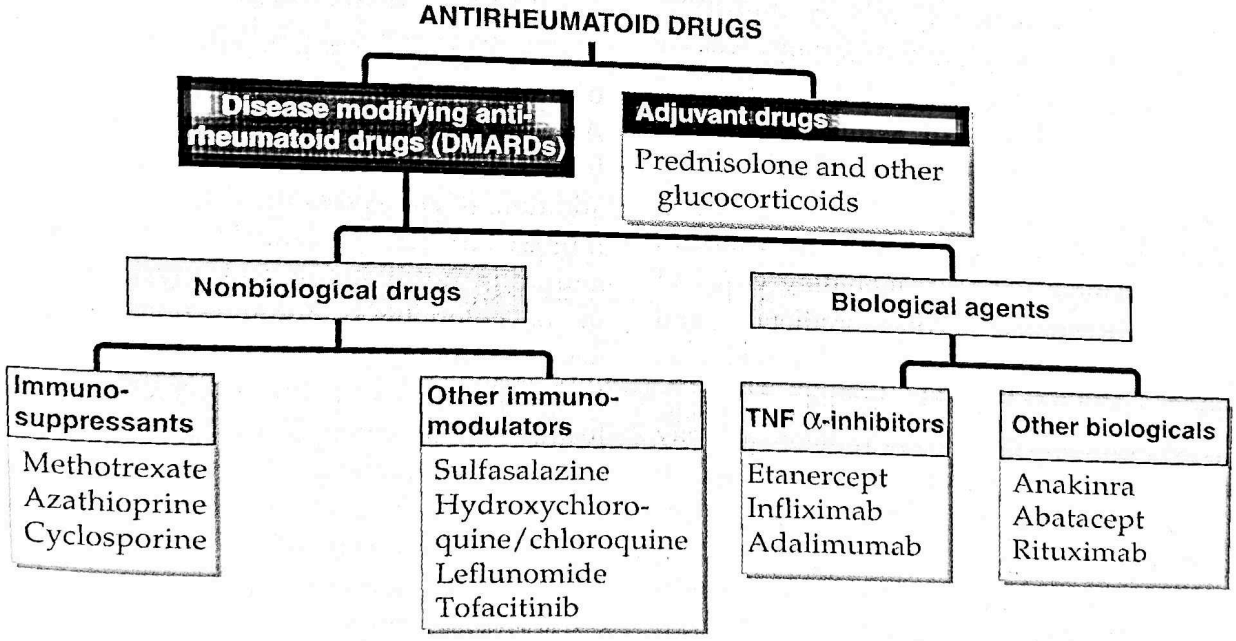
Chapter 15 Antirheumatoid and Antigout Drugs

ANTIRHEUMATOID DRUGS

These are drugs which (except corticosteroids), can suppress the rheumatoid process, bring about a remission and retard disease progression, but do not have nonspecific antiinflammatory or analgesic action. They are used in rheumatoid arthritis (RA) in addition to NSAIDs, and are also referred to as *disease modifying antirheumatic drugs* (DMARDs) or *slow acting antirheumatic drugs* (SAARDs). The onset of benefit with DMARDs takes a few months of regular treatment, and relapses occur at least a few months after cessation of therapy. Recently, some biological agents (antibodies and other proteins) have been added for resistant cases.

Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release cytokines (mainly TNFα and IL-1) which are chemotactic for neutrophils. These inflammatory cells secrete lysosomal enzymes which damage cartilage and erode bone, while PGs produced in the process cause vasodilatation and pain. RA is a chronic progressive, crippling disorder with a waxing and waning course. Multiple small joints of hands and feet are preferentially affected; deformities are produced as the disease progresses. NSAIDs are the first line drugs which afford symptomatic relief in pain, swelling, morning



stiffness, immobility, but do not arrest the disease process.

The goals of drug therapy in RA are:

- Ameliorate pain, swelling and joint stiffness
- Prevent articular cartilage damage and bony erosions
- Preserve joint function and prevent deformity.

Though mild/early cases are still mostly treated with NSAIDs alone, the current recommendation is to add DMARDs as soon as the diagnosis of RA is confirmed. However, use of DMARDs in early/mild RA should be weighed against their potential adverse effects, which may be serious. More than one DMARD may be used concurrently; advanced cases may require 2 or 3 drugs together, because all DMARDs tend to lose effectiveness with time.

Nonbiological drugs

1. Immunosuppressants (see Ch. 65)

Methotrexate (Mtx) This dihydrofolate reductase inhibitor has prominent immunosuppressant and antiinflammatory property. Beneficial effects in RA are probably related to inhibition of cytokine production, chemotaxis and cell-mediated immune reaction. Proliferation of immune-inflammatory cells is inhibited. Induction of oral low-dose (7.5–15 mg) weekly Mtx regimen has improved acceptability of this drug in RA. Onset of symptom relief is relatively rapid (3–6 weeks), therefore Mtx is preferred for initial treatment. Mtx is now the DMARD of first choice and the standard treatment for most patients, including cases of juvenile RA. Response is more predictable and sustained over long-term. Combination regimens of 2 or 3 DMARDs mostly include Mtx.

Oral bioavailability of Mtx is variable and may be affected by food. Its excretion is hindered in renal disease; therefore, not recommended for such patients. Probenecid and aspirin increase Mtx levels and toxicity. Trimethoprim can add to inhibition of dihydrofolate reductase and depress bone marrow. Oral ulceration and g.i. upset are the major side effects of low dose Mtx regimen. With prolonged therapy, dose dependent progressive liver damage leading to cirrhosis occurs in some patients, while this is not seen with short courses used for cancer. Incidence of chest infection is increased. Mtx is contraindicated in pregnancy, breast-feeding, liver disease, active infection, leucopenia and peptic ulcer.

NEOTREXATE, BIOTREXATE 2.5 mg tab.

Azathioprine This purine synthase inhibitor acts after getting converted to 6-mercaptopurine by the enzyme thiopurine methyl transferase (TPMT). It is a potent suppressant of cell-mediated immunity; appears to selectively affect differentiation and function of T-cells and natural killer cells. It also suppresses inflammation. However, remission is induced in smaller percentage of RA patients and it is less commonly used. Given along with corticosteroids, it has a steroid sparing effect, for which it is primarily used now, especially in cases with systemic manifestations. It is not combined with Mtx.

Dose: 50–150 mg/day; IMURAN; AZORAN, AZOPRINE 50 mg tab.

Immunosuppressants like cyclosporine, chlorambucil, cyclophosphamide are rarely used in RA. These drugs are reserved for cases not responding to other DMARDs.

2. Other immunomodulators

Sulfasalazine (*see* Ch. 49) It is a compound of sulfapyridine and 5-amino salicylic acid (5-ASA); exerts antiinflammatory activity in the bowel and is useful in ulcerative colitis. In addition, it suppresses the disease in a significant number of RA patients. The mechanism of action is not known. Sulfapyridine split off in the colon by bacterial action and absorbed systemically appears to be the active moiety (contrast ulcerative colitis, in which 5-ASA acting locally in the colon is the active component). Generation of superoxide radicals and cytokine elaboration by inflammatory cells may be suppressed. Efficacy of sulfasalazine in RA is modest and side effects may be unpleasant. Neutropenia/thrombocytopenia occurs in about 5–10% patients; regular blood count monitoring is needed. Hepatitis is possible. Sulfasalazine

is used as a second line drug for milder cases or is combined wih Mtx.
Dose: 1–3 g/day in 2–3 divided doses.
SALAZOPYRIN, SAZO-EN 0.5 g tab.

Hydroxychloroquine/Chloroquine (see Ch. 61) These are antimalarial drugs found to induce remission in upto 50% patients of RA, but take 3–6 months. Their advantage is relatively low toxicity, but efficacy is also low; bony erosions are not prevented. Their mechanism of action is not known, however, they have been found to reduce monocyte IL–I, consequently inhibiting B lymphocytes. Antigen processing may be interfered with. Lysosomal stabilization and free radical scavenging are the other proposed mechanisms.

For RA, these drugs have to be given for long periods: accumulate in tissues (especially melanin containing tissue) and produce toxicity, most disturbing of which is retinal damage and corneal opacity. This is less common and reversible in case of hydroxychloroquine, which is preferred over chloroquine. Other adverse effects are rashes, graying of hair, irritable bowel syndrome, myopathy and neuropathy.

Hydroxychloroquine/Chloroquine are employed in milder nonerosive disease, especially when only one or a few joints are involved, or they are combined with Mtx/sulfasalazine.
Hydroxychloroquine 400 mg/day for 4–6 weeks, followed by 200 mg/day for maintenance.
ZHQUINE, ZYQ, HCQS 200, 400 mg tab.
Chloroquine 150 mg (base) per day.

In patients of vitiligo, improvement in skin pigmentation has been noted after few months therapy with hydroxychloroquine, but vitiligo is not an approved use of this drug.

Leflunomide This immunomodulator inhibits proliferation of stimulated lymphocytes in patients with active RA. Arthritic symptoms are suppressed and radiological progression of disease is retarded. In clinical trials its efficacy has been rated comparable to Mtx and onset of benefit is as fast (4 weeks).

Leflunomide is rapidly converted in the body to an active metabolite which inhibits *dihydro-orotate dehydrogenase* and pyrimidine synthesis in actively dividing cells. Antibody production by B-cells may be depressed. The active metabolite has a long t½ of 2–3 weeks; leflunomide, therefore, is given in a loading dose of 100 mg daily for 3 days followed by 20 mg OD.

Adverse effects of leflunomide are diarrhoea, headache, nausea, rashes, loss of hair, thrombocytopenia, leucopenia, increased chances of chest infection and raised hepatic transaminases. It is not to be used in children and pregnant/lactating women. Leflunomide is an alternative to Mtx or can be added to it, but the combination is more hepatotoxic. Combination with sulfasalazine improves benefit.
LEFRA 10 mg, 20 mg tabs.

Tofacitinib It is a new synthetic drug approved for severe cases of RA that are not responding to Mtx. Tofacitinib can be used alone or concurrently with Mtx, but should not be combined with azathioprine, cyclosporine or biological DMARDs. It is a JAK-3 and JAK-1 kinase inhibitor, interferes with the JAK-STAT signaling pathway and DNA transcription. Production of inflammatory mediators and release of cytokines is inhibited. Adverse effects are headache, insomnia, diarrhoea, hypertension, anaemia, susceptibility to respiratory infections, flaring of tuberculosis and liver damage.
Dose: 5 mg BD (XELJANZ 5 mg tab).

Biological agents

Lately, several recombinant proteins/monoclonal antibodies that bind to and inhibit cytokines, especially TNFα or IL-1 have been produced and found to afford substantial benefit in autoimmune diseases like RA, inflammatory bowel diseases, psoriasis, scleroderma, etc. All of them produce prominent adverse effects, are expensive, and are used only as reserve drugs for severe refractory disease.

TNFα inhibitors

Because the cytokine TNFα plays a key role in the inflammatory cascade of RA by activating membrane bound receptors ($TNFR_1$ and $TNFR_2$) on the surface of T-cells, macrophages, etc., exogenously administered soluble TNF-receptor protein or antibody can neutralize it and interrupt the reaction. TNF inhibitors mainly suppress macrophage and T-cell function; inflammatory changes in the joint regress and new erosions are slowed. Quicker response than nonbiologic

DMARDs has been obtained. Though effective as monotherapy, they are generally added to Mtx when response to the latter is not adequate or in rapidly progressing cases. Susceptibility to opportunistic infections, including tuberculosis and pneumocystis pneumonia is increased, because TNFα plays important role in combating bacterial infection, especially granulomatous infections.

Etanercept: It is a recombinant fusion protein of TNF-receptor with Fc portion of human IgG_1; and is administered by s.c. injection 50 mg weekly. It binds to and prevents TNFα from activating TNF receptors on the membrane of T-cells/macrophages. Pain, redness, itching and swelling occur at injection site and chest infections may be increased, but immunogenicity is not a clinical problem.

Dose: 25–50 mg s.c. once or twice weekly;
ENBREL, ENBROL 25 mg in 0.5 ml, 50 mg in 1 ml inj.

Infliximab: It is a chimeral monoclonal antibody which binds and neutralizes TNFα; 3–5 mg/kg is infused i.v. every 4–8 weeks. An acute reaction comprising of fever, chills, urticaria, bronchospasm, rarely anaphylaxis may follow the infusion. Susceptibility to respiratory infections is increased and worsening of CHF has been noted. It is usually combined with Mtx which improves the response and decreases antibody formation against infliximab.

Adalimumab: This recombinant human monoclonal anti-TNF antibody is administered s.c. 40 mg every 2 weeks. Injection site reaction and respiratory infections are the common adverse effects. Combination with Mtx is advised to improve the response and decrease antibody formation.

Certolizumab and *Golimumab* are the other TNFα inhibitors.

Other biological agents

Anakinra: It is a recombinant human IL-1 receptor antagonist. Due to lower clinical efficacy it is rarely used now for RA. However, it is indicated in cases who have failed on one or more DMARDs.

Dose: 100 mg s.c. daily.

Local reaction and chest infections are the main adverse effects.

Several other IL-1 inhibitors like *Rilonacept* and *Canakinumab* have also been introduced.

Abatacept It is a recombinant fusion protein which combines part of Fc domain of human IgG with extracellular domain of T-cell inhibitory receptor CTLA4. By binding to CD80 and CD86 molecules, it prevents the 2nd signal for costimulation of T-cells. Beneficial response occurs in many RA patients who are refractory to a combination of Mtx + a TNFα antagonist. Abatacept is approved for use in moderate-severe active RA not responding to Mtx. It can be combined with Mtx and other DMARDs, but not with TNFα antagonists due to greatly increased risk of infections. It can be given by i.v. infusion as well as by s.c. injection.

Abatacept: (ORENCIA 250 mg powder for inj.)

Rituximab (*see* Ch. 64) This chimerized monoclonal antibody depletes B-lymphocytes and is indicated in B-cell lymphomas, as well as some autoimmune diseases. It has been combined with Mtx for treating active RA not responding to Mtx + a TNFα inhibitor.

Corticosteroids (*see* Ch. 20)

Glucocorticoids have potent immunosuppressant and antiinflammatory activity. They can be inducted almost at any stage in RA along with first or second line drugs, if potent antiinflammatory action is required while continuing the NSAID ± DMARD. Symptomatic relief is prompt and marked, but they do not arrest the rheumatoid process, though joint destruction may be slowed and bony erosions delayed.

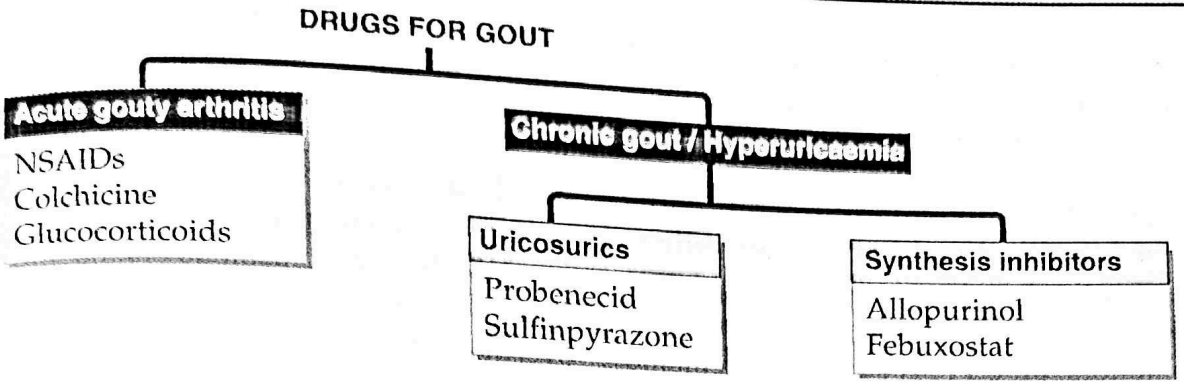
Long-term use of corticosteroids carries serious disadvantages. Therefore,

- Either low doses (5–7.5 mg prednisolone or equivalent) are used to supplement NSAIDs. Once used in this manner, it is difficult to withdraw the steroid—exacerbation is mostly precipitated and the patient becomes steroid dependent.
- Or high doses are employed over short periods in cases with severe systemic manifestations (organ-threatening disease, vasculitis) while the patient awaits response from a remission inducing drug.

In cases with single or a few joint involvement with severe symptoms, intraarticular injection of a soluble glucocorticoid affords relief for several weeks; joint damage may be slowed. This procedure should not be repeated before 3–4 months.

DRUGS USED IN GOUT

Gout It is a metabolic disorder characterized by hyperuricaemia (normal plasma urate 2–6 mg/dl). Uric acid, a product of purine metabolism, has low water solubility, especially at low pH. When blood urate levels are high,



precipitates and deposits in joints, kidney and subcutaneous tissue (tophi).

Secondary hyperuricaemia occurs in:

(a) Leukaemias, lymphomas, polycythaemia—especially when treated with chemotherapy or radiation. This is due to enhanced nucleic acid metabolism and uric acid production.

(b) Drug induced—thiazides, furosemide, pyrazinamide, ethambutol, levodopa reduce uric acid excretion by kidney.

ACUTE GOUTY ARTHRITIS

Acute gout manifests as sudden onset of severe inflammation in a small joint (commonest is metatarso-phalangeal joint of great toe) due to precipitation of urate crystals in the joint space. The joint becomes red, swollen and extremely painful and requires immediate treatment with strong antiinflammatory drugs, without attempting to lower blood urate level. When the attack subsides, urate lowering therapy is instituted, and antiinflammatory cover is continued for several weeks. If hyperuricaemia is not controlled, the attacks recur, involve many joints, and result in chronic deforming arthritis.

1. NSAIDs

One of the strong antiinflammatory drugs, e.g. *naproxen, piroxicam, diclofenac, indomethacin* or *etoricoxib* is given in relatively high and quickly repeated doses. They are quite effective in terminating the attack, but may take 12–24 hours, while complete resolution takes 5–10 days. Response is somewhat slower than with colchicine, but they are generally better tolerated. Majority of patients prefer NSAIDs over colchicine. Their strong antiinflammatory (not uricosuric) action is responsible for the benefit. Naproxen and piroxicam specifically inhibit chemotactic migration of leucocytes into the inflamed joint. After the attack is over, NSAIDs should be continued at lower doses for 3–4 weeks while drugs to control hyperuricaemia take effect.

2. Colchicine

It is an alkaloid from *Colchicum autumnale* which has been used in gout since 1763. The pure alkaloid was isolated in 1820. Colchicine is neither analgesic nor antiinflammatory, but it specifically suppresses gouty inflammation. It does not inhibit the synthesis or promote the excretion of uric acid.

An acute attack of gout is started by the precipitation of urate crystals in the synovial fluid. On being engulfed by the synovial cells, they release mediators and start an inflammatory response. Chemotactic factors are produced → granulocytes migrate into the joint; they phagocytose urate crystals and release a glycoprotein which aggravates the inflammation by:

- Increasing lactic acid production from inflammatory cells → local pH is reduced → more urate crystals are precipitated.
- Releasing lysosomal enzymes which cause joint destruction.

Colchicine does not affect phagocytosis of urate crystals, but inhibits release of chemotactic factors and of the glycoprotein, thus suppressing the subsequent events. By binding to fibrillar protein tubulin, it inhibits granulocyte migration into the inflamed joint and thus interrupts the vicious cycle. Other actions of colchicine are:

(a) Antimitotic: causes metaphase arrest by binding to microtubules of mitotic spindle.
(b) Increases gut motility through neural mechanisms.

Colchicine is rapidly absorbed orally, partly metabolized in liver and excreted in bile—undergoes enterohepatic circulation; ultimate disposal occurs in urine and faeces over many days. Inhibitors of CYP3A4 retard colchicine metabolism and enhance its toxicity.

Toxicity of colchicine is high and dose related. Nausea, vomiting, watery or bloody diarrhoea and abdominal cramps occur as dose limiting adverse effects. Accumulation of the drug in intestine and inhibition of mitosis in its rapid turnover mucosa is responsible for the toxicity. In overdose, colchicine produces kidney damage, CNS depression, intestinal bleeding; death is due to muscular paralysis and respiratory failure.

Use Colchicine is the fastest acting drug to control an acute attack of gout; 0.5 mg 1–3 hourly with a total of 4 doses in a day; maximum 6.0 mg in a course spread over 3–4 days. Control of attack is usually achieved in 6–12 hours, but complete resolution may take 3–5 days. A second course should not be started before 3–7 days. The response is dramatic, so much so that it may be considered diagnostic. However, because of higher toxicity, it is a second line option to NSAIDs. Maintenance doses (0.5–1 mg/day) may be given for 4–8 weeks in which time control of hyperuricaemia is achieved with other drugs.

Taken at the first symptom of an attack, small doses (0.5–1.5 mg) of colchicine abort it. ZYCOLCHIN, GOUTNIL 0.5 mg tab.

3. Corticosteroids

Intraarticular injection of a soluble steroid (e.g. triamcinolone acetonide 10 mg in small finger/toe joints, 30 mg in wrist) suppresses symptoms of acute gout. Crystalline preparations should not be used. It is indicated when only one or few joints are involved, and in those not tolerating NSAIDs/colchicine.

Systemic steroids are rarely needed. They are highly effective and produce nearly as rapid a response as colchicine, but are reserved for patients with renal failure/history of peptic ulcer bleed in whom NSAIDs are contraindicated or for cases not responding to or not tolerating NSAIDs. Prednisolone 40–60 mg may be given in one day, followed by tapering doses over 1–2 weeks.

CHRONIC GOUT/HYPERURICAEMIA

When pain and stiffness persist in a joint between attacks, gout has become chronic. Other cardinal features are hyperuricaemia, tophi (chalk-like stones under the skin in pinna, eyelids, nose, around joints and other places) and urate stones in the kidney. In majority of patients, hyperuricaemia is due to undersecretion of uric acid, while in few it is due to over production. Chronic gouty arthritis may cause progressive disability and permanent deformities.

A. Uricosuric drugs

Probenecid

It is a highly lipid-soluble organic acid developed in 1951 to inhibit renal tubular secretion of penicillin so that its duration of action could be prolonged. Probenecid competitively blocks active transport of organic acids by OATP at all sites; that in renal tubules being the most prominent. This transport is bidirectional: net effect of probenecid on excretion depends on whether secretion or reabsorption of the particular organic acid is quantitatively more important, e.g.:

- Penicillin is predominantly secreted by the proximal tubules, its reabsorption is minimal. Net effect of probenecid is inhibition of penicillin excretion; more sustained blood levels are achieved.
- Uric acid is largely reabsorbed by active transport, while less of it is secreted; only 1/10th of the filtered load is excreted in urine. The major transporter involved is URAT-1, which is a member of the OATP family. Probenecid, therefore, inhibits reabsorption

and promotes excretion of uric acid, and lowers its blood level.

Probenecid does not have any other significant pharmacological action; it is neither analgesic nor antiinflammatory.

Interactions

1. In addition to penicillins, probenecid inhibits renal urinary excretion of cephalosporins, sulfonamides, Mtx and indomethacin.
2. It inhibits biliary excretion of rifampicin. Pyrazinamide and ethambutol may interfere with uricosuric action of probenecid.
3. Probenecid inhibits tubular secretion of nitrofurantoin which may not attain antibacterial concentration in urine.
4. Aspirin blocks uricosuric action of probenecid.

Pharmacokinetics Probenecid is completely absorbed orally; 90% plasma protein bound: partly conjugated in liver and excreted by the kidney; plasma t½ is 6–8 hours.

Adverse effects Probenecid is generally well tolerated. Dispepsia is the most common side effect (upto 25% incidence with high doses). It should be used cautiously in peptic ulcer patients. Rashes and other hypersensitivity phenomena are rare.

Uses

1. Chronic gout and hyperuricaemia: Probenecid is a second line/adjuvant drug to allopurinol. Started at 0.25 g BD and increased to 0.5 g BD, it gradually depletes the urate pool in the body and lowers blood urate level. Arthritis, tophi and other lesions may take months to resolve. Colchicine/NSAID cover is advised during the initial 1–2 months to avoid precipitation of acute gout.

Probenecid and other uricosurics are ineffective in the presence of renal insufficiency. It should be used only when creatinine clearance is > 50 ml/min or serum creatinine is < 2 mg/dl. Patients with renal stones should not be given probenecid. Plenty of fluids should be given with probenecid to avoid urate crystallization in urinary tract.

2. Probenecid is also used to prolong penicillin or ampicillin action by enhancing and sustaining their blood levels, e.g. in gonorrhoea, SABE.
3. Probenecid is given along with cidofovir, a drug for CMV retinitis in AIDS patients, to prevent its nephrotoxicity.

BENEMID, BENCID 0.5 g tab.

Sulfinpyrazone It is a pyrazolone derivative, related to phenylbutazone, having uricosuric action, but is neither analgesic nor anti-inflammatory. It inhibits tubular reabsorption of uric acid. Though equally efficacious as probenecid, sulfinpyrazone has gone into disuse because of more gastric irritation and other side effects. It inhibits platelet aggregation as well.

Lesinurad It is a new uricosuric drug, approved recently by US-FDA as a treatment option for hyperuricaemia, either alone or in combination with a xanthine oxidase inhibitor. Its mechanism of action is similar to that of probenecid.

B. Uric acid synthesis inhibitors

Allopurinol

This hypoxanthine analogue was synthesized as a purine antimetabolite for cancer chemotherapy. However, it had no antineoplastic activity but was a substrate as well as inhibitor of *xanthine oxidase*, the enzyme responsible for uric acid synthesis (Fig. 15.1).

Allopurinol itself is a short-acting (t½ 2 hrs) competitive inhibitor of xanthine oxidase, but its major metabolite *alloxanthine (oxypurine)* is a long-acting (t½ 24 hrs) and noncompetitive inhibitor. Alloxanthine is thus primarily responsible for uric acid synthesis inhibition *in vivo*. During allopurinol administration, plasma concentration of uric acid is reduced and that of hypoxanthine and xanthine is somewhat increased. In place of uric acid alone, all 3 oxipurines are excreted in urine. Since xanthine and hypoxanthine are more soluble, have a higher renal clearance than that of uric acid and each has its individual solubility, precipitation and crystallization in tissues and urine does not occur.

Because of raised levels of xanthine and hypoxanthine, some feedback inhibition of *de novo* purine synthesis and reutilization of metabolically derived purine also occurs.

Pharmacokinetics About 80% of orally administered allopurinol is absorbed. It is not

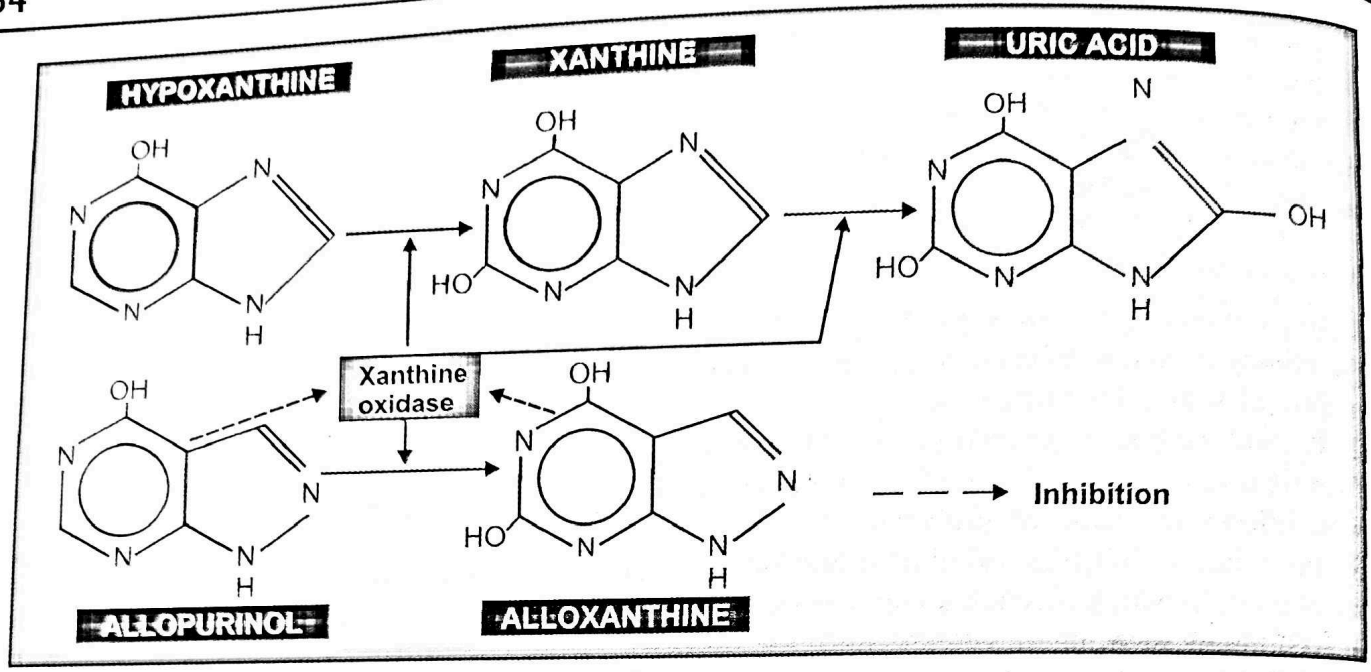


Fig. 15.1: Uric acid synthesis and the action of allopurinol

bound to plasma proteins; metabolized largely to alloxanthine. During chronic medication, it inhibits its own metabolism and about 1/3rd is excreted unchanged, the rest as alloxanthine.

Interactions

1. Allopurinol inhibits the degradation of 6-mercaptopurine and azathioprine: their doses should be reduced to 1/3rd, but not that of thioguanine, because it follows a different metabolic path (S-methylation).
2. Probenecid given with allopurinol has complex interaction; while probenecid shortens t½ of alloxanthine, allopurinol prolongs t½ of probenecid.
3. Allopurinol can potentiate warfarin and theophylline by inhibiting their metabolism.
4. A higher incidence of skin rashes has been reported when ampicillin is given to patients on allopurinol.

Adverse effects These are uncommon. Hypersensitivity reaction consisting of rashes, fever, malaise and muscle pain is the most frequent. It subsides on stopping the drug. Allopurinol should not be restarted in these patients, because serious reactions may follow. Renal impairment increases the incidence of rashes and other reactions to allopurinol. Stevens-Johnson syndrome is a rare but serious risk. Gastric irritation, headache, nausea and dizziness are infrequent; do not need withdrawal. Liver damage is rare.

Precautions and contraindications Liberal fluid intake is advocated during allopurinol therapy. It is contraindicated in hypersensitive patients, during pregnancy and lactation.
It should be cautiously used in the elderly, children and in patients with kidney or liver disease.

Uses Allopurinol is the first choice drug in *chronic gout*. It can be used in both *over producers* and *under excretors* of uric acid. The more severe cases with tophi or nephropathy also respond well. Uricosurics are infrequently used in India; they are less effective when g.f.r. is low and are inappropriate in stone formers. The two classes of drugs, *viz.* uricosurics and synthesis inhibitors, can be used together when the body load of urate is large.

Allopurinol therapy is generally long term (years, or even life long). During prolonged allopurinol therapy, tophi disappear gradually and nephropathy is halted, even reversed.

- *Secondary hyperuricaemia* due to cancer chemotherapy/radiation/thiazides or other drugs: can be controlled by allopurinol. It can even be used prophylactically in these situations.

Allopurinol can also be used to *potentiate 6-mercaptopurine or azathioprine* in cancer chemotherapy and immunosuppressant therapy.

Start with 100 mg OD, gradually increase as needed 300 mg/day; maximum 600 mg/day.

ORIC 100, 300 mg tabs., ZYLOPRIM, CIPLORIC 100 cap.

Caution Allopurinol as well as uricosurics should not be started during acute attack of gout. During the initial 1–2 months of treatment with these drugs, attacks of acute gout are more common—probably due to fluctuating plasma urate levels favouring intermittent solubilization and recrystallization in joints. This period should be covered by NSAIDs or colchicine.

Febuxostat

It is a newer nonpurine xanthine oxidase inhibitor, equally or more effective than allopurinol in lowering blood uric acid level in patients with hyperuricaemia and gout. It is rapidly absorbed orally, highly plasma protein bound, oxidized as well as glucuronide conjugated in the liver and excreted by kidney; the plasma t½ is ~ 6 hours.

Hypersensitivity reactions are rare with febuxostat, but it should be stopped if they occur. The most important adverse effect is liver damage; liver function needs to be monitored during febuxostat therapy. Diarrhoea, nausea and headache are the usual side effects. By inhibiting xanthine oxidase, febuxostat has the potential to interact with mercaptopurine, azathioprine and theophylline. It should not be given to patients receiving these drugs.

Febuxostat is an alternative drug to allopurinol, but should not be combined with it. However, the two can be given sequentially in case of intolerance/nonresponsiveness to one. It is not indicated in malignancy associated hyperuricaemia. Like other drugs used to treat hyperuricaemia, NSAID/colchicine cover should be provided for 1–2 months while initiating febuxostat therapy.

Dose: Start with 40 mg OD, increase to 80 mg OD if target uric acid level is not achieved; Maximum dose 120 mg/day.

FABULAS, FABUSTAT, ZURIG 40,80,120 mg tabs.

Pegloticase It is recombinant uricase, an enzyme which oxidizes uric acid to highly soluble allantoin, that is easily excreted by kidney. Humans lack this enzyme. In this preparation, the enzyme has been coupled with methoxy polyethylene glycol (mPEG) which serves to prolong its sojourn in the body, permitting i.v. infusion of the drug to be given every 2 weeks. It is indicated only in rare cases of refractory symptomatic gout. Pegloticase is immunogenic and carries high risk of infusion reactions, including anaphylaxis. It should be administered only by professionals in a setting where facilities for managing anaphylaxis are available. Due to formation of antibodies, the response is gradually lost in many patients.

PROBLEM DIRECTED STUDY

15.1 A 44-year-old lady presents with complaints of pain, swelling and stiffness of the interphalangeal and metacarpophalangeal joints of both hands for the last 8 months. Initially the symptoms were mild, but are increasing progressively despite treatment by her neighbourhood doctor. Her prescription reveals that she is taking Diclofenac sod. 75 mg SR tab twice daily and Pantoprazole 40 mg tab once daily in the morning. Though, initially she was getting good relief, but now the relief is incomplete, and she is disabled for 2–3 hours in the morning. Physical examination confirmed the swelling, tenderness and stiffness of hand and finger joints. Investigations were ordered. The significant findings of the test reports are: mild normocytic anaemia (Hb–10.2 g/dl), ESR-54 mm at 1 hour, TLC-6,800/mm^3, rheumatoid factor and Anti-CCP antibodies positive, C-reactive protein 2.2 mg/L (raised). X-ray of hand revealed mild soft tissue swelling around the affected joints, but no joint and bone abnormality. She was diagnosed as a case of active rheumatoid arthritis.

(a) Should the diclofenac dose be increased, or should it be substituted by another NSAID? Will these measures treat her adequately?

(b) Should any drug, other than an NSAID, be prescribed for this patient? If so, which one, and why?

(c) What needs to be done before prescribing this drug? When and what benefits are expected to be obtained from this drug?

(d) Why pantoprazole has been prescribed to this patient? Should it be continued or stopped?