ANTI TUBERCULAR AGENTS

* Tuberculosis - most important communicable disease in the world. Mycobacteria are intrinsically resistant to most antibiotics.

* Grow more slowly then other bacteria - antibiotics active against rapidly growing cell.

* Lipid - rich mycobacterium cell wall is impermeable to many agents.

* It grows inside macrophage - poorly penetrate by drugs.

* Excellent ability to develop resistance - Multiple drug resistant (MDR).

* Combination of two or more drugs

i) To overcome those obstacles.

ii) To prevent emergence to resistance during the course of therapy.

* The response of mycobacterial infections to chemotherapy is slow - treatment must be administred for month to years, depending on which drugs are used.

CLASSIFICATION:

According to their clinical utility the anti TB drugs can be divided into

* First line drugs.
* second line drugs.

First line drug:

Those drugs have high antitubercular efficacy as well as low toxicity are used routinely.

Ex:

* Isoniazid
* Rifampin
* pyrazinamide
* Ethambutol
* Streptomycin.

second line drugs:

These drugs have either low antitubercular efficacy or higher toxicity or both; and are used as reserve drugs.

* Para amino salicylic acid
* cycloserine.
* Kanamycin. } Injectable drugs
* Amikacin
* ciprofloxacin, } Flouroquinolones
* ofloxacin.
* clarithromycin.
* Azithromycin

FIRST LINE DRUGS:

1. ISONIAZID:

* Isonicotinic acid hydrazide.
* most active drug for the treatment of TB.
* Freely soluble in water.
* Bactericydal for actively growing tubercle bacilli.
* less effective against atypical mycobacterial species.
* penetrates into macrophages and is active against both extracellular and intracellular organisms.

Mechanism of action :

* Inhibits synthesis of mycolic acids - essential compounds of mycobacterial cell walls.
* Highly selective for mycobacterium.
* Resistance
  * Its prodrug - activated enzyme catalase - peroxidase
  * Mutation causes inhibition of this enzyme.

Pharmacokinetics :

* Readily absorbed from the gastrointestinal tract diffuse readily into all body fluids and tissues.
* Acetylation by liver N- acetyl transferase, is genitically determined.
* Half life 1 hour - 3 hours.
* Excreted, mainly in the urine - need not be adjusted in renal failure.
* Contraindicated - severe existing preexisting hepatic insufficiently.

Uses :

* It to be used in the treatment of neuropathy and latent, tuberclosis.

pose :

* Adult dose : 300 mg oral dose o.d.
* Latent TB for 300 mg 1day or 900 mg twic weekly for 9 months.

ADR :

CNS toxicity, nausea, vomiting, jaundice, promote excretion of pyridoxine.

ETHAMBUTOL :

* Synthetic, water-soluble, heat stable compound, dispensed as the dihydrochloride salt.
* Bacteriostatic
* Additionally it slows the rate of spectrum conversion.
* Development of resistance.
* Given the combination with RHZ

Mechanism of action:

* Inhibits mycobacterial arabinosyl transferase an essential component of the mycobacterial cell wall.
* Resistance - due to alteration in target gene
* NO cross resistance with other drug.
* Resistance to ethambutol emerges rapidly when the drug is used alone - combination with other anti TB drugs.

Pharmacokinetics:

* Well absorbed from the gut
* 20% of the drug is excreted in faces and 50% in urine in unchanged form.
* Crosses the BBB only when the meaning are inflammed.
* Temporarily stored in RBC.
* $T_{1/2}$ - 4 hrs. Caution taken for renal failure patient.

Use:

Ethambutol HCl - 15-25 mg/kg/day O.D

High dose recommended for treatment of TB meningitis.

RIFAMPIN :

* Semisynthetic derivative of rifamycin - produced by Streptomyces mediterranei. Active in vitro against gram positive and gram negative cocci, some enteric bacteria, mycobacteria and chlamydiae.

* Resistant mutants - approximately 1 in 10^6 organisms. Rapidly selected out if rifampin is used in combination.

* No crosses - resistance to other classes of antimicrobial drugs.

Mechanism of action :

* Binds to the bacterial DNA dependent RNA polymerase inhibits RNA synthesis. Bactericidal for mycobacteria.

* Readily penentrates most tissues and penetrates into phagocyte cells. can kill organisms that are body poorly accessible to many other drugs.

* Intracellular organisms.

* Sequestered in abscesses and lung cavities.

* Mutation results in reduced binding of rifampin to RNA polymerase.

pharmacokinetics :

* Well absorbed after oral administration and excreted mainly through the liver into bile.

* Enterohepatic recirculation - Bulk excreted as a deacylated metabolite in faces and a small amount excreted in the urine.

* Dosage adjustment for renal or hepatic insufficiency is not necessary. Distributed widely in body fluids and tissues.

Relatively highly protein bound.

Uses:

* Rifambin for 6 months in combination with INH to patient.
* Some atypical mycobacterial infections and in leprosy.
* It used to eliminate meningococcal carriage.
* Serious staphylococcal infections - osteomylitis and prosthetic value endocarditis.

STREPTOMYCIN

part of aminoglycoside antibiotic. First clinically useful anti TB drug, but less effective then INH or rifambin. Acts only on extracellular bacilli - poor penetration into cells. Doesn't cross the BBB, But penetrates tubercular cavities

Mechanism of action:

Irreversable inhibitors of protein synthesis. Bactericidal. inside the cell, aminoglycosides bind to specific 30S - subunit ribosomal proteins and inhibits protein synthesis.

pharmacokinetics:

Absorbed very poorly from the intact GIT. Intramuscular injection or usually administred intravenously as a 30-60 minute infusion. Normal T1/2 2-3 hours renal failure patient it reduced to 24-48 hours.

Uses:

* Treatment of infections resistant to other drugs.

Adult dose: 20-40 mg/kg/day for several weeks.

* Non-tubercular species of mycobacteria other then Mycobacterium avium complex (MAC) and mycobacterium Kansasii are resistance.

SECOND LINE DRUGS:

This drugs are considered only when

* Resistance to first-line agent.
* Failure of clinical response to conventional theraphy.
* serious treatment-limiting ADR.

PARA AMINOSALICYLIC ACID (PAS)

* Structural analogue of PABA. Highly specific for M. tuberclosis - not effective against other Mycobacterium species. combined with INH an alternative substrate & block hepatic acetylation of INH increasing free INH levels
* Limited to the treatment of MDR tuberclosis.

Discourage its use: primary resistant, poor compliance due to GI intolerance, and lupus like reactions.

ETHIONAMIDE

chemically related to INH. Block the synthesis of mycolic acids. poorly water soluble and available only in oral form. intense gastric irritation and neurologic symptoms as well as hepatotoxic.

CAPREOMYCIN

peptide protein synthesis inhibitor antibiotic obtained from streptomycin capreolus. Daily injection of 15 mg/kg/d -IM Treatment of Drug-resistance TB. Strains of M tuberclosis that are resistance to streptomycin and amikacin.

Nephrotoxic and ototoxic - Tinnitus, deafness and vestibular distribution occurs. local pain and sterile abscesses may occur.

CYCLOSERINE

Inhibitor of cell wall synthesis. 0.5-1 g/d in two divided oral doses. Clearly renally - Dose is reduced to half in case of renal dysfunction. peripheral neuropathy and CNS dysfunction, including depression and psychotic reactions. pyridoxine 150mg/d given in addition to it.

KANAMYCIN & AMIKACIN

Treatment of TB suspected or known to be caused by streptomycin - resistant or multidrug - resistant strains. Kanamycin is more toxic comparatively - absolute. prevalance of amikacin - resistant strains is low (<5%.) Also active against atypical mycobacteria. No cross - resistance between streptomycin and amikacin but it occurs with Kanamycin. used in combination with with atleast one and preferly two or three other drugs.

FLOUROQUINOLONES

In addition to their activity against many gram positive and gram negative bacteria inhibit strains of M. tuberculosis. Also active against atypical mycobacteria.

Standard dosage.

* ciprofloxacin : 750 mg orally twice a day.
* Levofloxacin : 500 - 750 mg once a day.
* Moxifloxacin : 400mg once a day.

ANTI LEPROTIC AGENTS

Chronic granulomatous infections caused by obligate intracellular acid fast bacilli Mycobacterium leprae. Survive within macrophages and schwann cells. prevalent in lower socio economic strata. Also known as Hansen's disease.

CLASSIFICATION OF DRUGS:

* Sulfone : Dapsone.
* Phenazine Derivative : Clofazimine.
* Antitubercular drugs : Rifampicin
  Ethionamide
  prothionamide.
* Fluoroquinolones : Ofloxacin
  Pefloxacin.
* Other antibiotics : Minocycin
  Clarithromycin.

DAPSONE

Oldest, cheapest and most effective. Diamino diphenyl sulfone (DDS). Resistance may develop if used as monotherapy.

Activity :

Resistance primary and secondary (mutation of folate synthase - lower affinity). However 100 mg/day - high MIC - 500 times and continued to be effective to low and moderately resistant Bacilli (low % of resistant patients). persistors present.

MOA of Dapsone:

Leprostatic - event at low concentration. chemically related to sulfonamides. Inhibition of incorporation of PABA into folic acid (Folic acid synthesis). Specificity to M. leprae - affinity for folate synthesis. Dose for acute infection - too toxic.

pharmacokinetics:

Completly and slowly absorption, peak concentration in 5 hours. Half life 24-36 hours. wide distribution, concentrated in skin, muscle, liver and kidney.

Acetylated and glucoronide and sulfate conjucate - Enterohepatic circulation.

Adverse reaction:

* GIT side effects - Anorexia, Nausea, vomiting.
* Hemolytic anemia - more in G6PD def individuals. Methaemglobinaemia. Sulfone syndrome - Fever, malaise, Exfoliative dermatitis, jaundise, Anemia, Lymphadenopathy. Lepra reaction.
* sulfones are powerful oxidants.

CLOFAZIMINE

* Dye with leprostatic and anti inflammatory property.
* Disrupts mitochondrial electron transport chain.
* M. leprae resistant to Dapsone respond to clofazimine.

CLOFAZIMINE

Dye with leprostatic and anti-inflammatory property. Disrupts mitochondrial electron transport chain. M. leprae to dapsone respond to clofazimine.

MOA:

Interfers with template functions of DNA in M. Leprae

Activity:

used alone resistance (1-3) years but dapsone resistance cases respond in 2 months. Half life 70 days.

Kinetics:

Orally effective

↓

Accumulates in fat in crystallin form.

↓

Entry at CSF poor.

orally active, Accumilates in macrophages and deposited in many tissues. used in MDT of leprosy, leprea reaction, MAC infection. should be avoid in pregnancy and liver, kidney disease.

ADverse reaction:

* Reddish black Discolouration of skin, hair and body secretions.
* Dryness of skin and itching, Acneform, eruptions, phototoxicity.
* conjuctival pigmentation.
* Nausea, anorexial, abdominal pain, weight loss

RIFAMPICIN

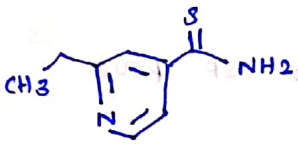
* Antitubercular, potent cidal drug for M. leprea. Rapidly renders leprosy patient non contagious; 99.99%. Bacilli killed within 3-7 days, Lesions start regressing in 2months.

* used in multidrug therapy. shortens duration of treatment. 600mg monthly dose given.

MOA:

* Inhibits bacterial DNA dependant RNA synthesis by inhibiting bacterial DNA dependent RNA polymerase.

ETHIONAMIDE



MOA:

* Inhibit synthesis of mycolic acids. . essential compound of mycobacterial cell walls. Highly selective for mycobacterium.

* Expensive and more toxic then dapsone but has faster bactereocidal action against M. leprae then full @damage dosage dapsone.

* It is administrated orally, daily.

* PROTHIONAMIDE has similar properties.

OFLOXACIN

FQ are highly active against M. leprae. Hasten Bacteriological and clinical response.

MOA:

Inhibit DNA gyrase, a type II topoisomerase IV, seperate replicated DNA, thereby inhibit bacterial cell division.

* used in duration of treatment. Reduces.
* Used in alternate regimens instead of rifambicin.
* Reduced chances of development of resistance.

MINOCYCLINE

High lipophilicity help to penetrate M. leprae. Efficacy in - between clarithromycin and rifambicin. Rapid relief from lepromatous symptoms.. vertigo on long time term use.

CLARITHROMYCIN

* only macrolide effective in leprosy.
* Rapid clinical improvement.
* Synergistic action with minocycline.
* Used in alternative regimens.

Reference:

Essential of medicinal pharmacology - K.D. Tripathi 6th edition

IMMUNOPHARMACOLOGY :

Definition :

* Immunity is a general ability of the host to resist damage from foreign substances such as microorganisms and harmful chemicals such as toxins released by microorganism

* The immune response that results is a specific and complex series of defensive reactions widely distributed throughout the human or animal body.

* The ability to ward off disease through our defense is called resistance

Components of the immune system :

2 major components of the immune system.

⇒ Innate :

physical - Skin, mucus membrane.

Biochemical - Complement lysozyme.

Cellular - macrophages, neutrophils

⇒ Adaptive :

Antibodies - Humoral immunity

T-lymphocyte - Cell mediated Immunity

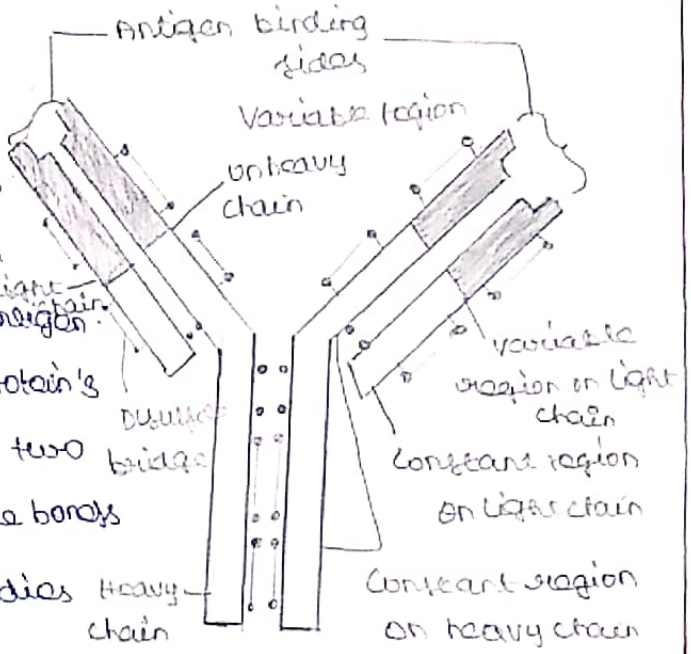
Antigen :

* A substance that when introduced that body, stimulates production of an antibody

* An antigen is an organic compound - Protein, Poly saccharide or glycolipid. It has 2 parts

- Hapten
- carrier.

- Antigens include
  - * Toxins
  - * Bacteria
  - * Foreign blood cells
  - * Microorganisms
  - * Allergens
  - * Viruses etc



Anti bodies:

⇒ They are gamma globulins or immunoglobulin's produced in the serum on exposure to antigen.

⇒ Chemically they are glycoprotein's containing two heavy chains and two light chains together by disulfide bonds

⇒ There are 5 types of Antibodies IgG. IgM, IgA, IgE, IgD.

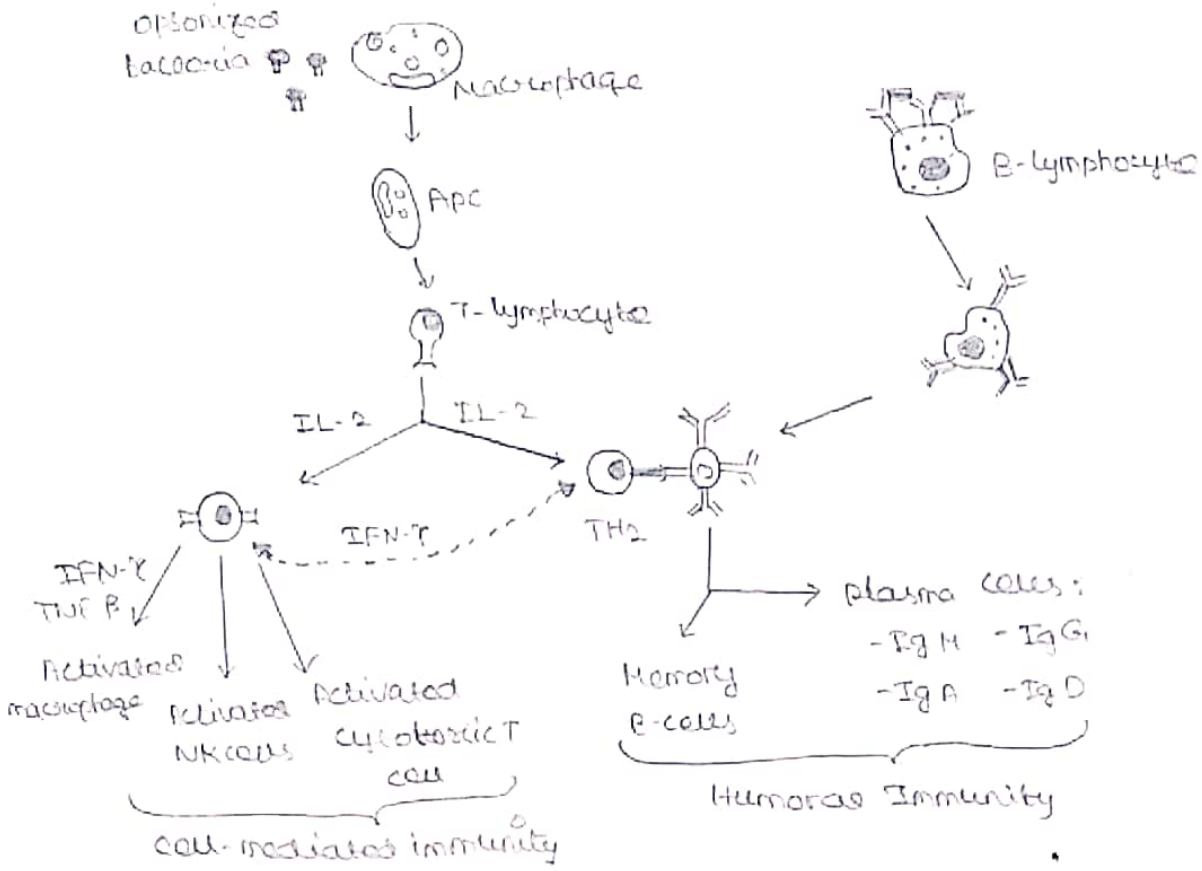
Humoral Immune response - Antibodies:

- The Antigen is processed by macrophages or APC combined with class 2 MHC and presented to the CD4 helper cells activated by interleukin 1 proliferate and secrete cytokines and in turn promote proliferation and differentiation of antigen activated B-cells into antibody secreted plasma cells. Antibody finally binds and inactivates the antigen.

Cell mediated immune Response - Tymphocytes:

- Foreign antigen is processed and presented to CD4 helper T-cells which elaborate IL-2 and other cytokines that in turn stimulate proliferation and maturation of Precursor cytotoxic lymphocytes (CTL).

Immunopharmacology :



Immunity :

Immunity is a general ability of the host to resist damage from foreign substance. The ability to ward off disease through our defenses is called resistance.

Classification of Immunity :

i) Innate Immunity

ii) Acquired Immunity

i) Innate Immunity :

* Native immunity

* It is the resistance which an individual process by virtue of his/her genetic & body constitution. Thus it is inborn.

* It act against many microorganisms (in absence of specificity), hence also called as non-specific immunity.

Types of Innate immunity:

i) species immunity - Resistance to infection varies over species eg: Human are susceptible to measles infection whereas dogs are resistant

ii) Racial immunity - within a species. different races exhibit differences in their resistance due to genetic factors.

iii) Individual Immunity - Different individuals in a race exhibit differences in innate immunity.

ii) Acquired immunity:

* The resistance that an individual acquires his/her life time is known as acquired immunity.

* Also called as specific immunity

Types of Acquired immunity:

i) Actively acquired immunity - Long lasting. Induces immunological memory.

ii) Passively acquired immunity - There are certain Individuals whose immune system does not respond and produce antibodies to foreign antigens.

* So such individuals are immunized.

Other types of immunity:

* Local immunity
* Head immunity
* Infection immunity
* Humoral immunity
* Cell mediated immunity.

THERAPIES IN IMMUNOPHARMACOLOGY:

- Immunomodulators
- Immunosuppressants
- Immunostimulant

IMMUNOMODULATORS:

Immunomodulators are the drugs which stimulate the immune system is called "immunostimulants" (or) suppress the immune system called "immunosuppressants"

immunosuppressant Drugs:

These are drugs which inhibit cellular / humoral or both immune response major use in organ transplantation and autoimmune diseases.

Classification:

1. Calcineurin inhibitors (specific T-cell inhibitors)

   Cyclosporine (ciclosporin), Tacrolimus

2. Antiproliferative Drugs (Cytotoxic Drugs)

   Azathioprine, cyclophosphamide, Methotrexate

3. Glucocorticoids:

   Prednisolone & Others

4. Antibodies:

   Muromonab CD3, Antithymocyte globulin (ATG).

Calcineurin inhibitors (specific T-cell inhibitors):

1. Cyclosporine:

* Cyclic polypeptide with 11 amino acids. Obtained from fungus
* Introduced in 1977 as highly selective immuno suppressant
* Successful drugs in organ transplantation
* It inhibits T-lymphocyte proliferation IL-2 and other cytokine production

MOA of cyclosporine

It inhibit antigen stimulated active and proliferation of a helper T-cells as well as expression of IL-2 other cytokines by them.

Adverse effect:

* sustained rise in BP
* precipitation of diabetes
* Anorexia (lack of appetite for food)
* opportunistic infections
* Hirsutism (abnormal growth of hairs)

Pharmacokinetics:

* oral bioavailability is low.
* Metabolized in liver by CYP3A4.
* Excreted in bile.
* Plasma t1/2 is 4-6 hrs & 12-18 hr

Dose: 10-15 mg/kg/day.

Immunostimulant or immunoEnhancers:

* Immunostimulant are biologic therapeutic agents designed to boost the body's natural defenses to fight the cancer and other disease

* It uses materials either made by the body or in a laboratory to improve, target or restore immune system function

* They works on cellular as well as humoral immune system or both.

Classification:

i) specific immunity

ii) non-specific immunity

immunostimulant Drugs:

1. Levamisole
2. Thalidomide
3. Isoprinosine
4. Immunisation.
   vaccines
   - immunoglobulins (Rho Ig)
   - Bacillus Calmette-Guerin (BCG)
   - Recombinant cytokines

Levamisole:

* Levamisole was synthesized originally as an anthelmintic / antiparasite agent.

* But it restores the depressed immune function of B lymphocytes, T-lymphocytes, monocytes & macrocytes.

* Potentiate action of fluorouracil in adjuvant therapy of Dukes class C colorectal CA.

Other uses:

* hodgkin's lymphoma
* RA

Adverse effect:

- flu-like symptoms, allergic manifestation
- nausea & muscle pain

Immunisation:

Vaccines & immunoglobulin (Rho Ig)

Bacillus calmette guerin (BCG):

* live culture of Bacillus calmette guerin strain of Mycobacterium bovis
* Induces granulomatous reaction at the site of administration

Therapeutic uses:

- Treatment and prophylaxis of carcinoma of the urinary bladder.
- Prophylaxis of primary & recurrent stage of papillary tumors.

Adverse effect: Hypersensitivity, shock, chills fever, malaise.

REFERENCE:

⇒ Rang and Dale's pharmacology 6th edition.

⇒ https://www.merriam-webster.com/medical/immunopharmacology.