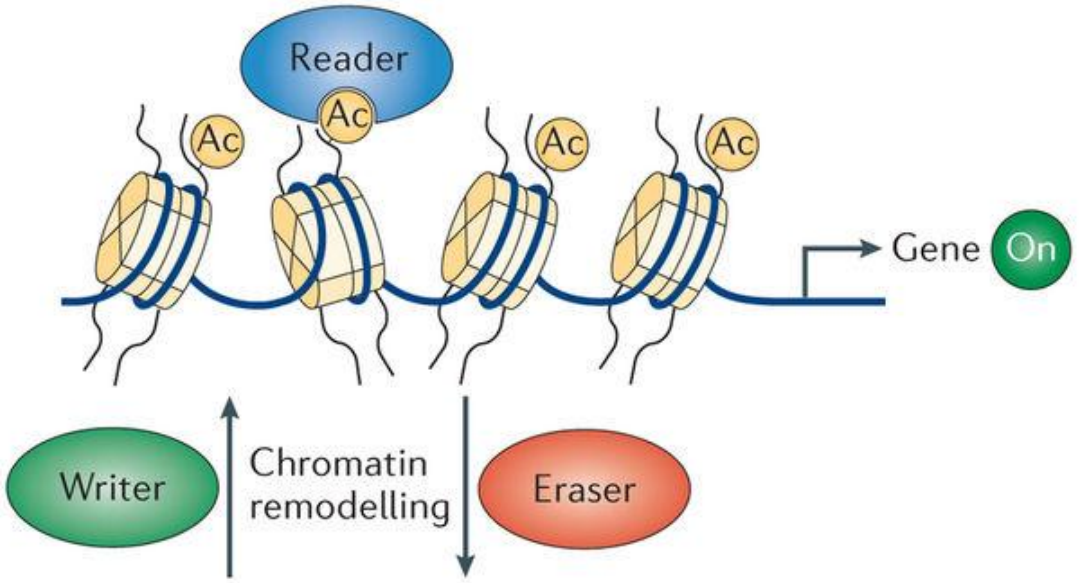



a
Inset
b

Corticosteroids

Mechanism of action

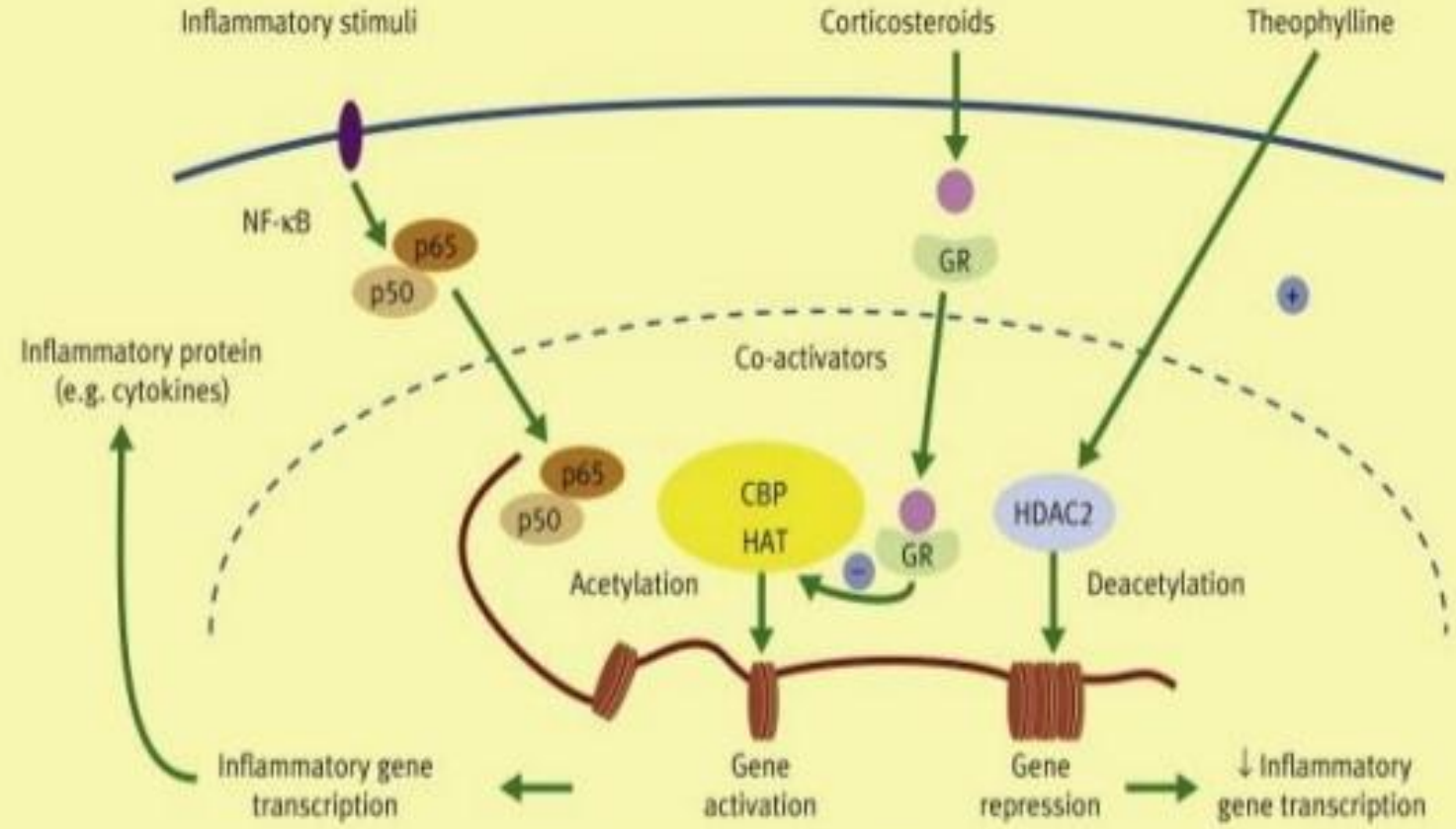
Acetylated chromatin
Open and transcriptionally active



Deacetylated chromatin
Compact and transcriptionally repressed

Nature Reviews | **Molecular Cell Biology**

Molecular mechanisms of action of corticosteroids



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

Adverse effects

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

Adverse effects

- Bone and muscle
- Cardiovascular
- Gastrointestinal
- Infections
- Metabolic and endocrine
- Dermatologic
- Neuropsychiatric
- Ophthalmologic

Muscle and bone

- Osteoporosis leading to fracture.
  - cumulative dose
- Osteonecrosis of bone
- Myopathy
  - peak dose of glucocorticoid rather than cumulative dose

Cardiovascular

- Hypertension
- Hyperlipidaemia
- Atherosclerotic vascular disease.

Dermatologic

- Skin thinning
- Ecchymoses
- Cushingoid appearance
- Acne
- Hirsutism
- Impaired wound healing

GI

- Gastritis
- Ulcers
- GI bleeding.
- Pancreatitis

Endocrine & metabolic

- Hyperglycemia
- Adrenal suppression

Neuropsychiatric

- Insomnia
- Depression
- Memory impairment

Ophthalmologic

- Cataracts
- Glaucoma

Hydroxychloroquine

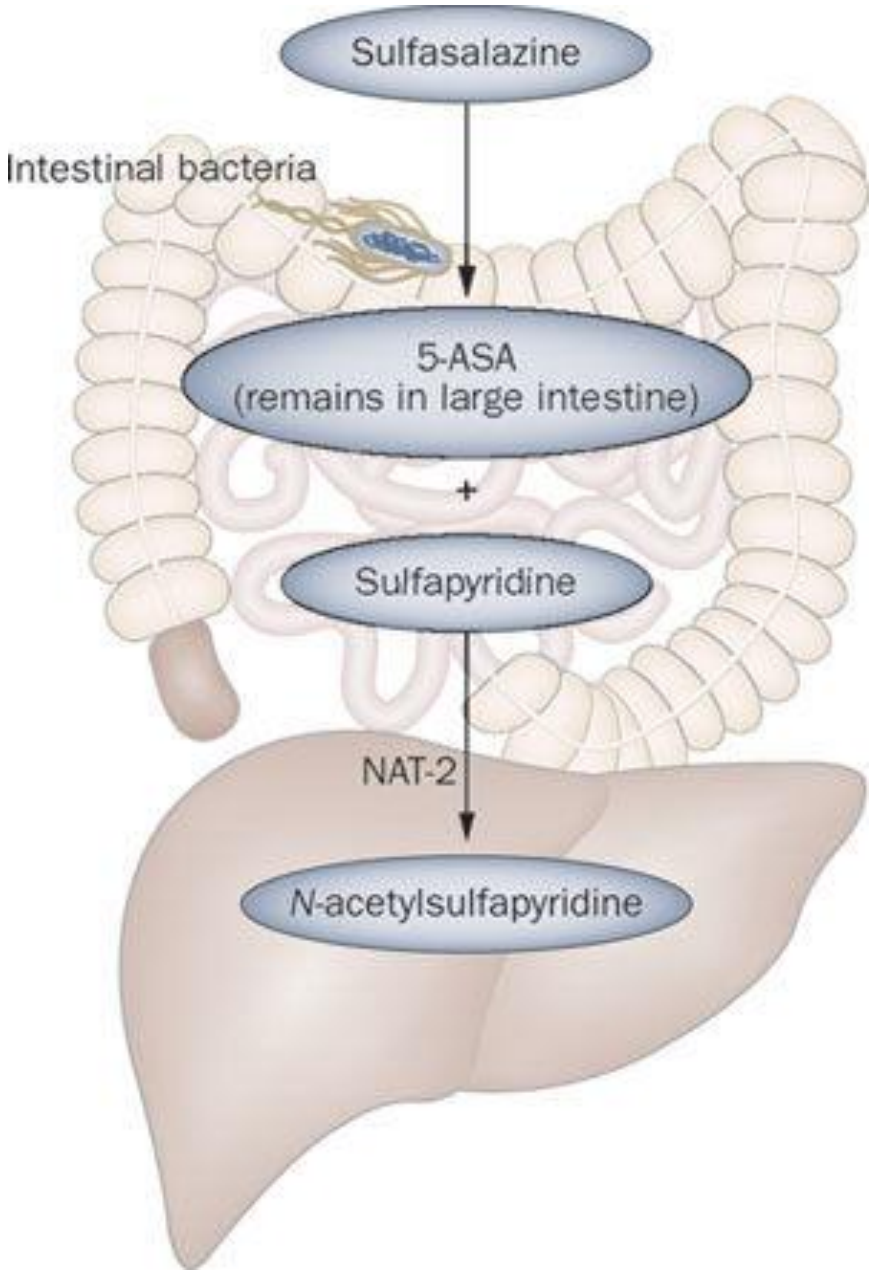
Hydroxychloroquine

- limited efficacy when used alone
- more effective when used in combination with MTX or sulfasalazine
- Retinopathy
  - Can lead to blindness
  - Extremely rare
  - Depends on cumulative dose (max 5 mg/kg)

Sulfasalazine (SSP)

Sulfasalazine (SSP)

- Sulfapyridine + 5-ASA
- 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
- decreases the progression of radiologic damage


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

Adverse effects of SSP

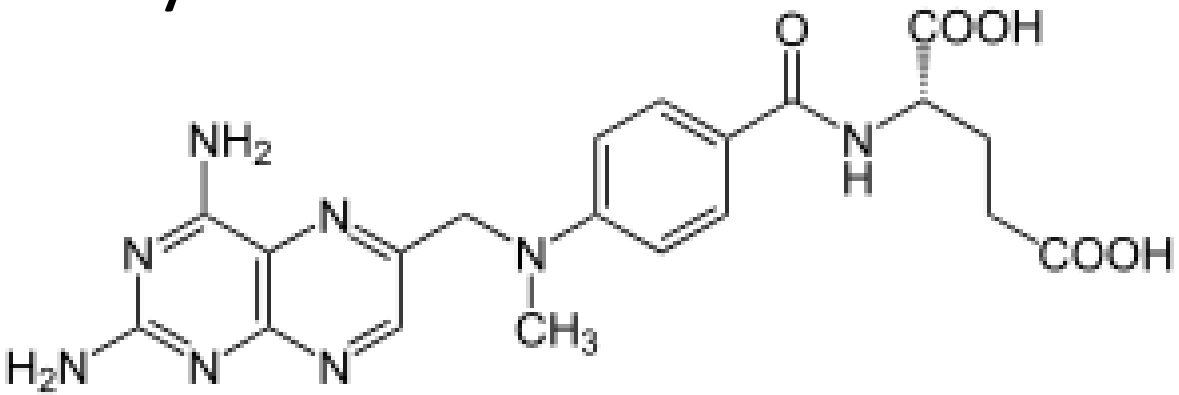
- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Leucopenia
- Rashes
- Hepatotoxicity

Methotrexate (MTX)

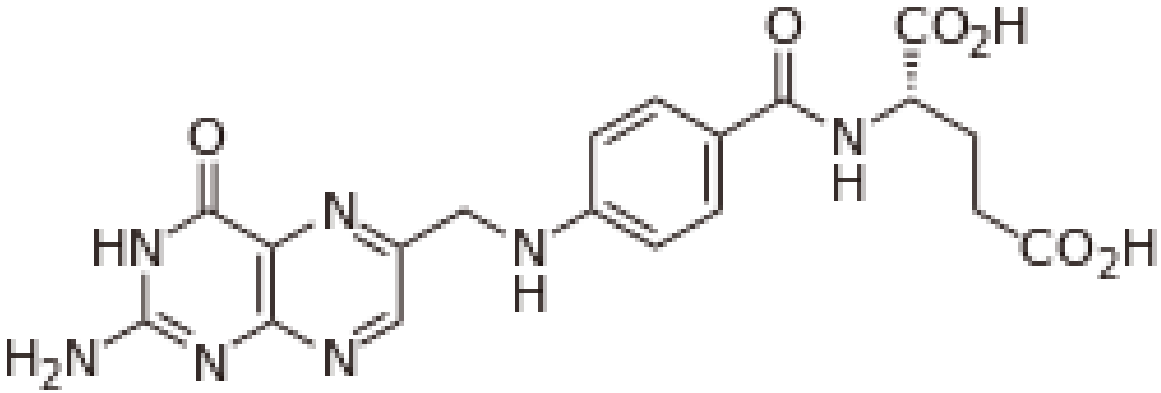
Methotrexate (MTX)

- First-line agent in the treatment of RA
- Structurally similar to folic acid

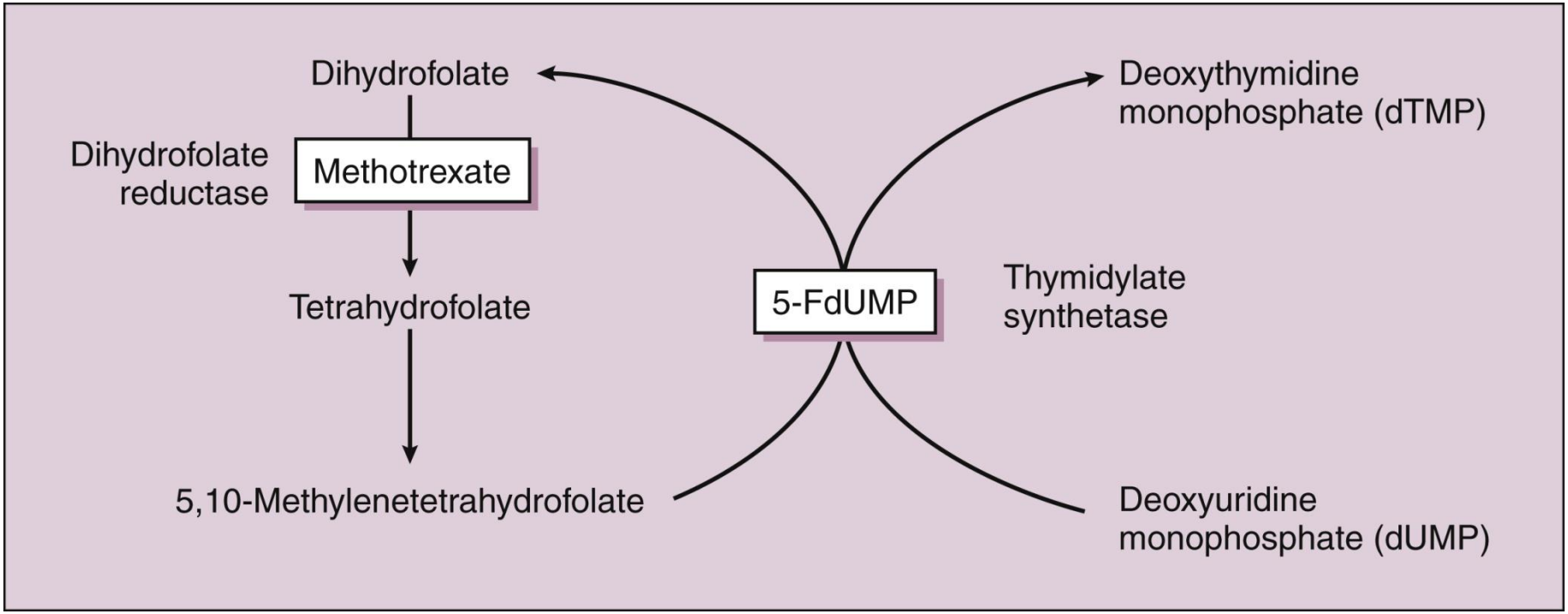
MTX



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
- Hematologic abnormalities:
  - leukopenia (most common)
  - Anemia
  - thrombocytopenia.

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

- 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 anti-folate drugs such as trimethoprim

Contraindications to MTX

- Active liver disease (including chronic hepatitis B and C infection)
- Alcohol abuse
- Pregnancy
- Breastfeeding.

Leflunomide

Leflunomide

- 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.
- 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

Azathioprine

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

Biologic DMARDs

Anti-TNF

Anti-TNF

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

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

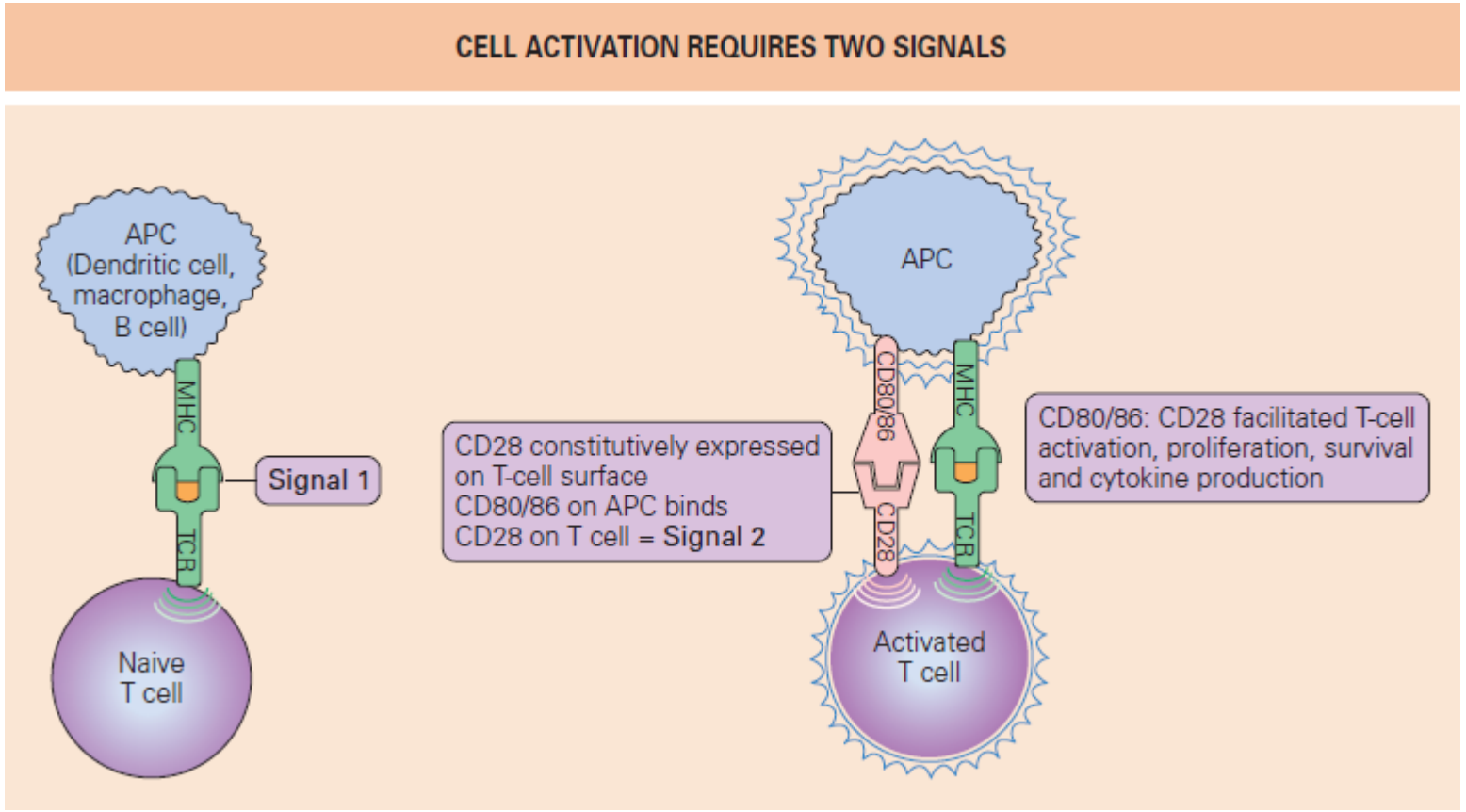
- Systemic lupus erythematosus, lupus overlap syndrome
- Multiple sclerosis, optic neuritis, demyelinating disorders
- Current, active, serious infections
- Recurrent or chronic infections
- Untreated latent or active mycobacterial infection
- Hepatitis B infection
- Congestive heart failure
- Pregnancy

T-cell co-stimulation

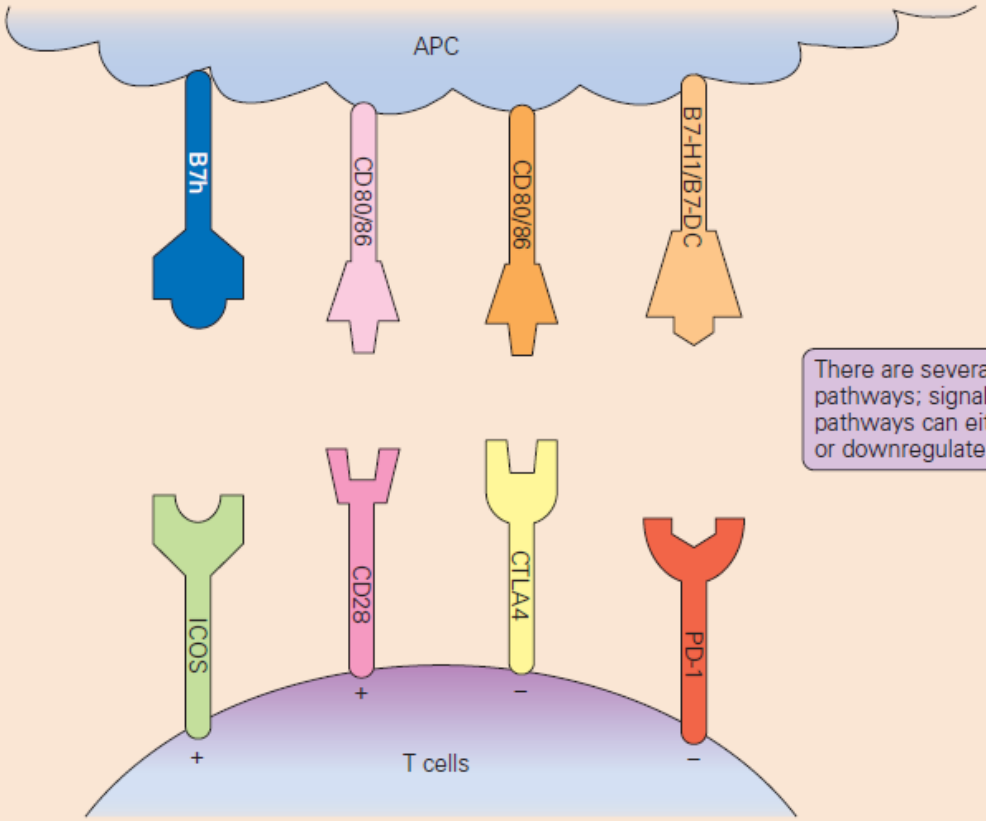
T-cell activation requires two signals:

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

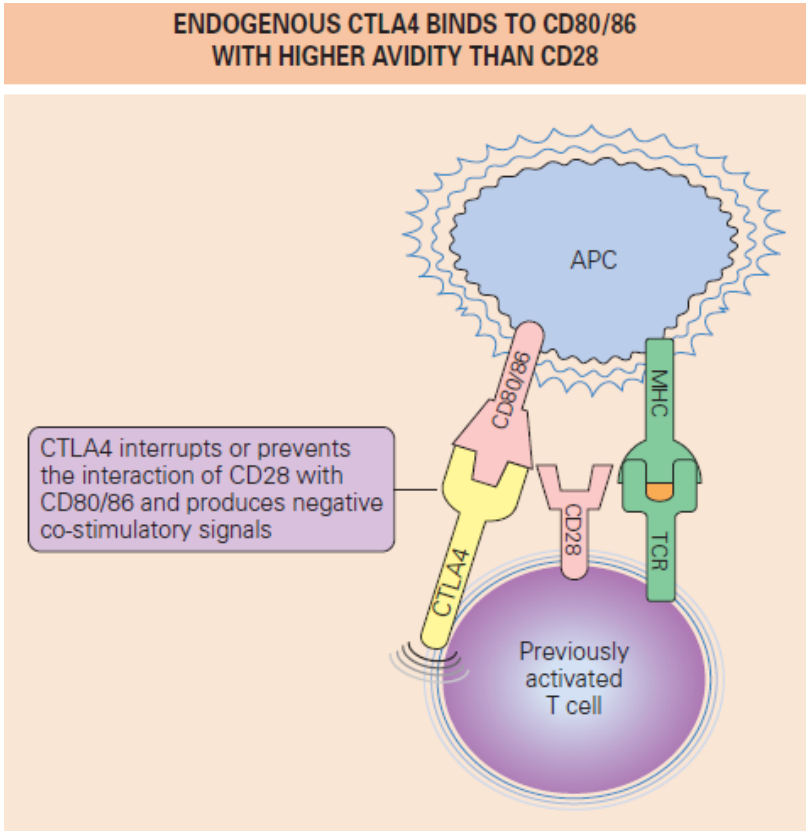


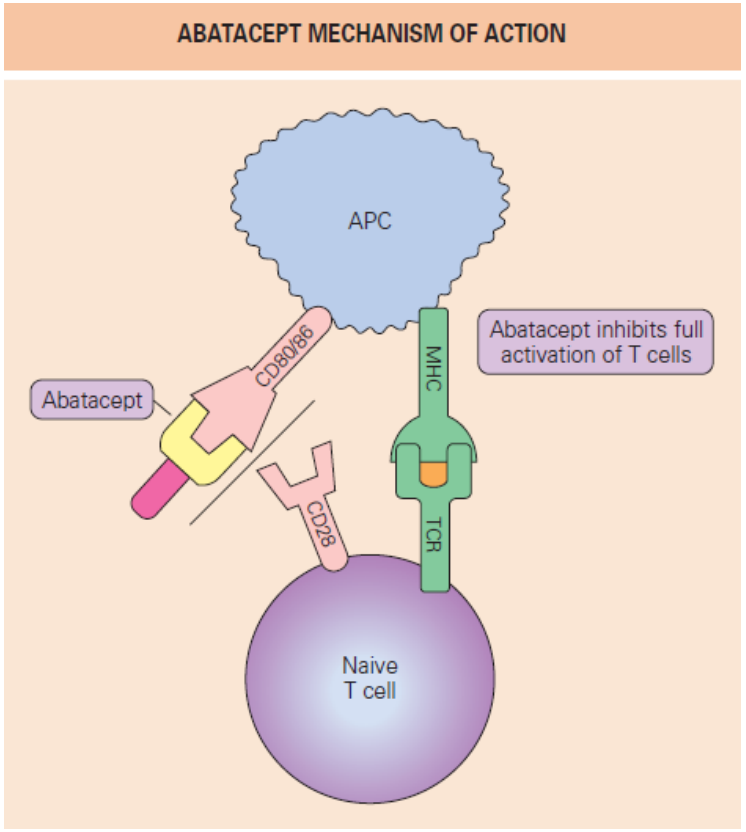
CO-STIMULATION IS REQUIRED FOR FULL T-CELL ACTIVATION



CTLA4 binds to CD80/86 with higher avidity than CD28

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





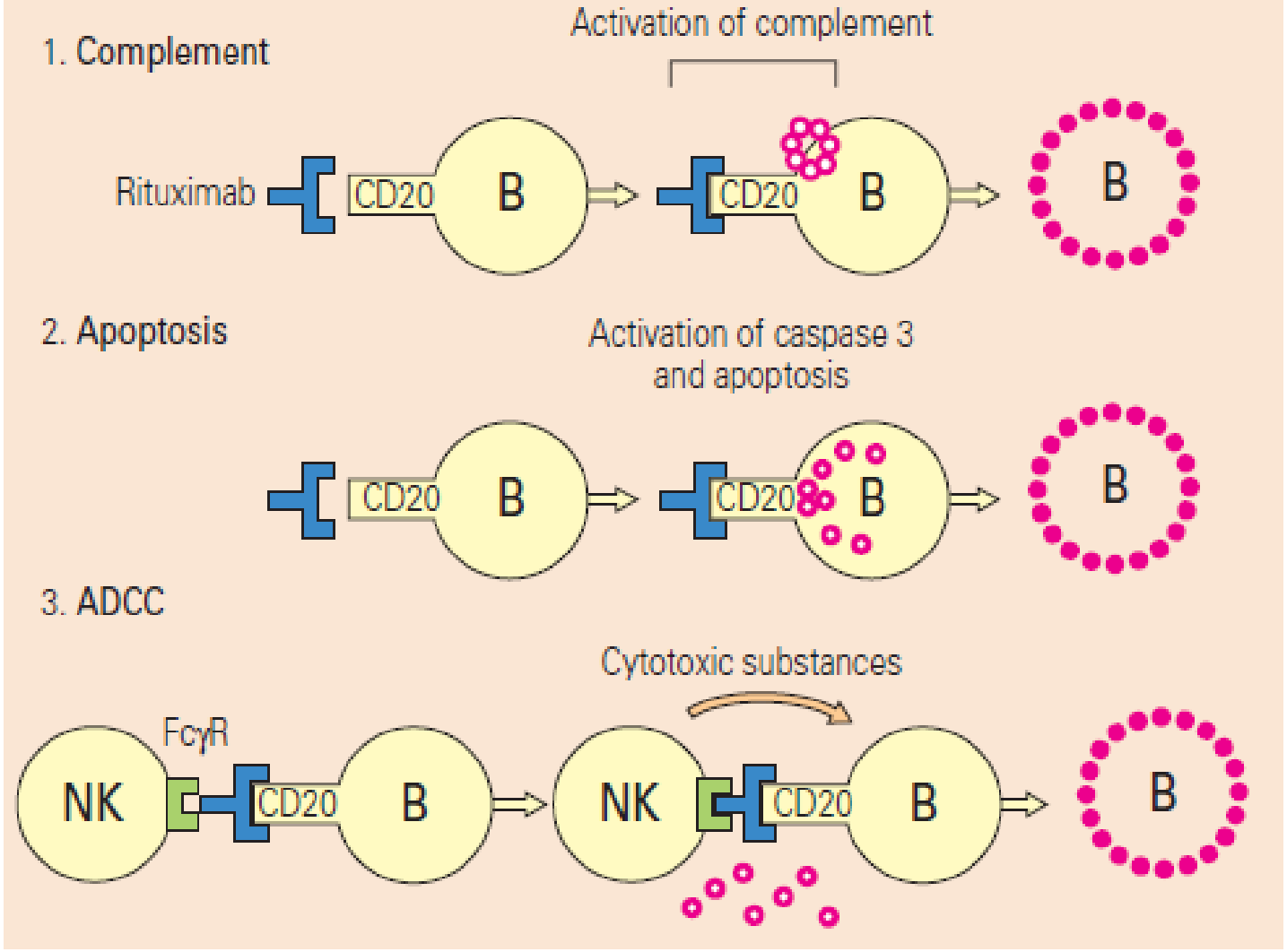
Anti-B Cell (Rituximab)

Anti-B Cell (Rituximab)

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

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

MECHANISMS OF B-CELL KILLING BY RITUXIMAB



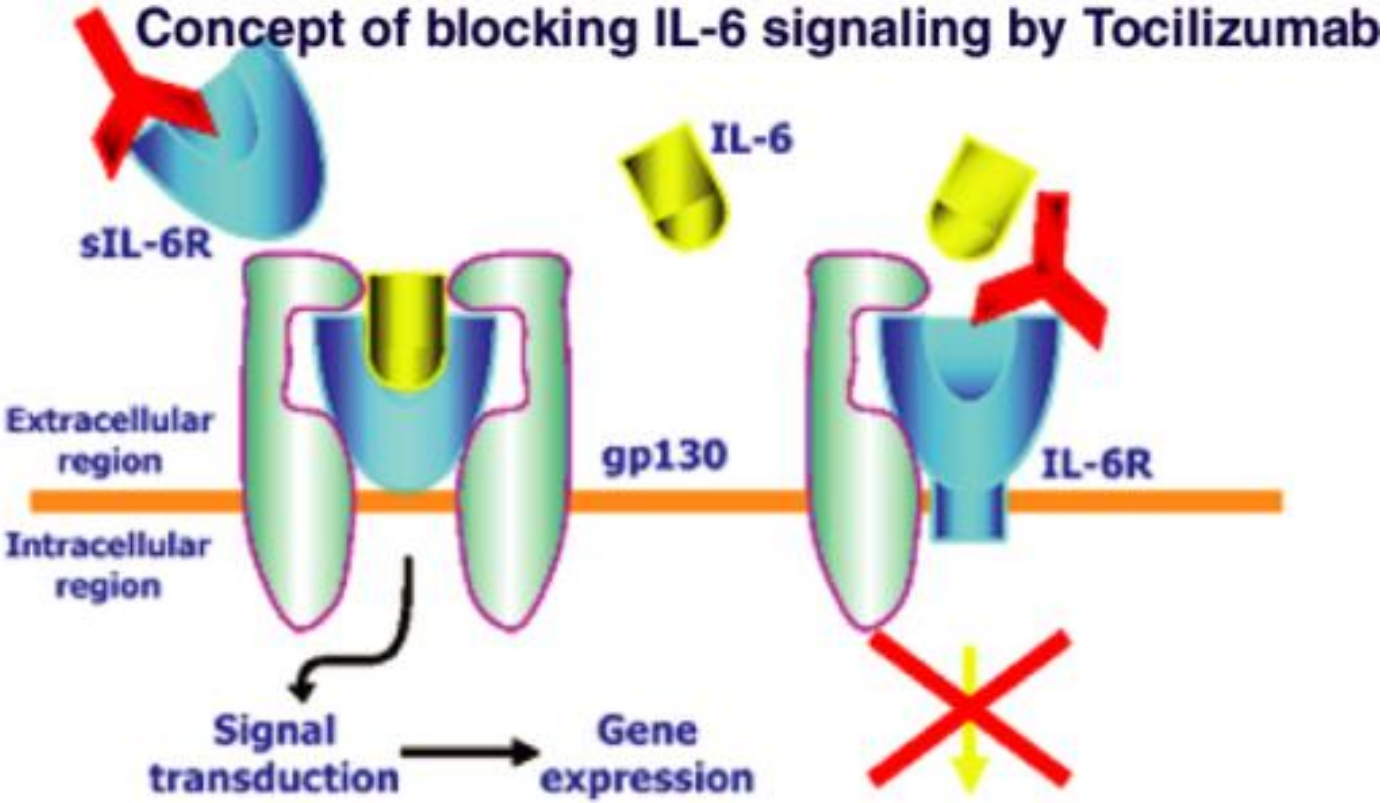
- Rituximab is given intravenously

Anti-IL-6

Anti-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).


Concept of blocking IL-6 signaling by Tocilizumab
IL-6
sIL-6R
Extracellular region
gp130
IL-6R
Intracellular region
Signal transduction
Gene expression

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
- Braces
- Cane/stick
- Local heat/ice
- Acupuncture
- Transcutaneous electrical nerve stimulation
- 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