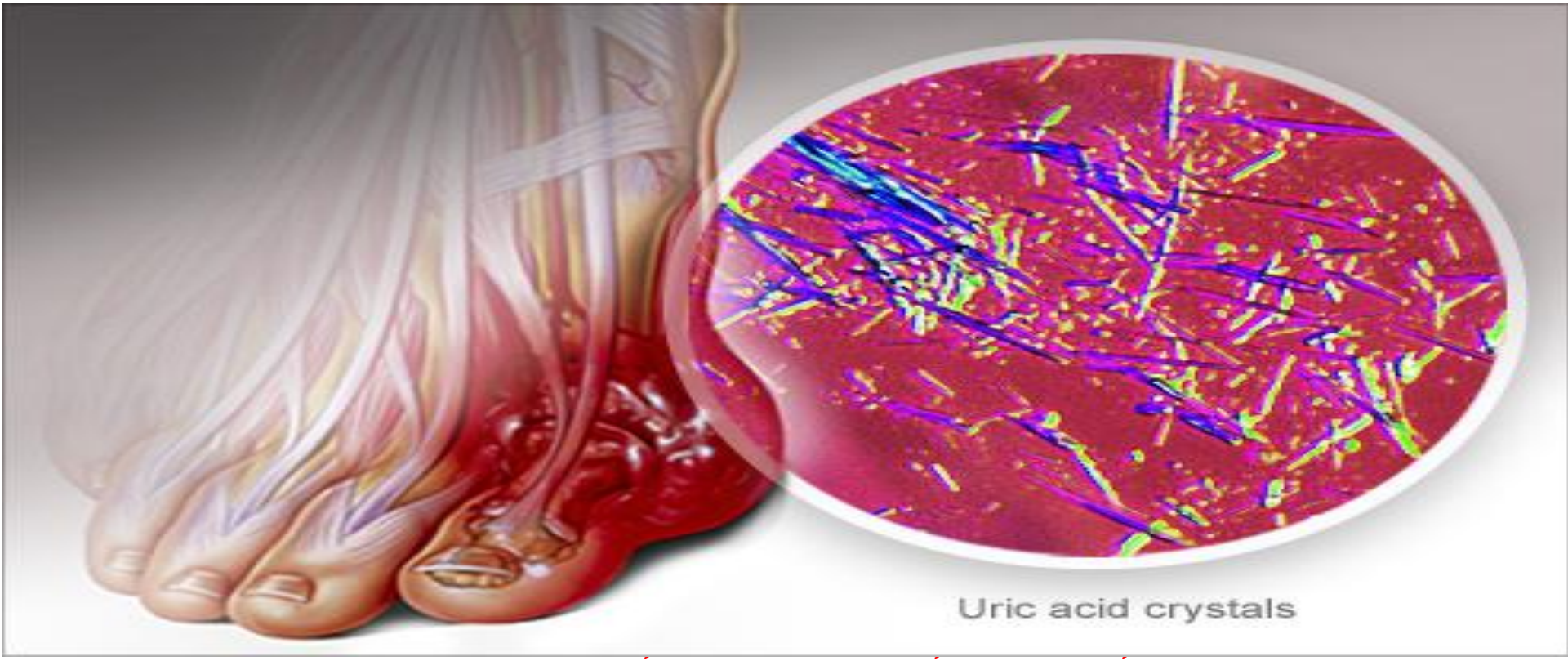
Gout and DMARDs



Gout

is a rheumatic disease that results from an **excess** body burden of **uric acid .**

Hyperuricemia is variably defined as a serum **urate** concentration **>6.8** or **7mg/dL**.

Urate is end product of **purine metabolism**.

not all patients with hyperuricemia will **develop gout,**

the **risk** of developing gout **increases** with the **chronicity** and **increased** concentrations of uric acid **(>9 mg/dL).**

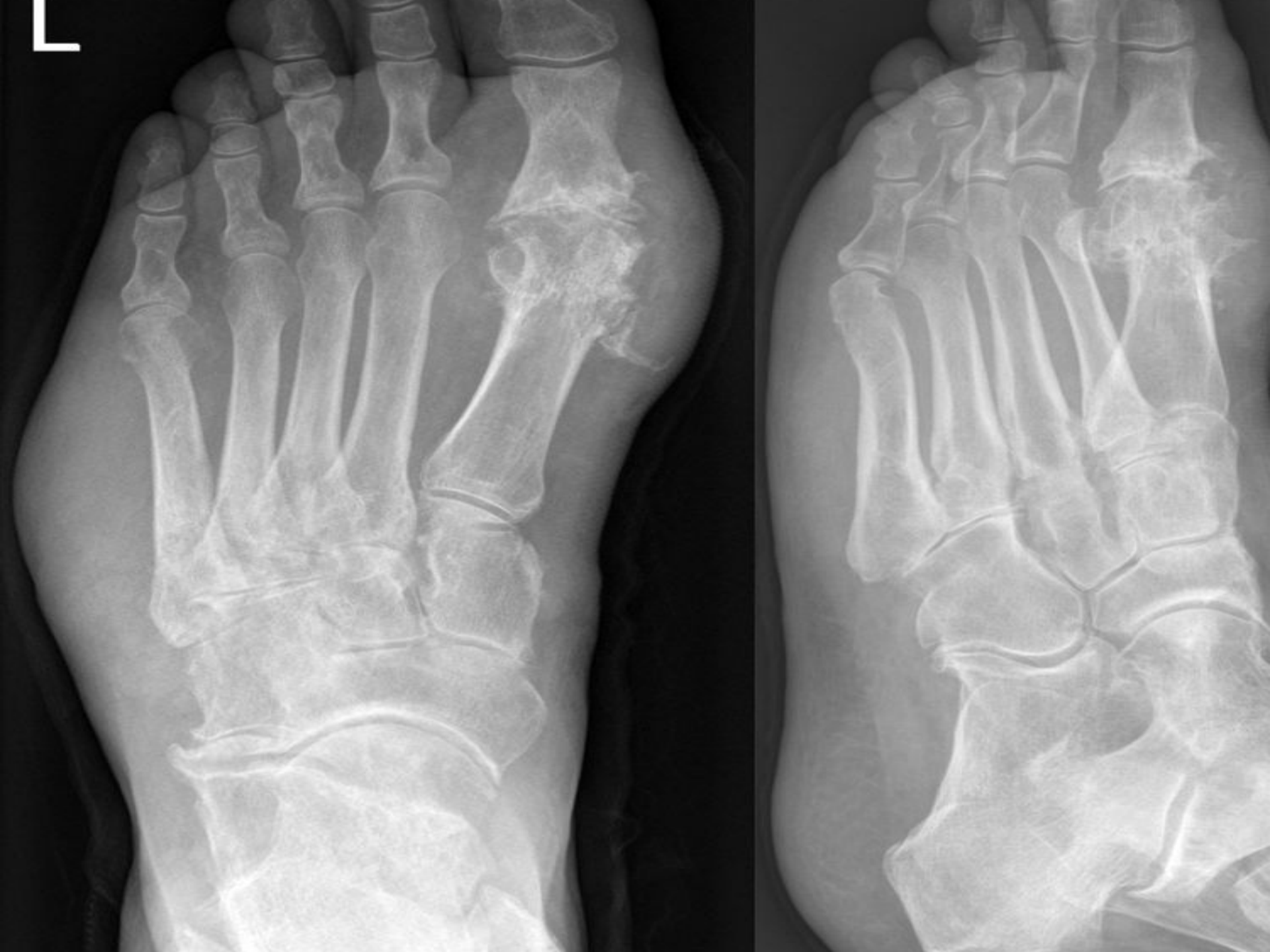
Gout commonly **manifests** as recurrent **episodes** of **acute** joint **pain** and **inflammation**

The **joint at the base of the big toe** (**metatarsal-phalangeal joint**) is affected.

At **high** levels, uric acid **crystallizes,** and the **crystals** deposit in **joints**, **tendons** and surrounding **tissues**, resulting in an attack of gout.

It may result in **kidney stones**.

** Gout : male-to-female ratio of **3:1**. usually at **adulthood**.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Risk factors

1- comorbidities that promote hyperuricemia as: hypertension, obesity, diabetes and chronic kidney disease (CKD).

2- The **purines** rich **foods:** in meat and seafood.

3- **Drugs** predispose to hyperuricemia.(as in table: for your informations)

Table 2. Drugs Associated With Hyperuricemia

Mechanism	Drugs
Decreased urate excretion/clearance	Cyclosporine, ethambutol, levodopa, tacrolimus, diazoxide, certain ACE inhibitors (lisinopril, ramipril, trandolapril)
Inhibition of renal tubular urate secretion	Pyrazinamide, low-dose salicylates, thiazides
Increased uric acid production	Ethanol, fructose
Cell lysis	Cytotoxic chemotherapy (e.g., aldesleukin, asparaginase, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, fludarabine, hydroxyurea, mechlorethamine, melphalan, mercaptopurine, thioguanine, vincristine, vinblastine); glucocorticoids (tumor lysis with antineoplastics); ribavirin and interferon (hemolysis)
Catabolic effect	Didanosine (>9.6 mg/kg/day)
Increased WBC production	Filgrastim (high doses)
High purine content	Pancreatic enzymes (pancrelipase, pancreatin)
Volume contraction and increased uric acid reabsorption in proximal tubule	Acetazolamide, bumetinide, chlorthalidone, ethacrynic acid, furosemide, indapamide, metolazone, torsemide, triamterene
Hypervitaminosis A	Isotretinoin
Assay interference	Theophylline
Mechanism unknown	Niacin

ACE: angiotensin-converting enzyme; WBC: white blood cell.
Source: Reference 8.

Gout and hyperuricemia **depend on main two processes:**

1- Over production of urate (due to excessive cell destruction).

2- Under excretion of urate (due to renal insufficiency).

Treatment

A. Non pharmacological Treatment

1-Lifestyle modifications

- **Diet** (avoid foods high in purine content e.g.liver, kidney)
- Avoid **alcohol** intake.
- Regular **exercise** .

2-General health promotion to control obesity, ……, and chronic kidney disease(CKD).

3-Drug causing hyperurecemia which is determined as **nonessential**, it should be **discontinued** once diagnosis of gout.

B. Pharmacological treatment:

1-Urate-lowering therapy (ULT)

A- Interfering with uric acid **synthesis** e.g. **allopurinol and febuxostat (**xanthine oxidase inhibitor(**XOIs**)**).**

B- Increasing uric acid **excretion (Uricosuric agents)** e.g. **probenecid and sulfinpyrazone**.

C- **Uricase** agent (**pegloticase**) convert uric acid into **soluble** allantoin.

2- Inhibiting leukocyte entry into the affected joints e.g. **colchicine.**

3- NSAIDs. e.g: naproxen,…….

4- Corticosteroid

*The Rx **target** is reduction of serum urate to **<6 mg/dl**

Allopurinol

is a purine analog. It decrease the production of uric acid by competitively **inhibiting** **xanthine oxidase** (XOIs).

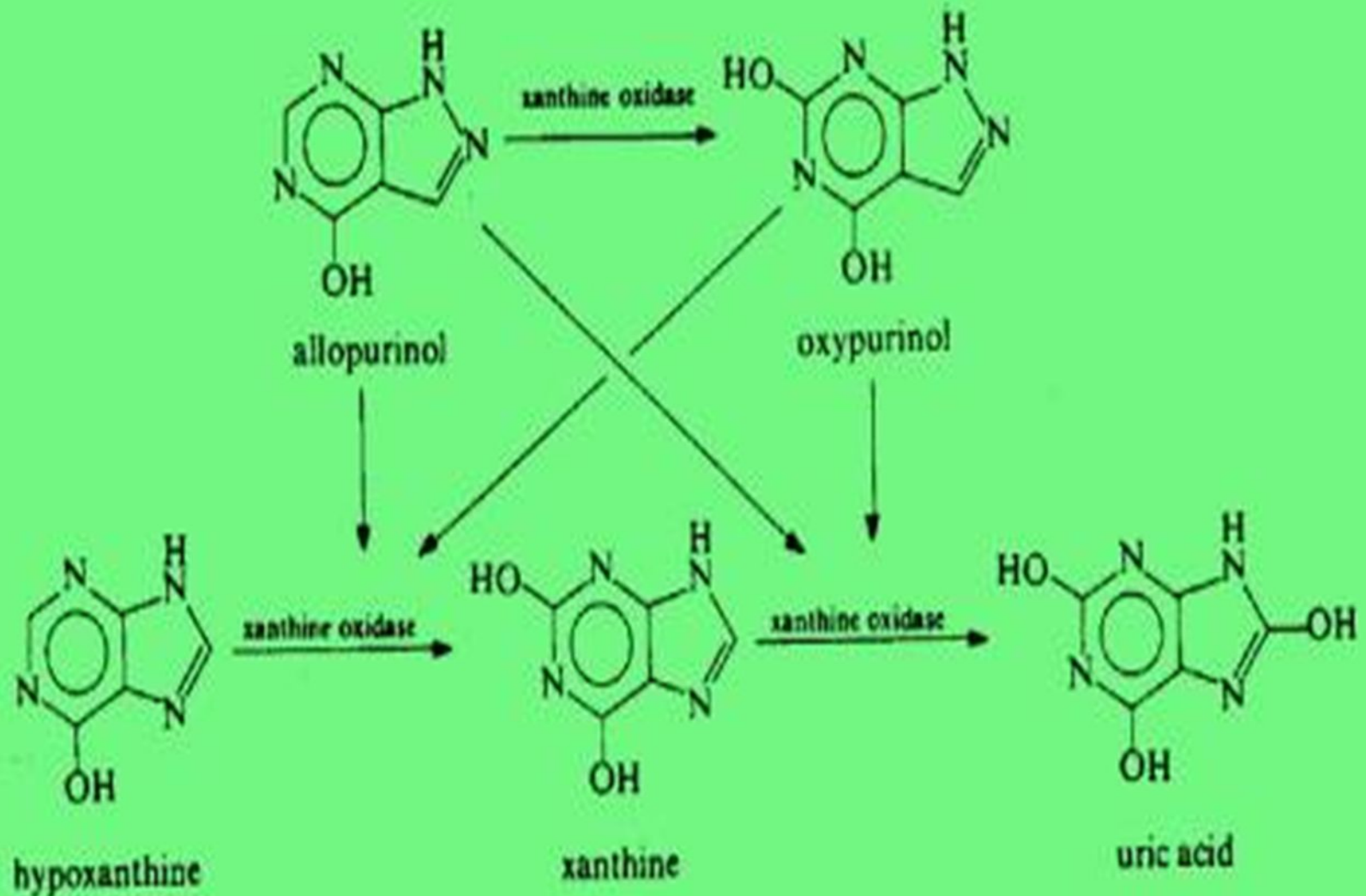
When xanthine oxidase is inhibited, the circulating xanthine and hypoxanthine are **more soluble** and less likely to precipitate.

Given **orally**

initiated at **low doses** to reduce the risk of **hypersensitivity** reactions and acute injury

Used as **monotherapy** and should be **titrated** over 2 to 5 weeks

febuxostat is XOIs, a **1st line** Rx of hyperuricemia associated with **gout**.



Figgure 18.4 Design and mechanism of action of allopurinol.

Side effects of allopurinol: -

It is **well tolerated** but may cause:

- Allergic reaction
- Nausea and diarrhea.

Acute attacks of gout may occur during the first weeks of treatment thus **colchicine and NSAIDs** should be added

This is because some of the crystals can dislodge into the) (joint as they get smaller which can cause an attack

•Side Effects of feboxastat

- Arm, back pain
- cloudy urine.
- diarrhea
-

Uricosuric agents

Members : Probenecid, Sulfinpyrazone and Lesinurad

.**MOA: They competitivly block reabsorption of uric acid at the proximal convoluted tubule. Also, inhibits renal tubular secretion of weak organic acids, such as penicillins.

Thus **Probenecid blocks tubular secretion of penicillin, naproxen and indomethacin.(it is used if contraindication to allopurinol).**

*They are well tolerated

***During early therapy,** high fluid intake is needed.

**Side effects of probencid

- nausea, vomiting, stomach pain
- **painful urination**
- severe **pain** in your **side**
- urine looks **cloudy**

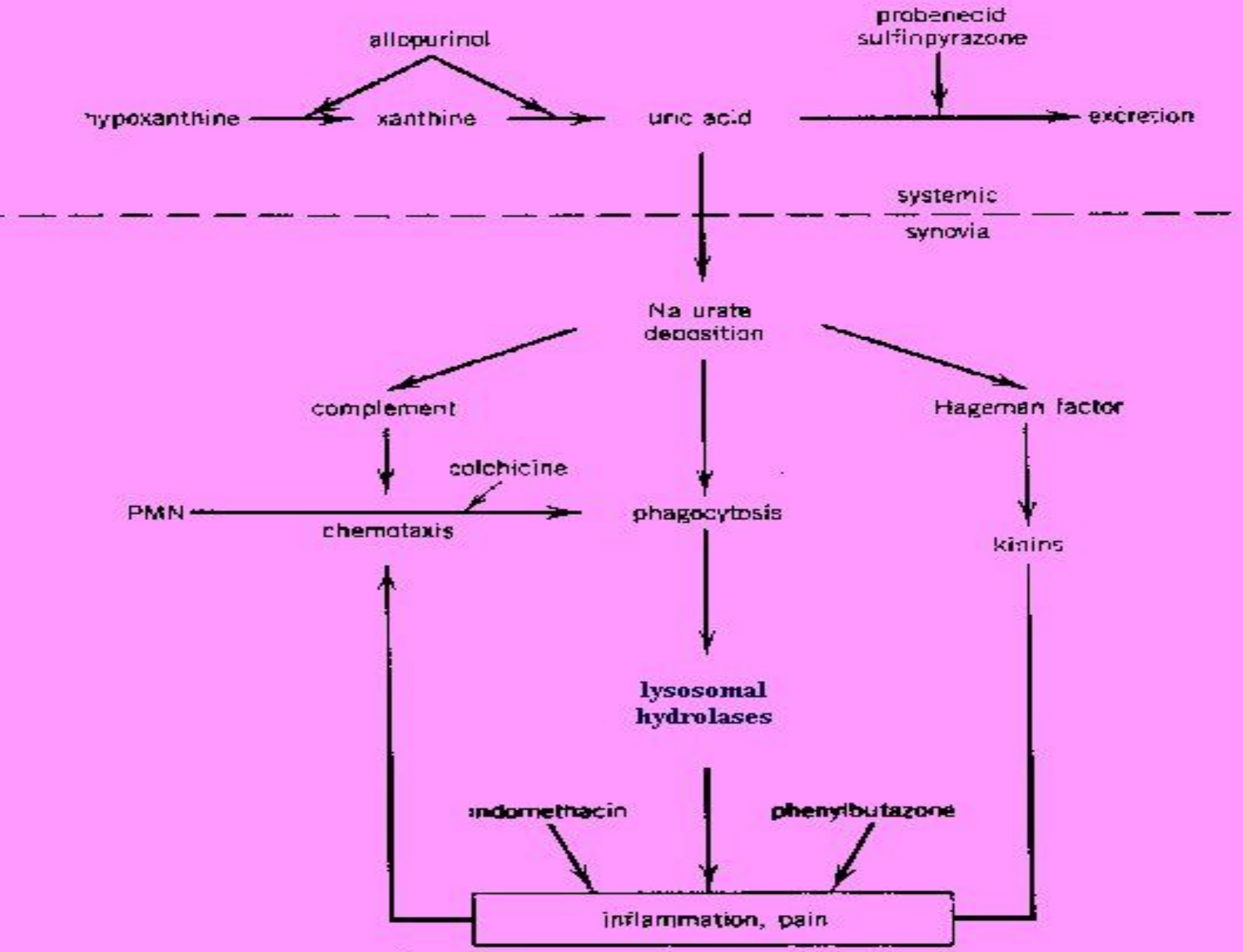
*Sulfinpyrazone side effects:

Heartburn, nausea, and upset stomach are the most common.

Take each dose **with food**, milk, or an antacid to decrease these side effects , it is **contraindicated** in **peptic ulcer.**

Lesinurad **selective uric acid reabsorption inhibitors (SURIs)]**** , used for **gout is not controlled** by current medications

***Fenofibrate** is an **antihyperlipidemic** drug with **uricosuric** action.


allopurinol
probenecid
sulfinpyrazone
hypoxanthine
xanthine
uric acid
excretion
systemic
synovia
Na urate
deposition
complement
Hageman factor
colchicine
PMN
chemotaxis
phagocytosis
kinins
lysosomal
hydrolases
indomethacin
phenylbutazone
inflammation, pain

Uricase agent (**pegloticase**): convert uric acid into **soluble** allantoin.

used in chronic gout that is **refractory** to **conventional** treatments

side effect including *injection site reaction

*anaphylaxis

*Nausea, vomiting, sore throat

Colchicine is an alkaloid, **rapidly relieves** the **pain** and **inflammation** of an **acute attacks** of gout.

-Effective **orally**

- t1/2 is 1 hr

This rapid effect is of high benefit for **diagnosis**, it is **more useful** if taken **within 24 hrs** of onset of attack.

It is **useful** in patients whom **NSAIDs** **are contraindicated**.

Mechanism of action:

1- It **decreases granulocytes** migration

2- It **blocks cell division** by binding to mitotic spindles

3-**Inhibs** the synthesis & release of **leukotrienes**.

Side effects:

- **Nausea** and vomiting
- Abdominal pain and **diarrhea**
- **Aplastic** anemia, agranulocytosis
- Should be **Reduced** in **CKD**
- **Not used** with erythromycin, clarythromycin, cyclosporin

Contraindication : **pregnancy**

Drugs regimen in gout:

A- Treating acute gout: - if it is

Mild to moderate pain must used **monotherapy (unless no .benefit)**

.**Severe** pain should use **combination** therapy

colchicine to decrease movement of granulocytes into the **-1** affected area

.**NSAIDs** to decrease pain and inflammation **-2**

Systemic **corticosteroid** -3

. **intraarticular steroid -4**

Aspirin is **contraindicated** because it **compete** with **uric** acid for the .**organic** acid **secretion** mechanism in the **proximal** tubule of the kidney

- :B- Treating chronic gout

- :include using two lines

Uricosuric -1

Allopurinol -2

DMARDS (Disease modifying antirheumatic drugs) :

They are immune modulators that act to restore a more normal immune environment within the joint synovium.

Characteristic features:

1- **Slow** acting(called **slow acting anti rhumatic agent (SAARA)** (**bs** onset 10-14 weeks or even more).

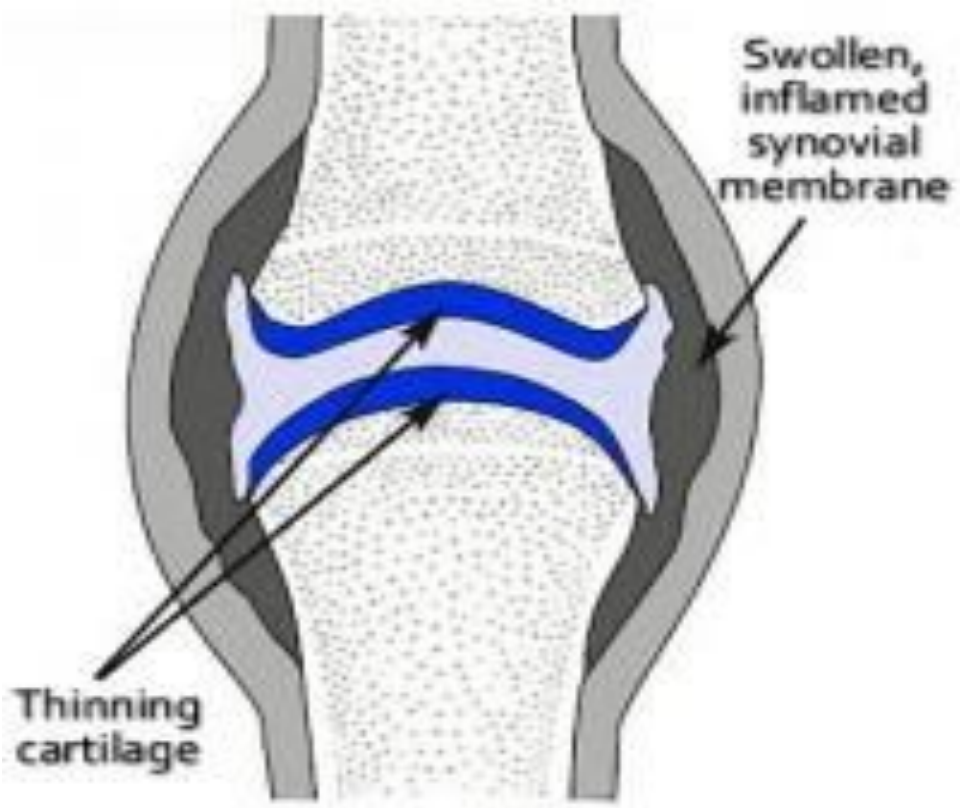
2- **Not** act by inhibiting **COX** and

3- Has **no** or little **analgesic** activity.

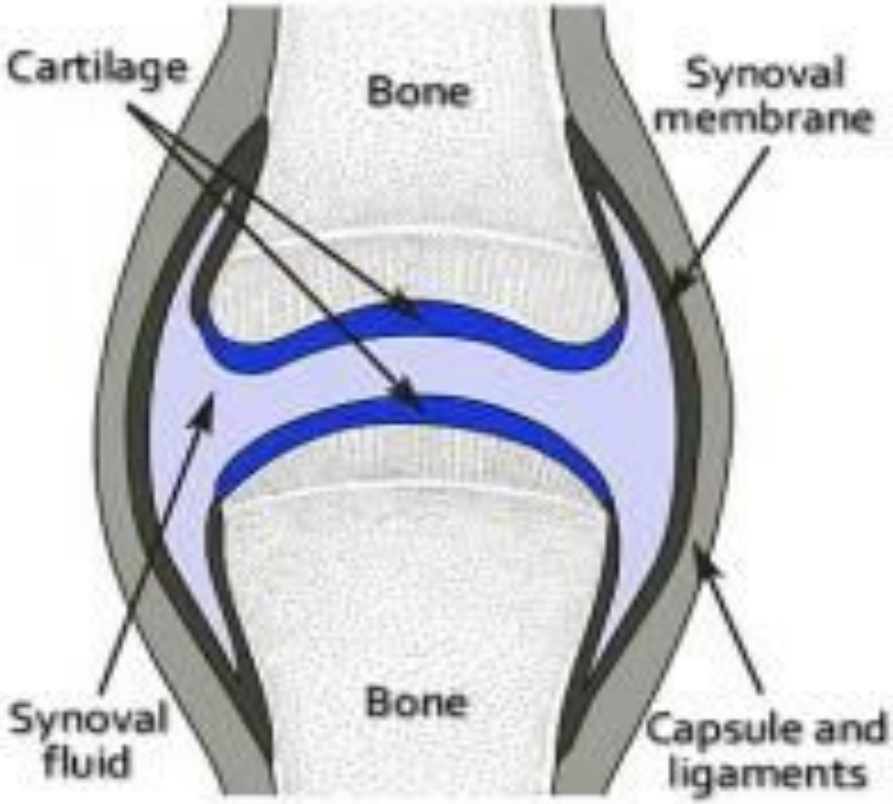
4- Has **no** or little **anti-inflammatory** activity.

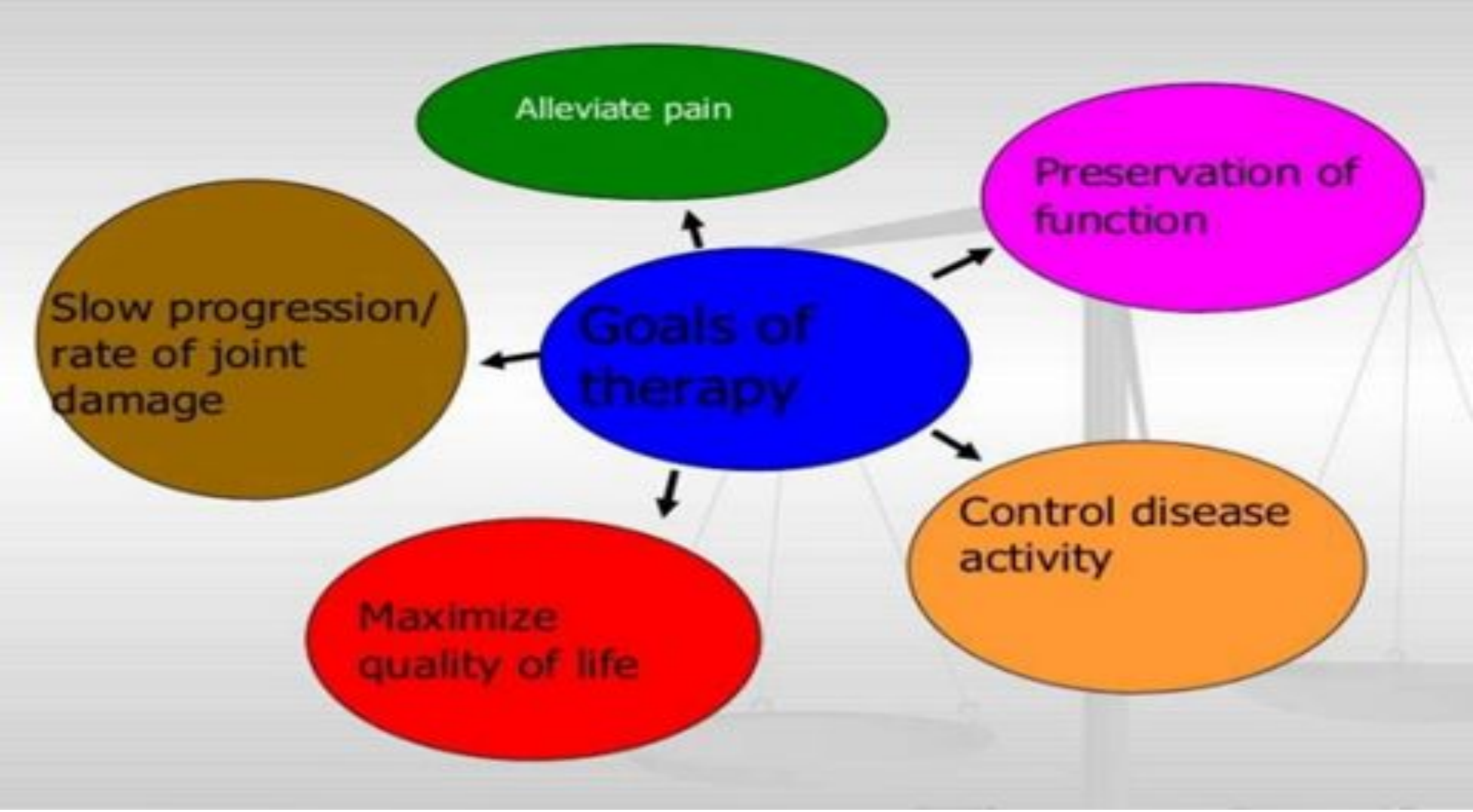
Used for patients with **rheumatoid arthritis** (**RA**) if the disease does **failed** to respond to **COX** inhibitors (NSAIDs).

RA



Normal





Drug is **stopped** when there is **no response** after **3 months** and change to other drug

:The **most common** DMARDs are*

.Methotrexate -1

.Sulfasalazine -2

.Hydroxychloroquine -3

.Leflunomide -4

Less frequently used **DMARA** include*

gold salts

azathioprine

cyclosporine

1-Methotrexate:

is an **antimetabolite** or antifolate. It is an **immunosuppressant** that inhibits the metabolism of **folic** acid, which is necessary in the production of **key immune** .system cells

.**It is a common first-choice drug**

MOA:

An anticancer, acts by competitive **inhibition** of the enzyme **dihydrofolate reductase** and enzyme involved in **protein synthesis** as well as **anti-inflammatory** and **cytokine-modulating** effects.

Kinetics

- absorbed **orally** .
- $t_{1/2}$ = 5 hr.
- It has a more **rapid onset** of action than other DMARDs
- **Doses** are **less** than that in **cancer** therapy.

Side effects:

- mucosal ulceration,
- nausea
- acute pneumonia like syndrome.
- It is **teratogenic**

Drug interaction:

1-NSAIDs increase its toxicity (**slowing** its rate of **excretion**).

2-Antifolate drugs (**trimethoprim**) increase **toxicity**.

2-Sulfasalazine:

It comprises sulfapyridine and 5-aminosalicylic acid linked by an **azo-bond** which is split by colonic bacteria.

-Sulfapyridine has an antifolate action which is believed to benefit RA

-It may act by **scavenging** the **toxic oxygen metabolites** produced by neutrophils

a common first-choice DMARD

Side effects: feeling sick, heartburn, diarrhea, stomach pain .and dizziness

3- Hydroxychloroquine and chloroquine:

They are **antimalarial drugs**,

MOA: the exact MOA is **unclear**

they may exert anti-inflammatory and immune modulating activity by

1-inhibiting nuclic acid synthesis,

2-stabilize lysosomal membranes and free radicals trap).

3-suppression of t-lymphocyte responses .

4-Decreased leukocyte chemotaxis.

** $t_{1/2}$ is 18 days.

Side effects: Retinal damage (accumulated in tissue), so that frequent ophthalmological examination (every 6 months) is needed.

alopecia and GI upset can also occur.

4- Leflunomide:

MOA:

1-Selectively inhibits pyrimidine synthesis

2-prevents T-cell proliferation.

Features :

-It **decreases** pain and inflammation in RA.

-It is well absorbed orally.

-It has faster onset of action than other DMARDs.

-It is teratogenic

Side effects:

GIT disturbances, mouth ulcers, abdominal cramp and diarrhea

abnormal liver function tests

skin disorders(rash).

5- Azathioprine: is metabolized to 6-mercaptopurine (an **inhibitor of purine** synthesis).

It causes **inhibition** to cellular **immune** response.

Side effects: nausea, rash, bone marrow suppression, liver toxicity.

Allopurinol potentiates its effect

Biological agents:

They are derived from natural substances they are chemically altered and they include:

Etanercept: **Inhibits activity of cytokine(TNF)** which predominates in synovium of RA .it is engineered fusion protein **IgG-TNF-receptor** binds two molecules of TNF and prevents them from binding to cellular receptors. Given **S.C**

S.E : injection site reactions, infection, Dyspnea

Infliximab It binds selectively to human **TNF-α** and **neutralizing** **it**. It is given by **i.v. infusion**

S.E: **anti infliximab Ab, infection**

Adalimumab& Golimumab : binds to human **TNF-α receptor** **sites, given S.C…… S.E: headache , injection site reaction**

Anakinra : IL1 receptor antagonis others

Table 34–3 Disease-Modifying Anti-Rheumatic Drugs

DRUG	CLASS OR ACTION
Small molecules	
Methotrexate	Anti-folate
Leflunomide	Pyrimidine synthase inhibitor
Hydroxychloroquine	Anti-malarial
Minocycline	5-lipoxygenase inhibitor, tetracycline antibiotic
Sulfasalazine	Salicylate
Azathioprine	Purine synthase inhibitor
Cyclosporine	Calcineurin inhibitor
Cyclophosphamide	Alkylating agent
Biologicals	
Adalimumab	Ab, TNF-α antagonist
Golimumab	Ab, TNF-α antagonist
Infliximab	IgG-TNF receptor fusion protein (anti-TNF)
Certolizumab	Fab fragment toward TNF-α
Abatacept	T-cell co-stimulation inhibitor (binds B7 protein on antigen-presenting cell)
Rituximab	Ab toward CD20 (cytotoxic toward B cells)
Anakinra	IL-1-receptor antagonist

Thank you