DRUGS USED IN THE CHEMOTHERAPY OF TUBERCULOSIS

Pulmonary disease is the most frequent clinical presentation of tuberculosis (T.B.). Less common clinical manifestations include meningitis, renal disease, vertebral osteomyelitis (Pott's disease), skin involvement (lupus vulgaris) and miliary dissemination.

Mycobacteria are intrinsically resistant to most antibiotics because:

1-They grow slowly compared with other bacteria, antibiotics that are most active against growing cells are relatively ineffective.

2-Mycobacterial cells can also be dormant and thus completely resistant to many drugs or killed only very slowly.

3-The lipid-rich mycobacterial cell wall is impermeable to many agents.

4-Mycobacterial species are intracellular pathogens, and organisms residing within macrophages are inaccessible to drugs that penetrate these cells poorly.

5-Mycobacteria are notorious for their ability to develop resistance.

CLASSIFICATION OF ANTITUBERCULOUS DRUGS:

Drugs employed in the treatment of TB can be classified into two categories:

l-"First line" drugs: They include isoniazid, rifampin, ethambutol, streptomycin and pyrazinamide.

2-"Second line" drugs: They include quinolones, ethionamide, aminosalicylic acid, cycloserine, capreomycin, kanamycin and amikacin.

ISONIAZID (INH):

lsoniazid (INH). It is the most active drug for patients who can tolerate it and whose mycobacteria are sensitive.

Isoniazid is a prodrug that is converted by mycobacterial catalase-peroxidase into an active metabolite.

Mechanism of action:

Isoniazid is bactericidal against actively dividing bacilli and bacteriostatic against "resting" bacilli. The primary action of isoniazid is to inhibit the biosynthesis of mycolic acids.

Pharmacokinetics:

It is metabolized in the liver by enzymatic acetylation (acetylisoniazid) and enzymatic hydrolysis (isonicotinic acid). The acetylation is under genetic control via the activity of acetyltransferase. The plasma concentration of the drug is affected by whether a given patient is a fast or a slow acetylator of the drug.

Untoward effects:

1-Hepatitis: the incidence increases with age and the risk is greater in alcoholics. The drug is only discontinued when there is definite hepatic impairment with transaminases greater than five times the normal value.

2-Neurological disorders: mainly peripheral neuritis, others include insomnia, restlessness, muscle twitchings, convulsions and psychotic episodes.

3-Skin rash, fever, arthritic symptoms.

4-Isoniazid can reduce the metabolism of phenytoin increasing its blood level and toxicity.

Therapeutic uses:

l-Isoniazid is the most important drug for the treatment of active tuberculosis. It must be used concurrently with one or more drugs. The usual oral adult dose is 300 mg/ day. Intramuscular doses are identical although rarely used. Toxic effects can be minimized by simultaneous administration of pyridoxine.

2-Isoniazid as a single agent is also indicated for treatment of latent TB or for prophylaxis.

RIFAMPIN (RIMACTANE)

Rifampin is a semisynthetic derivative of rifamycin B which belongs to a group of complex macrocyclic antibiotics.

Mechanism of action:

Rifampin is bactericidal for gram-positive and gram-negative cocci, some enteric bacteria, mycobacteria, and chlamydia. lt inhibits RNA synthesis in bacteria by inhibiting DNA-dependent RNA polymerase.

Pharmacokinetics:

1t imparts a harmless orange red color to urine, saliva, sweat, tears and sputum and patients should be warned about this.

Untoward effects:

l-Occasional side effects include rashes, thrombocytopenia, impaired liver function with jaundice, light chain proteinuria and some impairment of immune response.

2-If given intermittently less than twice weekly or if daily doses of 1200 mg or greater are used, an influenza like syndrome develops. It includes fever, chills, myalgia, headache, acute tubular necrosis, thrombocytopenia, hemolytic anemia and shock.

3-Rifampin is a potent enzyme inducer and increases the metabolism of some drugs as warfarin, digitoxin, oral contraceptives, methadone, ketoconazole, propranolol, sulfonylureas and prednisone. Appropriate increase in dosage is required to compensate for increased drug metabolism.

Therapeutic uses:

l-In the treatment of TB. rifampin (like isoniazid) should never be used alone because of the rapidity with which resistant organisms may develop. It is usually combined with isoniazid or ethambutol. Oral adult dose is 600 mg once daily.

2-lt is used in chemoprophylaxis of meningococcal meningitis.

3-ln staphylococcal infections rifampin combined with vancomycin or nafcillin is useful for therapy in some selected cases of staphylococcal endocarditis or osteomyelitis. Also combined with trimethoprim-sulfamethoxazole it is used in infections with methicillin resistant staphylococci in patients allergic to B-lactam antibiotics.

ETHAMBUTOL

Mechanism of action:

Ethambutol is a bacteriostatic agent. It inhibits mycobacterial arabinosyl transferases which are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall.

Pharmacokinetics:

It is well absorbed after oral administration. The majority of ingested dose is excreted unchanged mainly in urine.

Untoward effects:

l-Optic neuritis. It is dose-related and manifested by decreased color perception, impaired visual fields or reduced visual acuity. Eye examinations should be done prior to therapy and periodically thereafter. This complication is reversible with early drug withdrawal.

2-Hyperuricemia due to decreased renal excretion of uric acid.

3-Other side effects include GlT upset, headache, dizziness, confusion, hallucinations, peripheral neuritis.

Ethambutol (lg daily) is used in the therapy of TB. of various forms when given concurrently with isoniazid.

PYRAZINAMIDE

Pyrazinamide exhibits bactericidal activity against tubercle bacilli. **Mechanism of action**: is unknown.

Side effects:

1- **Hepatotoxicity**: is the major adverse effect.

2-Nausea, vomiting and drug fever can occur.

3-**Hyperuricemia:** It inhibits the excretion of urates resulting in hyperuricemia in nearly all patients; acute episodes of gout have occurred.

Therapeutic uses:

The drug is used with increased frequency in T.B. (1.5-2 g once daily) because of its efficacy in short term multiple drug therapy regimens.

STREPTOMYCIN

Streptomycin is bactericidal for extracellular mycobacteria. It penetrates poorly into living cells and thus cannot kill intracellular microbes.

Therapeutic uses in TB:

1-In extensive organ tuberculosis, in miliary dissemination or meningitis, three or four drugs are often given and streptomycin (1g daily I.M.) is one of them.

2-The use of streptomycin in pulmonary T.B. has been sharply reduced because other effective drugs have become available.

"Second-Line" drugs

These drugs are considered only in:

1-In case of resistance to first-line agents

2-In case of failure of clinical response to conventional therapy

3-In case of serious treatment-limiting adverse drug reactions

4-When expert guidance is available to deal with the toxic effects.

They have lesser efficacy and greater toxicity.

Quinolones

The fluoroquinolones are highly active against *M. tuberculosis* and are important drugs for multidrug resistant tuberculosis. Agents such as gatifloxacin and moxifloxacin are most active and least likely to select for quinolone resistance. Mycobacterial resistance to one fluoroquinolone imparts cross-resistance for the entire class.

Ethionamide:

Mechanism of action:

Chemically related to isoniazid and also blocks the synthesis of mycolic acids.

Side effects:

1- GIT irritation 2-CNS manifestations

3-hepatotoxicity

Capreomycin:

Mechanism of action:

Peptide protein synthesis inhibitor antibiotic.

Side effects:

1-Ototoxicity 2-nephrotoxicity

Cycloserine:

Mechanism of action:

An inhibitor of cell wall synthesis.

Side effects:

CNS toxicity.

Para-aminosalicylic acid, PAS:

Mechanism of action:

Folate synthesis antagonist that is active almost exclusively against *M tuberculosis.*

Side effects:

GIT irritation, hypersensitivity reactions.

THERAPEUTIC PROTOCOL of T.B.

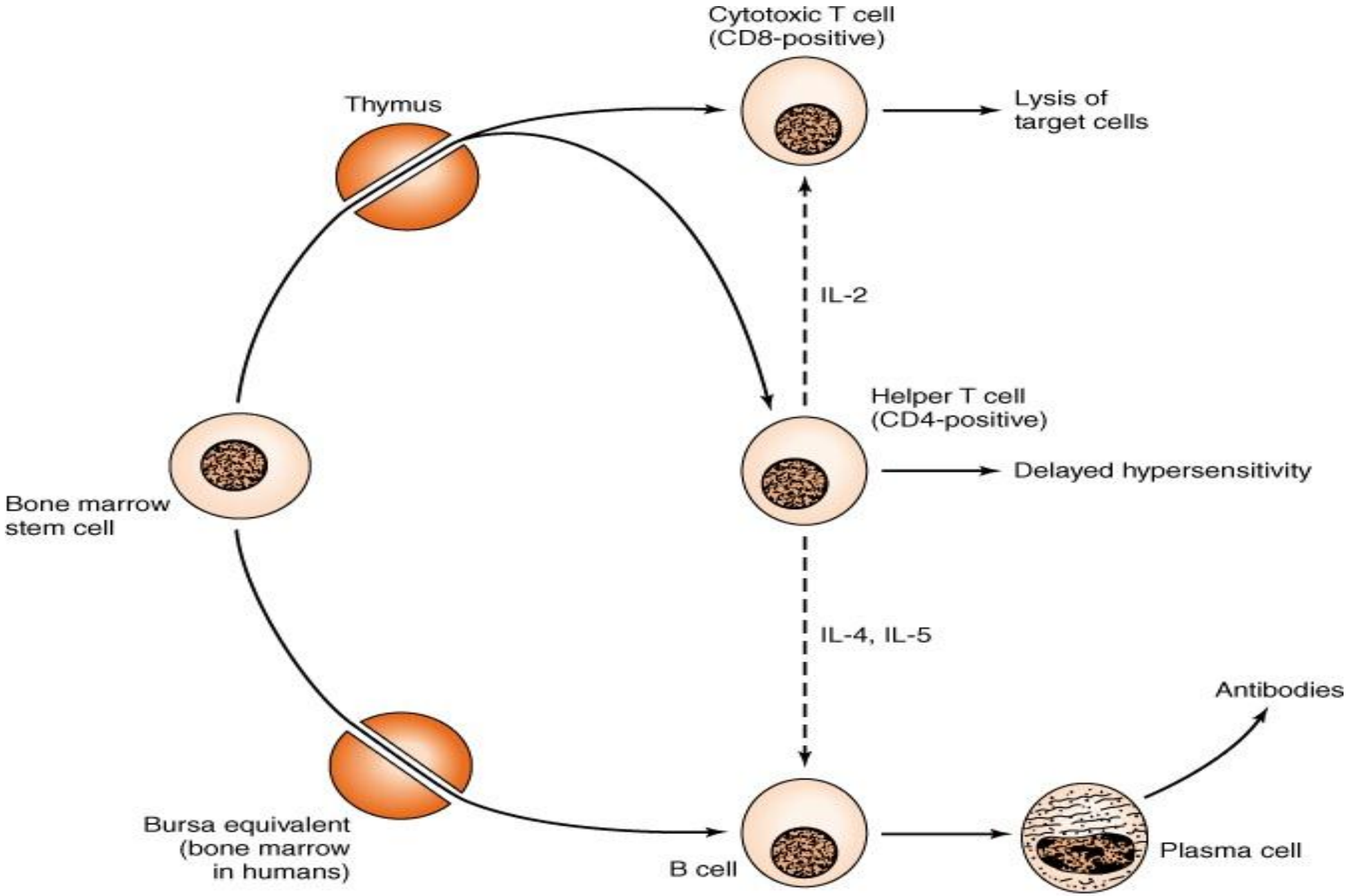
l-In uncomplicated drug-sensitive pulmonary T.B:

Short course therapy for 6 months can be satisfactory. For the first 2 months, isoniazid, rifampin, and pyrazinamide are given, followed by isoniazid and rifampin for the remaining 4 months.

Administration of isoniazid in combination with rifampin for 9 months is also effective.

2-**In extensive pulmonaty T.B**., those with **extrapulmonary disease**, **miliary T.B**., **meningitis** or **drug resistance** another drug is added to the above regimen which is usually ethambutol or streptomycin.

IMMUNOSUPPRESSIVE AGENTS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target cells
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Helper T cell
(CD4-positive)
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Delayed hypersensitivity
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Antibodies
Bursa equivalent
(bone marrow
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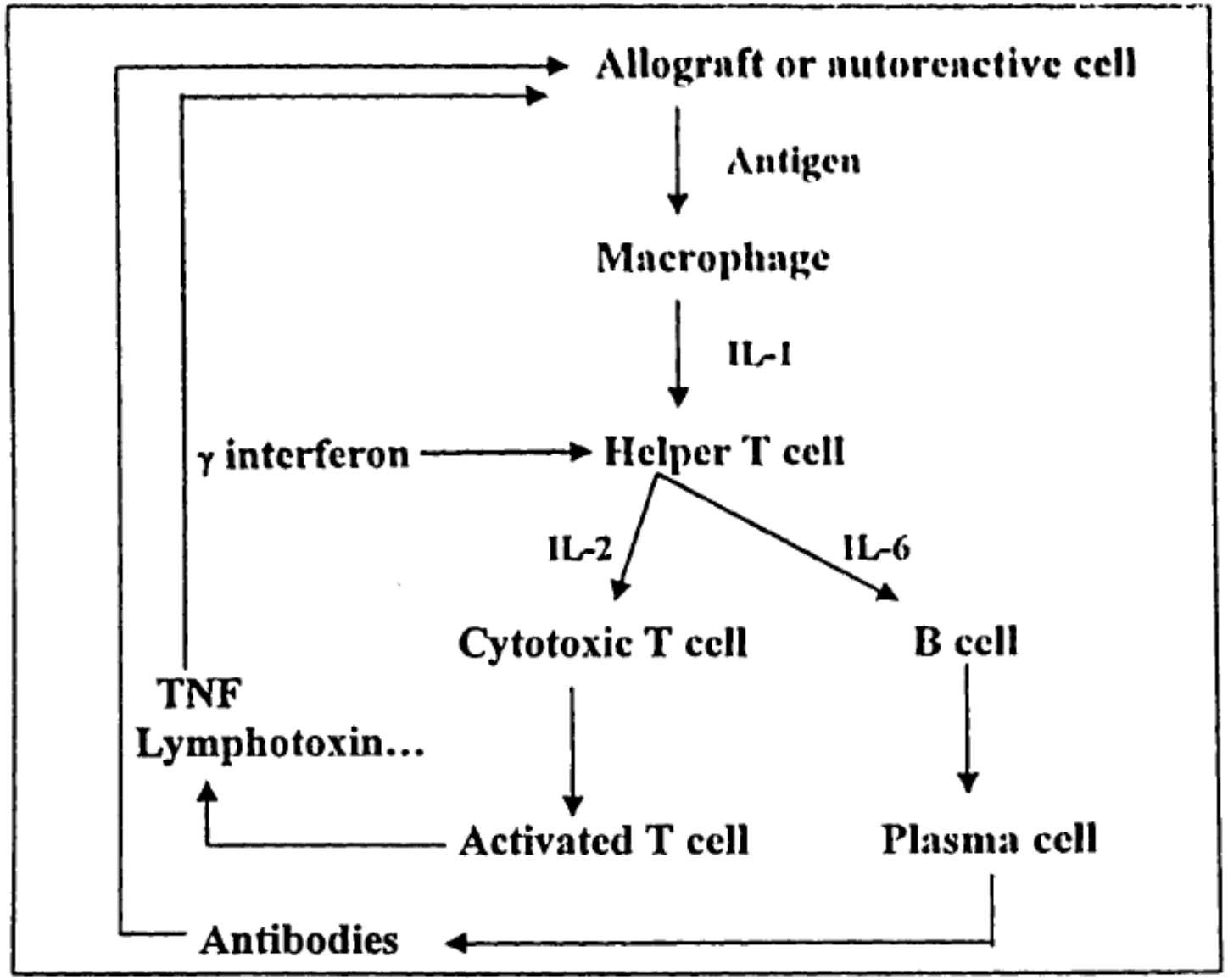
B cell
Plasma cell


Allograft or autoreactive cell
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IL-1
γ interferon
Helper T cell
IL-2
IL-6
Cytotoxic T cell
B cell
TNF
Lymphotoxin...
Activated T cell
Plasma cell
Antibodies

Clinical indications of immunosuppressive agents:

l-To prevent rejection of organ transplants in allograft transplantation.

2-To manage a wide variety of autoimmune disorders. Autoimmune diseases arise when the immune system is sensitized by "foreign antigens".

3-To prevent Rh hemolytic disease of the newborn (Erythroblastosis fetalis).

Hazards of immunosuppressive agents:

Nonspecific suppression of the immune responses produces:

l-An increased risk of infection by bacterial, viral and fungal organisms.

2-An increased incidence (3-100 fold) of malignant neoplasms in patients after allograft transplantation. This generally occurs after 4-7 years of therapy and cancers most likely to occur are those thought to have viral origin (lymphoma, leukemia, skin).

SPECIFIC IMMUNOSUPPRESSIVE AGENTS

Four classes of immunosuppressive drugs are currently used:

(1) Corticosteroids.

(2) Calcineurin inhibitors.

(3) Antimetabolites and antiproliferative drugs.

(4) Antibodies.

I-Corticosteroids

1-Block the processing of antigen by phagocytic cells (macrophages, monocytes) and its subsequent presentation to T cells.

2-Block the activation of T cells by interleukin-l derived from macrophages.

3-Inhibit the actions of cytotoxic T cells.

Therapeutic uses:

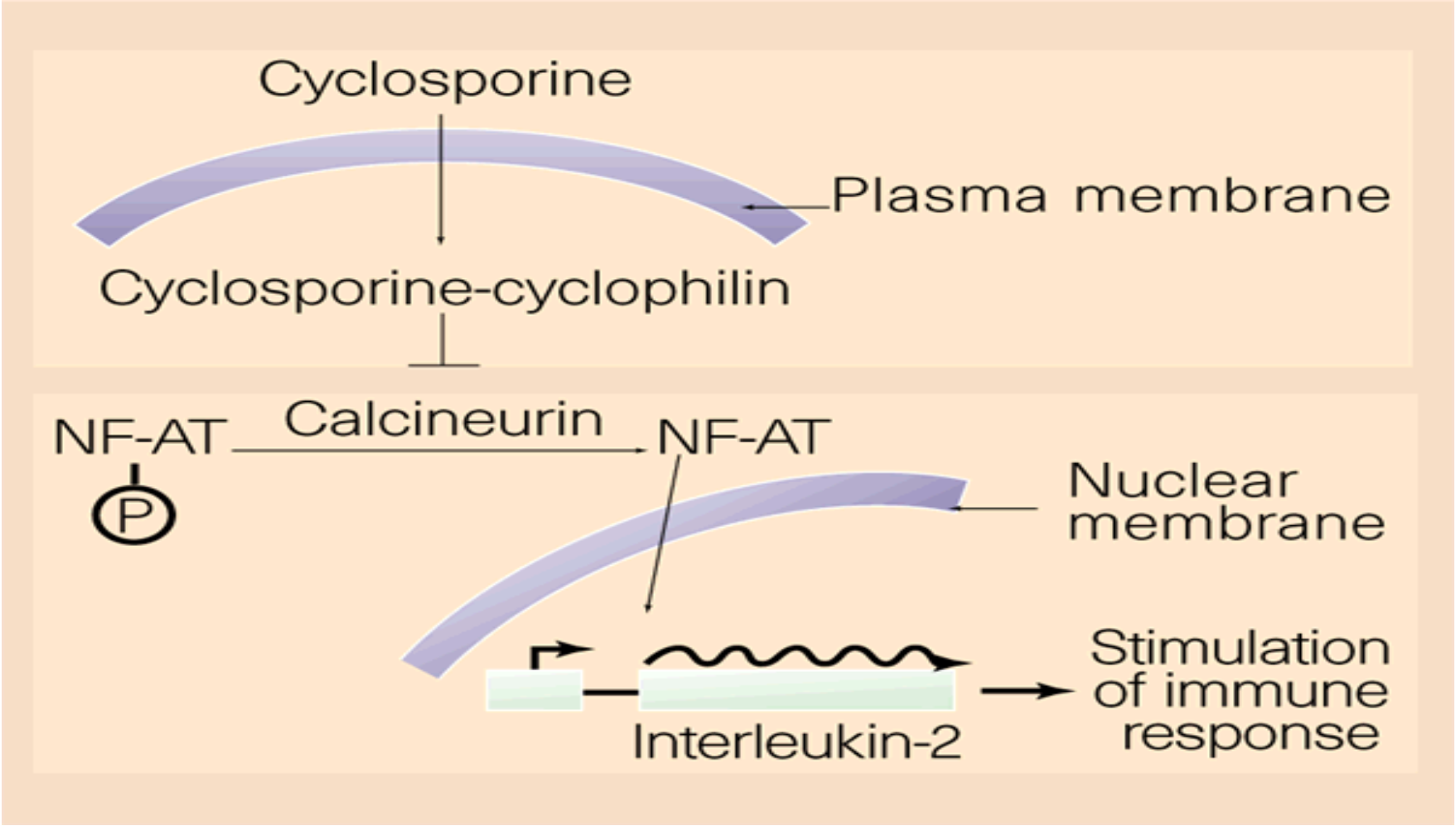
1-Glucocorticoids are useful in autoimmune diseases as idiopathic thrombocytopenic purpura and rheumatoid arthritis due to both immunosuppressive and anti-inflammatory effects.

2-In organ transplant recipients particularly during rejection crisis.

3-Modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for other agents (eg, blood products, chemotherapy) that might cause undesirable immune responses.

II-CALCINEURIN INHIBITORS

A-CYCLOSPORINE (SANDIMMUNE):



Pharmacokinetics:

Given as intravenous infusion or orally (slowly and incompletely absorbed (bioavailability 20–50%). The absorbed drug is primarily metabolized by the P450 3A enzyme system in the liver with multiple drug interactions that contributes to significant interpatient variability in bioavailability, such that cyclosporine requires individual patient dosage adjustments.

Side effects:

l-Nephrotoxicity

2-Hypertension, hyperglycemia, neurological toxicity (altered mental status and seizures), hepatotoxicity, hyperuricemia may lead to worsening of gout, hirsutism and gingival hyperplasia may occur.

3-Cyclosporine causes very little bone marrow toxicity. While an increased incidence of lymphoma and other cancers (Kaposi's sarcoma, skin cancer) have been observed in transplant recipients receiving cyclosporine.

Therapeutic uses:

1-Cyclosporine is used primarily in combination with other immunosuppressive agents, particularly glucocorticoids, to prevent rejection of renal, hepatic and cardiac transplants.

2-In a variety of autoimmune diseases as in rheumatoid arthritis and psoriasis, cyclosporine may be useful but relapses occur in a significant number of patients when therapy is terminated.

B-TACROLIMUS:

Mechanism of action:

It binds to an intracellular protein, FK-binding protein-l2 (FKBP-12), that leads to inhibition of the phosphatase, calcineurin i.e. it is calcineurin inhibitor. (10-100 fold more potent).

Therapeutic uses:

1-When cyclosporine has proved ineffective or too toxic.

2-It is now considered a standard prophylactic agent (usually in combination with methotrexate or mycophenolate mofetil) for graft-versus-host disease.

III-ANTIMETABOLITES AND ANTIPROLIFERATIVE DRUGS

These drugs have their effects on actively dividing cells and at low doses appear to have a relatively selective action on lymphocytes.

A-Sirolimus:

Mechanism of Action:

Sirolimus inhibits T-lymphocyte activation and proliferation downstream of the IL-2 and other T-cell growth factor receptors. It binds FKBP-12, this complex does not affect calcineurin activity but rather inhibits a protein kinase that is a key enzyme in cell-cycle progression, called (mTOR).

Side effects:

A common side effect of sirolimus is hyperlipidemia.

Therapeutic uses:

1-Indicated for prophylaxis of organ transplant rejection in combination with a calcineurin inhibitor and glucocorticoids.

2-In patients experiencing or at high risk for calcineurin inhibitor–associated nephrotoxicity, it has been used with glucocorticoids and mycophenolate mofetil to avoid permanent renal damage.

B-AZATHIOPRINE (IMURAN):

Mechanism of action:

Azathioprine is a prodrug for the purine antagonist 6-mercaptopurine. It thus exerts its effects by interfering with the synthesis of DNA and RNA. It kills rapidly dividing cells and so inhibits proliferation of lymphocytes as well as macrophages.

Pharmacokinetics:

The dose of azathioprine reduced by 25-33% in patients who are receiving the xanthine oxidase inhibitor, allopurinol.

Side effects:

The major toxic effect of azathioprine and mercaptopurine is bone marrow suppression (commonly leukopenia).

Therapeutic uses:

1-Azathioprine is used to suppress organ transplantation rejection.

2-Treat severe refractory rheumatoid arthritis.

C-MYCOPHENOLATE MOFETIL:

Mechanism of action:

Mycophenolate mofetil is a prodrug that is rapidly hydrolyzed to the active drug, mycophenolic acid, which is a selective inhibitor of inosine monophosphate dehydrogenase, an enzyme critical for de novo synthesis of purines. It is, therefore, more effective in inhibiting T and B cells which depend on this pathway for cell proliferation.

Side effects:

The principal toxicities of mycophenolate mofetil are leukopenia, diarrhea, and vomiting.

Therapeutic uses:

The drug is approved for oral use in the prophylaxis and treatment of organ rejection following renal and cardiac transplantation. It is usually given in combination with glucocorticoids and a calcineurin inhibitor.

Other Cytotoxic Drugs

Most of the cytotoxic drugs used in cancer chemotherapy are immunosuppressive due to their actions on lymphocytes and other cells of the immune system.

- **Methotrexate** has been used to induce remission in refractory rheumatoid arthritis and in treatment of severe disabling psoriasis.
- **Cyclophosphamide** is a very potent immunosuppressive drug and is used to prevent organ transplant rejection. It is also used in rheumatoid arthritis, systemic lupus erythematosus and nephrotic syndrome in children

ANTIBODIES

l-Antithymocyte globulin:

It is used primarily to treat and prevent acute renal transplant rejection in combination with other immunosuppressive agents

2-Monoclonal antibodies:

i-Anti-CD3 monoclonal antibodies, as Muromonab CD3 have been used in the treatment of acute organ transplant rejection.

ii-Anti-TNF α monoclonal antibodies, as lnfliximab, are used in patients with rheumatoid and patients with Crohn's disease.

iii-Anti-IL-2-receptor monoclonal antibodies, as Daclizumab, are used to prevent organ transplant rejection as a part of combination therapy with other immunosuppressive agents.

3-Rh(D) immune globulin:

It is used specifically in Rh-negative mothers sensitized to Rh(D) antigen of the red cell. As this sensitization occurs at the time of birth or abortion, the Rh(D) antibody is administered IM to the mother within 72 hours after birth of an Rh-positive baby.