CHEMOTHERAPY OF TUBERCULOSIS AND LEPROSY

AGBOOLA, SAMUEL SUNDAY
(B PHARM, M.SC, PHD)

Introduction

- Definition:
- Tuberculosis is a chronic granulomatous disease caused by Mycobacterium tuberculosis, which most commonly affects the lungs.
- M. tuberculosis organisms are also called tubercle bacilli
- The organism was discovered by Robert Koch in March 1882
- A major health problem in developing countries.
- It is currently estimated that 1/2 of the world's population is infected by M. tuberculosis.

Introduction

- AETIOLOGY
- Tuberculosis is a worldwide, chronic infectious disease caused by:
- *Mycobacterium tuberculosis hominis*
- Less commonly *Mycobacterium tuberculosis bovis* may cause human infection.
- Acquired most commonly by inhalation of infective droplets.

What about *Mycobacterium*?

- The causative organism belongs to the genus Mycobacterium, which are slender , aerobic rods that have a unique cell wall composed predominantly of mycolic acid
- This makes them acid fast.
- They are weakly gram positive.
- The reservoir for tuberculosis is humans with active tuberculosis.
- Infection with HIV makes people suceptible to rapidly progressive tuberculosis.

Dictators/Determinants of the course of the disease

- Infecting dose
- Virulence of the organism
- Degree of resistance of the host

Classification of Tuberculosis

- Broad Classification
  - Pulmonary TB
  - Extra-pulmonary TB
- Clinical Classification
  - Primary TB: exogenous first infection which is usually self-limiting
  - Progressive TB: inadequate acquired immunity (infants or elderly); progression of original infection; less than 10% of patients.
  - Post-primary TB (adult, reactivation, re-infection or secondary): endogenous reactivation

DRUGS FOR THE TREATMENT OF TB

- FIRST LINE DRUGS
  - Isoniazid
  - Rifampicin
  - Ethambutol
  - Pyrazinamide
  - Streptomycin (reserve)
- SECOND LINE DRUGS
  - Thiacetazone
  - Para-amino-salicylic acid
  - Ethionamide
  - Cycloserine
  - Ciprofloxacin
  - Ofloxacin
  - Levofloxacin
  - Clarithromycin
  - Azithromycin
  - Amikacin
  - Capreomycin

TREATMENT OF PULMONARY TB

- DOTS Strategy recommended by WHO is employed
- DOTS means Directly Observed Treatment- Short course
- Two phases of drug therapy are generally used:
- Initial phase: In this phase 4 drugs namely Rifampicin, isoniazid, Pyrazinamide and ethambutol are used
- All these drugs are used for 2 months.

TREATMENT OF PULMONARY TB

- Continuation Phase
  - Two drugs i.e. Rifampicin and isoniazid are used for a period of the next 4months.
  - The entire course of medication must be completed
  - The drugs must be swallowed in the presence of the care giver
  - This strategy is to ensure patient's compliance

IZONIAZID

- Description:
- The antibacterial activity of izoniazid is limited to mycobacteria.
- It halts the growth of resting organisms (i. e. is bacteriostatic) but can kill dividing bacteria (bactericidal).
- It is effective against intracellular organisms
- It combines with an enzyme that is uniquely found in isoniazid-sensitive strains of mycobacteria, disrupting cellular metabolism.
- Resistance to the drug, caused by reduced penetration into the bacterium, may be encountered.

ISONIAZID

- **Description:**
  Isoniazid is bacteriostatic for "resting" bacilli but bactericidal for dividing microorganisms.
- Isoniazid is a prodrug that is converted by mycobacterial catalase-peroxidase into an active metabolite.
- It inhibits biosynthesis of mycolic acids
- The target of the isoniazid derivative is enoyl-ACP reductase of fatty acid synthase II, which converts unsaturated to saturated fatty acids in mycolic acid biosynthesis.

Unwanted effects of Isoniazid

- Unwanted effects depend on the dosage and occur in about 5% of individuals, the commonest being allergic skin eruptions
- Isonaizid also enhances the hepatotoxcity of acetaminophen.
- Other adverse reactions include fever, hepatotoxicity, haematological changes, arthritic symptoms and vasculitis.
- Adverse CNS effects or PNS are largely consequences of a deficiency of pyridoxine and are common in malnourished patients.
- Pyridoxal-hydrazone formation occurs mainly in slow acetylators. Isoniazid may cause haemolytic anaemia in individuals with glucose 6-phosphate dehydrogenase deficiency,

RIFAMPICIN

- Description
- Rifampicin acts by binding to, and inhibiting, DNA-dependent RNA polymerase in prokaryotic but not in eukaryotic cells.
- It is one of the most active anti-tuberculosis agents known
- It is active against most Gram-positive bacteria as well as many Gram-negative species.
- It enters phagocytic cells and can therefore kill intracellular micro-organisms including the tubercle bacillus.
- Resistance can develop rapidly in a one-step process
- Resistance is thought to be caused by chemical modification of microbial DNA-dependent RNA polymerase, resulting from a chromosomal mutation

RIFAMPICIN

- Pharmacokinetics
- Rifampicin is given orally and is widely distributed in the tissues and body fluids
- It gives an orange tinge to saliva, sputum, tears and sweat.
- In the CSF, it reaches 10-40% of its serum concentration.
- It is excreted partly in the urine and partly in the bile, some of it undergoing enterohepatic cycling.
- The metabolite retains antibacterial activity but is less well absorbed from the gastrointestinal tract.
- The half-life is 1-5 hours, becoming shorter during treatment because of induction of hepatic microsomal enzymes

RIFAMPICIN:UNWANTED EFFECTS

- Unwanted effects are relatively infrequent
- The commonest are skin eruptions, fever and gastrointestinal disturbances.
- Liver damage with jaundice has proved fatal in a very small proportion of patients
- Liver function should be assessed before treatment is started.
- Rifampicin causes induction of hepatic metabolising enzymes, resulting in an increase in the degradation of **warfarin, glucocorticoids**, narcotic analgesics, oral antidiabetic drugs, **dapsone** and **oestrogens**
- This effect could lead to failure of oral contraceptives.

ETHAMBUTOL

- *Description:*
- Nearly all strains of M. tuberculosis and M. kansasii and many strains of M. avium complex are sensitive to ethambutol.
- Sensitivities of other mycobacteria are variable.
- Ethambutol has no effect on other bacteria.
- Growth inhibition by ethambutol requires 24 hours
- It is mediated by inhibition of arabinosyl transferases involved in cell wall biosynthesis.
- Resistance to ethambutol develops very slowly in vitro.
- Ethambutol is given concurrently with isoniazid and largely has replaced para-amino-salicylic acid.
- Ethambutol is available for oral administration in tablets.

UNWANTED EFFECTS OF ETHAMBUTOL

- The most important side effect is optic neuritis, resulting in decreased visual acuity and red–green colour blindness.
- The incidence of this reaction is proportional to the dose of ethambutol and is <1% in patients receiving the recommended daily dose of 15 mg/kg.
- The intensity of the visual difficulty is related to the duration of therapy after visualimpairment first becomes apparent and may be unilateral or bilateral.
- Tests of visual acuity and red green discrimination prior to the start of therapy and periodically thereafter are recommended.
  Recovery usually occurs when ethambutol is withdrawn.

PYRAZINAMIDE

- Description:
- Pyrazinamide is inactive at neutral pH but tuberculostatic at acid pH.
- It is effective against the intracellular organisms in macrophages
- Resistance develops rather readily, but cross-resistance with INH does not occur.
- The drug is well absorbed after oral administration and widely distributed, penetrating well into the meninges.
- It is excreted through the kidney, mainly by glomerular filtration

PYRAZINAMIDE: UNWANTED EFFECTS

- Hepatic injury is the most serious side effect of pyrazinamide.
- Current regimens (15–30 mg/kg/day) are much safer than higher doses used previously.
- Prior to pyrazinamide administration, all patients should have liver function tests, which should be repeated at frequent intervals.
- If evidence of significant hepatic damage appears, therapy must be stopped.
- Pyrazinamide should not be given to individuals with any degree of hepatic dysfunction unless this is absolutely unavoidable.
- The drug inhibits urate excretion, rarely precipitating an acute flare of gout.
- Other adverse effects are arthralgias, nausea and vomiting, dysuria, malaise, and fever.

STREPTOMYCIN

- Description:
  - Streptomycin is bactericidal for the tubercle bacillus in vitro.
  - The vast majority of strains of M. tuberculosis are sensitive.
  - M. kansasii is frequently sensitive, but other mycobacteria are only occasionally susceptible.
  - Streptomycin in vivo does not eradicate the tubercle bacillus, probably because the drug does not readily enter living cells and thus cannot kill intracellular microbes

STREPTOMYCIN: UNWANTED EFFECTS

- Unwanted effects include:
- Auditory (Loss of hearing) or vestibular damage(dizziness, vertigo) or both.
- Streptomycin is the most vestibulo toxic aminoglycoside.
- Nephrotoxicity is also possible
- Other problems included rash and fever.

CYCLOSERINE

- Description:
  - Cycloserine is an inhibitor of cell wall synthesis
  - Concentrations of 15–20 mcg/mL inhibit many strains of *M tuberculosis*
  - The dosage of cycloserine in tuberculosis is 0.5–1 g/d in two divided doses
  - Cycloserine is cleared renally, and the dose should be reduced by half if creatinine clearance is less than 50 mL/min

CYCLOSERINE: UNWANTED EFFECTS

- Cycloserine has unwanted effects mainly on the central nervous system
- Other reported unwanted effects are:
- headache and irritability
- peripheral neuropathy
- Depression
- convulsions
- psychotic states
- Its use is limited to tuberculosis that is resistant to other drugs.

The Role played by each anti-TB drugs

- The role of individual drugs in first-line chemotherapy of TB is unique:
  - Isoniazid is responsible for the initial kill of about 95% organisms during the first two days of treatment.
  - Its bactericidal role is then replaced by rifampicin and pyrazinamide during the intensive phase.
  - In the continuation phase, rifampin is the most effective drug against dormant bacilli (persisters), as shown by the similarity of response by patients with initially isoniazid-resistant or sensitive strains.

ROLE OF EACH ANTI-TB DRUGS CONTD

- When either rifampin or isoniazid is not used, the duration of chemotherapy is 12 to 18 months.
- When both isoniazid and rifampin are used in treatment, the optimum duration of chemotherapy is 9 months.
- Addition of pyrazinamide, but not neither streptomycin nor ethambutol reduces the duration to six months.
- Prolongation of chemotherapy beyond these periods increases the risk of toxicity while providing no additional benefit.
- Second-line therapy duration ranges from 18 to 24 months.

ANTI-TB DRUGS AND THEIR DOSAGES

	Typical Adult Dosage[1]
First-line agents (in approximate order of preference)	
Isoniazid	300 mg/d
Rifampin	600 mg/d
Pyrazinamide	25 mg/kg/d
Ethambutol	15–25 mg/kg/d
Streptomycin	15 mg/kg/d

SECOND LINE ANTI-TB DRUGS/DOSAGES

Second-line agents	
Amikacin	15 mg/kg/d
Aminosalicylic acid	8–12 g/d
Capreomycin	15 mg/kg/d
Ciprofloxacin	1500 mg/d, divided
Clofazimine	200 mg/d

SECOND-LINE ANTI-TB DRUGS/DOSAGES

Cycloserine	500–1000 mg/d, divided
Ethionamide	500–750 mg/d
Levofloxacin	500 mg/d
Rifabutin	300 mg/d[b]
Rifapentine	600 mg once or twice weekly

[a]Assuming normal renal function.

[b]150 mg/d if used concurrently with a protease inhibitor.

Source: Katzung Basic and Clinical Pharmacology

DRUG RESISTANT TB

- MDR TB
- Multidrug resistant TB is caused by bacteria resistant to at least Isoniazid and Rifampicin
- These are the two most potent TB drugs
- XDR TB
- Resistant to Isoniazid and Rifampicin plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e. Amikacin, Kanamycin, or Capreomycin)

ANTI-LEPROSY CHEMOTHERAPY

- **Leprosy Defined**:Leprosy is one of the most ancient diseases known to mankind and has been mentioned in texts dating back to 600BC.
- It is a chronic disfiguring illness with a long latency
- Historically sufferers have been ostracised and forced to live apart from their communities, although, in fact, the disease is not particularly contagious
- Once viewed as incurable, the introduction in the 1940s of **dapsone**, and subsequently rifampicin and **clofazimine** in the 1960s, completely changed our perspective on leprosy

LEPROSY

- It is now considered relatively easy to diagnose and to cure
- Global figures show that the prevalence rates for the disease have dropped by 90% since 1985
- The disease has been eliminated from 108 out of 122 countries where it was considered to be a major health problem
- The bulk of these (70%) are in the Indian subcontinent.

WHEN TO SUSPECT LEPROSY

- Leprosy should be suspected in people with any of the following symptoms or signs:
  - light (hypo-pigmented) or reddish patches on the skin (the most common sign of leprosy);
  - loss or decrease of feeling in the skin patches;
  - numbness or tingling of the hands or feet;
  - weakness of the hands, feet or eyelids;
  - painful or tender nerves;
  - swelling of or lumps in the face or earlobes;
  - Painless wounds or burns on the hands or feet.

DRUGS USED IN LEPROSY

- The cornerstone of global elimination strategy is the provision of effective multidrug chemotherapy, namely dapsone, rifampin, and clofazimine, to all leprosy patients in the world.
- The success of the strategy is evident; by the end of 2003, over half of the countries considered endemic for leprosy in 1985 had achieved disease elimination *(i.e.,* a prevalence rate of <1 case per 10,000 inhabitants).

TREATMENT OF LEPROSY

- WHO Recommendation
- Multibacillary (Lepromatous) Leprosy:
  - A combination of Rifampicin, clofazimine & dapsone
  - Paucibacillary (Tuberculoid) Leprosy:
  - Rifampicin and dapsone
  - Multidrug therapy aims at effective eradication of M. leprae
  - This strategy is ultimately to prevent drug resistance

SULFONES

- The sulfones are derivatives of 4,4′-diaminodiphenylsulfone (dapsone), all of which share certain pharmacological properties. E.g. dapsone and sulfoxone
- Because Mycobacterium leprae does not grow on artificial media, in vivo assays with rat footpads have been used to test potential therapeutic agents.
- Dapsone is bacteriostatic for M. leprae due to competitive inhibiton of dihydropteroate synthase, which prevents bacterial utilization of paraaminobenzoic acid
- M. leprae may develop drug resistance during therapy, which is termed secondary resistance
- This typically occurs in lepromatous (multibacillary) patients treated with a single drug.

SULFONES: UNWANTED EFFECTS

- Hemolysis is the most common untoward reaction and develops in almost every individual treated with 200–300 mg of dapsone per day.
- Doses of 100 mg or less in normal healthy persons and 50 mg or less in healthy individuals with glucose-6-phosphate dehydrogenase deficiency do not cause hemolysis.
- Methemoglobinemia is common.
- A genetic deficiency in the NADH-dependent methemoglobin reductase can result in severe methemoglobinemia after dapsone administration
- Gastrointestinal intolerance, fever, pruritus, and various rashes occur
- During dapsone therapy of lepromatous leprosy, erythema nodosum leprosum often develops

RIFAMPICIN AS ANTI-LEPROSY DRUG

- Rifampin in a dosage of 600 mg daily is highly effective in lepromatous leprosy
- Because of the probable risk of emergence of rifampin-resistant *M leprae,* the drug is given in combination with dapsone or another antileprosy drug
- A single monthly dose of 600 mg may be beneficial in combination therapy
- Unwanted effects same as mentioned in TB treatment above

CLOFAZIMINE

- Clofazimine is a phenazine dye that can be used as an alternative to dapsone
- Its mechanism of action is unknown but may involve DNA binding
- Absorption of clofazimine from the gut is variable, and a major portion of the drug is excreted in feces
- Clofazimine is given for sulfone-resistant leprosy or when patients are intolerant to sulfones
- A common dosage is 100 mg/d orally

CLOFAZIMINE: UNWANTED EFFECTS

- The most prominent untoward effect is skin discoloration ranging from red-brown to nearly black
- Gastrointestinal intolerance occurs occasionally.