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AN OVERVIEW OF TUBERCULOSIS MANAGEMENT: MECHANISM AND THERAPEUTIC APPLICATIONS

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ABSTRACT

Tuberculosis infections have exceptional virulence factors compared to other pathogens and they infect host cell and persist inside phagosomes. First symptoms of active pulmonary TB can include weight loss, night sweats, fever, and loss of appetite etc. The infection can either go into remission or become more serious with onset of chest pain and coughing up bloody sputum. The exact symptoms of extra-pulmonary TB vary according to the site of infection in the body. The Mantoux tuberculin skin test, also called as the PPD (purified protein derivative) test, is primarily used to identify TB infection. According to their clinical utility the anti-TB drugs can be divided into two categories; one is first line, these drugs have high anti-tubercular efficiency as well as low toxicity; are used routinely, as for examples- Rifampin (R), Isoniazid (H), Streptomycin (S), Pyrazinamide (Z), Ethambutol (E) and another is second line, these drugs have either low anti-tubercular efficacy or high toxicity or both; are used in special circumstances only. There are six classes of second-line drugs likes amino glycosides, fluoro quinolones, polypeptides, thioamides, cycloserine, p-amino salicylic acid. Another group of scientists found that a newly identified protein with carboxy-esterase activity is required for the virulence of Mycobacterium tuberculosis. Preliminary treatment for tuberculosis involved eats nourishing food and have plenty of fresh air.

***Keywords*:** TB, Mantoux, symptoms, anti-TB drugs, Mechanism of Actions.

INTRODUCTION

Tuberculosis is a chronic infectious disease caused by the tubercle bacillus (*Mycobacterium tuberculosis*) and currently, the World Health Organization estimates that over 13 million people globally develop active TB and about 1.7 million die each year from the disease. Tuberculosis most commonly affects the lungs (pulmonary TB). Tb can also occur outside the lungs (extra pulmonary), most commonly in the central nervous, lymphatic, or in the bones and joints [1-2].

Tuberculosis infections have unique virulence factors compared to most pathogens and they infect host cell and persist inside phagosomes where there are limited nutrients [2-4]. Mycobacterium tuberculosis is an acid fast bacterium, which can form acid-stable complexes when certain aryl-methane is added [4]. All species of mycobacterium have rope like structures of peptidoglycan that are arranged in such a way to give them properties of an acid fast bacterium [4]. Most commonly used strain of M. tuberculosis is the H37Rv strain. One way to study M. tuberculosis in culture is to collect samples of mononuclear cells in peripheral blood samples from a healthy human donor and challenge macrophages with the MTC. Their acid fast property is the strongest when there is glycerol around. However, when glucose is the main source of nutrient, the utilization of glycerol by M. tuberculosis is inhibited. Therefore, it's been shown that glutamate, and not glucose, is actually the main source of nutrient for initiating growth [4]. M. tuberculosis has circular chromosomes of about 4,200,000 nucleotides long. The genomes contain about 4000 genes. *M. tuberculosis* has a tough cell wall that prevents passage of nutrients into and excreted from the cell therefore giving it the characteristic of slow growth rate. Cell envelope contains polypeptide layer, a peptidoglycan layer and there is also a complex structure of fatty acids such as mycolic acids, cell wall also contains lipid complexes such as acyl glycolipids and beneath the cell wall there are layers of arabino-galactan and peptidoglycan.

Classification-
Domain-Bacteria
Phylum- Actinobacteria
Class- Actinobacteria
Order-Actinomycetales
Family-Mycobacteriaceae
Genus-Mycobacterium
Species- *M. africanmum, M. bovis, M. canettii, M. microti, M. tuberulosis*

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Symptoms

Early symptoms of active pulmonary TB can include weight loss, night sweats, fever, and loss of appetite [1]. The infection can either go into remission or become more serious with onset of chest pain and coughing up bloody sputum [5]. The exact symptoms of extra-pulmonary TB vary according to the site of infection in the body.

Transmission

TB is spread through the air from one person to another. Microscopic droplets that contain the bacteria may be expelled when a person who has infectious TB coughs or sneezes. They can remain suspended in the air for several hours, depending on the environment. When a person breathes in M. tuberculosis, the bacteria can settle in the lungs and begin to grow. From there, they can move through the blood to other parts of the body. Tb in other parts of the body, such as kidney or spine, is not infectious [1].

Risk groups

Anyone can get TB. However, some groups are at higher risk to get active TB disease.

People at high risk include those [6]:

- With HIV infection.
- In close contact with those known to be infectious with TB.
- With medical conditions that make the body less able to protect itself from disease (for example: diabetes or people undergoing treatment with drugs that can suppress the immune system, such as long-term use of corticosteroids)
- From countries with high TB rates
- Who work in or are residents of long-term care facilities (nursing homes, prisons, some hospitals)
- Who are malnourished?
- Who are alcoholics or IV drug users?

Diagnosis

The Mantoux tuberculin skin test, also known as the PPD (purified protein derivative) test, is used to detect TB infection. It is performed by injecting a small amount of tuberculin, a complex of purified M. tuberculosis proteins, into the skin of the arm. A positive reaction for TB only reports that a person has been infected with TB bacteria. It does not tell whether or not the person has active disease [7]. Other tests including a chest x-ray are often seen in the apical segments of the upper lobe or in the upper segments of the lower lobe. Chest x-rays may be used to rule out the possibility of pulmonary TB in a person who has a positive reaction to the tuberculin skin test and no symptoms of disease. Person suspected of having pulmonary TB will have sputum specimens examined by acid-fast bacilli smear and culture. Detection of acid-fast bacilli in stained smears examined microscopically may provide the first clear evidence of the presence of M. tuberculosis. Positive cultures for M. tuberculosis are used to confirm the diagnosis of TB [7].

Historical background

Historically, TB has been associated with significant morbidity and mortality, and still remains a major global health problem. The *Mycobacterium tuberculosis* forms a complex with other higher related bacteria called the *M. tuberculosis* complex that consists of 6 members: *M. Tuberculosis* and *M. africanmum*, which infect humans; *M. microti*, which infects vole; *M. bovis*, which infects other mammalian species as well as humans; *M. bovis* BCG, a variant of *M. bovis* and *M. canettii*, a pathogen that infects human [8]. M. tuberculosis first infected humans 10,000-15,000 years ago. It has been found in early hominids originating in East-Africa. Therefore, studying the population structure of the species might provide insights about Homo sapiens' migratory and demographic history.

In 1993, the World Health Organization declared TB a global public health emergency. A new dimension got added in the 1980s due to spread of HIV with high prevalence of tuberculosis a Mycobacterium avium complex (MAC) infection among these patients and India has large load of HIV infected subjects and these patients are especially vulnerable to serve forms of tubercular infection [9]. While lately the increase in TB case rate associated with HIV infection has been halted in the USA, no such trend is apparent in India. Remarkable progress has been made in the last 60 years since the introduction of Streptomycin in 1947 for the treatment of TB and its full therapeutic potential could be utilized only after 1952 when isoniazid was produced to accompany it [9]. The discovery of ethambutol was in 1961, and rifampin was in 1962.

The sanatorium movement for treatment of Tuberculosis

Until the discovery of tubercle bacillus, TB was treated in the home and doctors prescribed a variety of treatments including snake oil and wearing a beard [3]. The sanatorium made its first appearance in the 1850s in Germany. The idea was developed by Herman Brehmer after he was apparently cured by living in the Himalayan climate [10-14]. Sanatoria treatment was reserved for the middle and upper class due to the costs associated with providing the 24 hours care, surgeries, and resort type activities found at these institutions.

The Prince Albert Sanatorium was the largest and most modern sanatorium in Saskatchewan, it opened in 1930 at Prince Albert, Saskatchewan. Part of idea behind Sanatoria was patient education and educational programs taught the infected what was known about the disease, new health habits and how to live with and protect others [15]. After treatment was completed Sanatoria was offered rehabilitation to assist patients in achieving a satisfactory economic status. Rehabilitation involved slowly introducing occupational therapy into the treatment regimen. Preliminary treatment for tuberculosis involved following two rules [16].

- Absolute and utter rest of mind and body, no bath, no movement except to toilet once a day, no sitting up except propped by pillows and semi-reclining, and no deep breaths.
- Eat nourishing food and have plenty of fresh air.

Old and new TB drugs: mechanisms of action and resistance

Among the unique features of Mycobacterium tuberculosis is its ability to establish persistent infection, requiring prolonged antibiotic treatment in order to achieve clinical cure and the basic goals of anti tuberculosis therapy include rapid killing of actively multiplying bacilli, prevention of acquired drug resistance, and sterilization of infected host tissues to prevent clinical relapse [10]. Consequently treatment requires the use of multiple drugs for several months [11].

According to their clinical utility the anti-TB drugs can be divided into [9]-

First line: These drugs have high anti-tubercular efficacy as well as low toxicity; are used routinely. Example- Isoniazid (H), Rifampin (R), Pyrazinamide (Z), Ethambutol(E), Streptomycin(S)[9].

Second line: These drugs have either low anti-tubercular efficacy or high toxicity or both; are used in special circumstances only. There are six classes of second-line drugs amino glycosides, fluoro quinolones, polypeptides, thioamides, cycloserine, p-amino salicylic acid.

Therapeutic applications (targets of anti TB drugs)

Because TB requires cholesterol to persist during an infection, inhibiting the Mce4 transporter [uptake of cholesterol uses the Mce4 transport system on M. tuberculosis cell wall and catabolic pathway is regulated bt KstR [2&3], Mce4 is an ATP-binding cassette transport system consisting of more than 8 proteins and is able to transport other steroids that are similar in structure to cholesterol including 4-androstene-3,17-dione,which is a metabolite of cholesterol catabolism [12] can be a novel therapeutic option. Targeting the KstR regulation system may also be a possible treatment. As a result, the ability for TB to persist inside macropheges would be lost and thus would be faster to treat. Within the cholesterol catabolism pathway, there are many metabolites that may be toxic. Cholestenone the first product of the cholesterol pathway has shown to be toxic and can kill the cell [17-19]. Cholestenone is used up by CYP125 and kicking out CYP125 causes an accumulation of toxic cholestenone which kills the cell [20].

Biology of TB

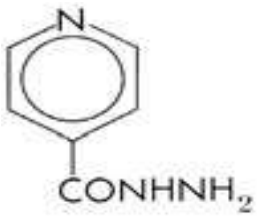
Microscopic droplets that contain the bacteria may be expelled when a person who has infectious TB coughs or sneezes. They can remain suspended in the air for several hours, depending on the environment. When a person breathes in M. tuberculosis, the droplets reach the alveoli of the lungs where the bacilli can be deposited [21]. Alveolar macrophages ingest the tubercle bacilli and destroy most of them. Some can multiply within the macrophage and be released when macrophage dies. From there the bacilli can spread to other regions of the body through the bloodstream. The areas in which TB is most likely to develop are: the apex of the lung, the kidneys, the brain, bones, and lymph nodes. This process of dissemination prepares the immune system for a reaction [6]. In most infected individuals the response from the immune system kills most of the bacilli. At this stage, a latent TB infection has been created, which may be detected by using the Mantoux tuberculin skin test. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression

Intrinsic and acquired drug resistance

Intrinsic resistance refers to the ability of bacterium to resist the activity of a particular antimicrobial agent through its inherent structural or functional characteristics and unique properties of cell wall of M. tuberculosis is the presence of mycolic acids, which are high molecular weight a-alkyl, B-hydroxy fatty acids covalently attached to arabinogalactan, and which constitute a very hydrophobic barrier responsible for resistance to certain antibiotics [12, 22]. In addition, M. Tuberculosis possesses B-lactamase enzymes, which confer intrinsic resistance to B-lactam antibiotics [10].

Acquired drug resistance when micro organism obtains the ability to resist the activity of a particular microbial agent to which it was previously susceptible [10]. Acquired drug resistance is caused by mutations in genes [13].

ISONIAZID (ISONICOTINIC ACID HYDRAZIDE, INH)



Absorption, distribution, and excretion

Isoniazid is readily absorbed after oral or parenteral administration, diffuses readily into all body fluids and cells and the drug achieves significant quantities in pleural and ascitic fluids; concentrations in the cerebrospinal fluid.

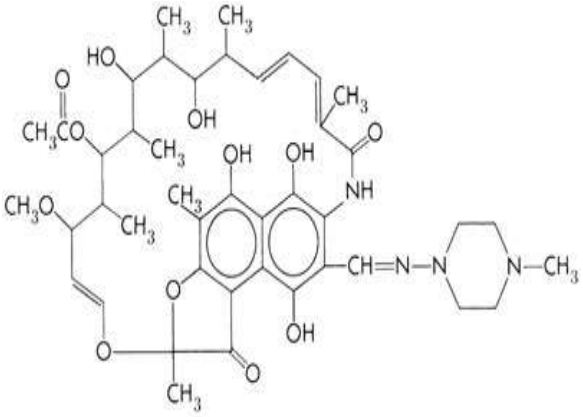
Mechanism of action

Isoniazid is bacteriostatic for "resting" bacilli but bactericidal for dividing microorganisms [11]. The most plausible mechanism of action of INH is inhibition of synthesis of mycolic acids which are unique fatty acid component of mycobacterial cell wall [9]. A gene labelled inh A which encodes for a fatty acid synthase enzyme is the target of INH action [9]. Isoniazid is a prodrug that is converted by mycobacterial catalase-peroxidase KatG into an active metabolite and the target of the isoniazid derivative is NADH dependent enoyl-ACP (acyl carrier protein) reductase inhA, a component of fatty acid synthase II, which converts unsaturated to saturated fatty acids in mycolic acid biosynthesis [11]. INH does not directly interact with Inh A, as x-ray crystallographic and mass spectrometry data revealed that the activated form of INH covalently attaches to the nicotinamide ring of NAD bound within the active site of Inh A, causing NADH to dissociate from Inh A [14].

Mechanism of resistance

Isoniazid resistance most commonly results from mutations in catalase-peroxidase that prevents conversion of the prodrug isoniazid to its active metabolite and Mutations in genes involved in mycolic acid biosynthesis also cause resistance [11]. Mutations in InhA gene resulting in reduced affinity of the enzyme for NADH without affecting its enoyl reductase activity [15] .Mutation in NDH gene which encodes a NADH dehydrogenase confer resistance to INH [16]. Metabolites and the main excretory products in humans result from acetylation (acetyl isoniazid) and hydrolysis (isonicotinic acid) and the serum $t_{1/2}$ in fast acetylators is 1 hour versus 2–5 hours in slow acetylators, resulting in serum isoniazid levels in fast acetylators that are 30–50% of those in slow acetylators [10]. Because isoniazid is relatively nontoxic, sufficient drug can be administered to fast acetylators to achieve a therapeutic effect [10].

RIFAMPIN AND OTHER RIFAMYCINS



The rifamycins (rifampin, rifabutin, rifapentine) are related macrocyclic antibiotics produced in 1957 by Amycolatopsis mediterrane; rifampin (RIFADIN; RIMACTANE) is a semi synthetic derivative of rifamycin B [11]. Their incorporation into the standard anti tuberculosis regimen allowed reduction of the duration of treatment from 18 to 9 months [10].

Mechanism of action and bacterial resistance

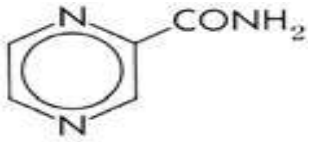
Rifampin easily diffuses across the *M. tuberculosis* cell membrane due to their lipophilic profile [11, 23]. Rifampin forms a stable complex with DNA dependent RNA polymerase, leading to suppression of initiation of chain formation (but not chain elongation) in RNA synthesis (transcription) [10]. High concentrations of rifampin can inhibit RNA synthesis in mammalian mitochondria, viral DNA–dependent RNA polymerases, and reverse transcriptase [11]. Rifampin is bactericidal for both intracellular and extracellular microorganisms [11]. Mycobacteria may rapidly develop rifampin resistance as a one-step process, and 1 of every 107–108 tubercle bacilli is resistant to the drug; thus, rifampin should not be used alone. Microbial resistance is due to single point mutations in rpoB gene which encodes the B-subunit of DNA-dependent RNA polymerase that reduce drug binding to the polymerase [17].

Absorption, distribution, and excretion

Following gastrointestinal (GI) absorption, rifampin [24-26] is eliminated rapidly in the bile, and an enterohepatic circulation ensues. During this time, the drug is progressively deacetylated by hepatic CYPS; after 6 hours, nearly all drugs in the bile are in the deacetylated form, which retains antibacterial activity. Intestinal reabsorption is reduced by deacetylation (and by food); thus, metabolism facilitates drug elimination.

The rifampin $t_{1/2}$ is progressively shortened (~40%) during the first 14 days of treatment due to induction of hepatic CYPs; $t_{1/2}$ is increased by hepatic dysfunction and may be decreased in slow acetylators concurrently receiving isoniazid. Dosage adjustment is not necessary in patients with renal insufficiency. Rifampin is distributed throughout the body and reaches effective concentrations in the CSF. The drug may impart an orange-red color to bodily fluids.

PYRAZINAMIDE



Mechanism of action

Pyrazinamide exhibits bactericidal activity in vitro only at a slightly acidic pH; this poses no problem since the drug kills tubercle bacilli residing in acidic phagosomes within the macrophage. Pyrazinamide enters tubercle bacilli passively and via an ATP dependent transport system [18]. Pyrazinamide like INH is a pro-drug requiring activation to its active form, pyrazinoic acid (POA) by the enzyme pyrazinamidase (PZase)[19]. Uptake and intrabacillary accumulation of POA is enhanced when the extracellular pH is acidic [20]. The target of pyrazinamide is the mycobacterial fatty acid synthase I gene involved in mycolic acid biosynthesis.

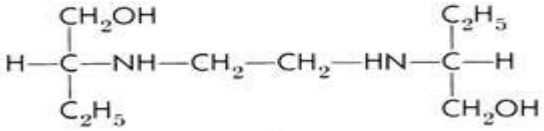
Mechanism of resistance

Resistance develops rapidly if pyrazinamide is used alone. Pyrazinamide resistance is result from mutation in the pncA gene encoding PZase [21, 24]

Absorption, distribution, and excretion

Pyrazinamide is well absorbed from the GI tract and widely distributed throughout the body, including the CNS, lungs, and liver. The plasma $t_{1/2}$ is 9–10 hours in patients with normal renal function. The drug is excreted primarily by glomerular filtration. Pyrazinamide is hydrolyzed to pyrazinoic acid and subsequently hydroxylated to 5-hydroxypyrazinoic acid.

ETHAMBUTOL



Antibacterial activity, mechanism of action, resistance

Nearly all strains of *M. tuberculosis* and *M. kansasii* and many strains of MAC are sensitive to ethambutol. Ethambutol has no effect on other bacteria. Growth inhibition by ethambutol requires 24 hours and is mediated by inhibition of arabinosyl transferases involved in cell wall biosynthesis. Ethambutol also inhibit RNA metabolism [22], transfer of mycolic acids into the cell wall [23], phospholipid synthesis [24], spermidine biosynthesis [25]. Resistance to ethambutol is results from point mutations in the embCAB operon [26]. Resistance to ethambutol develops very slowly in vitro, but can result from single amino acid mutations when given alone.

Absorption, distribution, and excretion

About 80% of an oral dose of ethambutol is absorbed from the GI tract. Concentrations in plasma peak 2–4 hours after the drug is taken and are proportional to the dose. The drug has a $t_{1/2}$ of 3–4 hours. Within 24 hours, 75% of an ingested dose of ethambutol is excreted unchanged in the urine; up to 15% is excreted in the form of aldehyde and dicarboxylic acid derivatives.

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STREPTOMYCIN

Mechanism of action

Streptomycin is bactericidal for the tubercle bacillus in vitro [11]. Streptomycin binds with 30s subunit which affects polypeptide synthesis ultimately resulting in inhibition of translation [10].

Mechanism of resistance

Primary resistance to streptomycin is found in only 2–3% of isolates of M. Tuberculosis and selection for resistant tubercle bacilli occurs in vivo; the longer therapy, the greater the incidence of resistance. Resistance to Streptomycin develops by mutation of the ribosome target binding sites.

FLUOROQUINOLONES

The fluoroquinolones [moxifloxacin (AVELOX), gatifloxacin (TEQUIN), sparfloxacin, levofloxacin, ofloxacin, and ciprofloxacin] are highly active against M. tuberculosis and are currently used as second-line drugs in TB treatment [10].

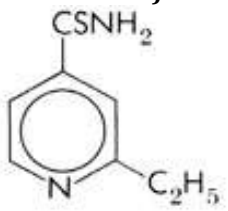
Mechanism of action

They exert their powerful antibacterial activity by trapping gyrase and topoisomerase IV on DNA as ternary complexes thereby blocking the movement of replication forks and transcription complexes [27].

Resistance

Fluoroquinolones resistance results from mutation in the conserved QRDR (quinolone resistance-determining region) of gyrA and gyrB involved in the interaction between the drug and DNA gyrase [28]. Individual mutation in gyr A may confer low level resistance, high level resistance to fluoroquinolones usually requires multiple mutations in gyrA or concurrent mutations in gyrA and gyrB [29]. Mycobacterial resistance to one fluoroquinolone imparts cross-resistance for the entire class [11].

ETHIONAMIDE (TRECATOR-SC)



Mechanism of action and antibacterial activity, resistance

Ethionamide a synthetic compound structurally related to INH, is a pro drug requiring activation by the NADPH-specific monooxygenase EthA to a sulfoxide, and hence to 2-ethyl-4-aminopyridine [30]. Like isoniazid, ethionamide inhibits mycobacterial growth by inhibiting the activity of the enoyl-ACP reductase of fatty acid synthase II. Both drugs thus inhibit mycolic acid biosynthesis with consequent impairment of cell-wall synthesis [11]. Resistance can develop rapidly in vivo when ethionamide is used as a single-agent treatment; including low-level cross-resistance to isoniazid [11] and high level ethionamide resistance have mutations in ethA or inhA [31]. Recently other potential mechanisms of resistance have been identified as M. tuberculosis mshA deletion mutants were found to be defective in mycothiol biosynthesis and resistant to ethionamide like it due to defective activation of the drug [32].

Absorption, distribution, and excretion

The $t_{1/2}$ of the drug is 2 hours. Approximately 50% of patients are unable to tolerate a single dose >500 mg because of GI disturbance. Ethionamide is rapidly and widely distributed, with significant concentrations in CSF. Ethionamide is cleared by hepatic metabolism; like aminosalicylic acid, ethionamide inhibits the acetylation of isoniazid in vitro.

PARAAMINOSALICYLIC ACID

Aminosalicylic acid is bacteriostatic,in vitro, most strains of M. tuberculosis are sensitive to a concentration of 1 mg/mL and microorganisms other than M. tuberculosis are unaffected [11] .

Mechanism of action and bacterial resistance

Aminosalicylic acid is a structural analogue of para-aminobenzoic acid, and has the same mechanism of action as the sulphonamides and the sulfonamides are ineffective against M. tuberculosis, and aminosalicylic acid is inactive against sulfonamide-susceptible bacteria [11]. PAS inhibit folic acid biosynthesis and uptake of iron [3]. Mutations in the thyA gene encoding the enzyme thimidylate synthesis of the folate biosynthesis pathway have been identified in PAS resistant M. tuberculosis clinical isolates, suggesting that PAS may act as a folate antagonist [14].

Absorption, distribution, and excretion

Aminosalicylic acid is readily absorbed from the GI tract. The drug is distributed throughout total body water; it reaches high concentrations in pleural fluid and caseous tissue, but CSF levels are low. It has a $t_{1/2}$ of 1 hour, and concentrations in plasma are negligible within 4–5 hours after a single dose. Over 80% of the drug is excreted in the urine; >50% as an acetylated derivative; the largest portion of the remainder is the free acid. The drug should not be used in the setting of renal insufficiency.

CYCLOSERINE

Cycloserine is a broad-spectrum antibiotic that is used with other drugs in the treatment of tuberculosis when primary agents have failed and Cycloserine is D-4-amino-3-isoxazolidone.

Mechanism of action

Cycloserine and D-Alanine are structural analogue; thus, cycloserine inhibits reactions in which D-Ala is involved in bacterial cell-wall synthesis in other words cycloserine interrupts peptidogyacan synthesis by inhibiting the enzymes d-alanine racemose (AlrA) and d-alanine:d-alanine ligase(Ddl) [15]. Over expression of M. tuberculosis AlrA and Ddl on a multicopy vector results in resistance to D-cycloserine in M. Smegmetis and M. Bovis BCG [16] although whether similar mechanisms are responsible for cycloserine resistance in M. tuberculosis remain to be determined.

Absorption, distribution, and excretion

When given orally, 70–90% of cycloserine is rapidly absorbed. Cycloserine is distributed throughout body fluids and tissues. CSF concentrations are comparable to those in plasma. About 50% of a parenteral dose of cycloserine is excreted unchanged in the urine in the first 12 hours; a total of 65% is recoverable in the active form over a period of 72 hours. Very little of the antibiotic is metabolized. The drug may reach toxic concentrations in patients with renal insufficiency; it is removed from the circulation by hemodialysis.

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Therapeutic uses

Cycloserine is used only when retreatment is necessary or microorganisms are resistant to other drugs. It must be given together with other effective agents. The usual dose for adults is 250–500 mg twice daily.

MACROLIDES

Clarithromycin and azithromycin are used to treat MAC and other non tuberculous mycobacteria. Clarithromycin alters the metabolism of many other drugs that are metabolized by CYPs, leading to many potential drug interactions.

Antibacterial activity and bacterial resistance

Clarithromycin [10, 17] is approximately fourfold more active than azithromycin against MAC and is active against most nontuberculous mycobacteria. Azithromycin's lower potency may be compensated for by its greater penetration; tissue levels exceed plasma levels by 100-fold. Use of clarithromycin or azithromycin alone is associated with the development of resistance, and they therefore should not be used as monotherapy of MAC infection.

QUINOLONES

The quinolones (e.g., ciprofloxacin, levofloxacin, moxifloxacin, and gatifloxacin) inhibit MAC bacteria in vitro. M. fortuitum and M. kansasii also are sensitive to these quinolones but M. chelonae usually are resistant. Single-agent therapy of M. fortuitum infection with ciprofloxacin has led to resistance. Ciprofloxacin, 750 mg twice daily or 500 mg three times daily, has been used in a 4-drug regimen (with clarithromycin, rifabutin, and amikacin) as salvage therapy for MAC infections in HIV-infected patients. Multidrug-resistant tuberculosis has been treated with ofloxacin, 300 or 800 mg/day, in combination with second-line agents. Moxifloxacin and gatifloxacin are more active than the older fluoro quinolones and would be expected to be useful agents clinically [10, 18].

AMIKACIN

Amikacin may have a role as a third or fourth agent in a multiple-drug regimen for MAC treatment.

CHEMOTHERAPY OF MYCOBACTERIUM AVIUM COMPLEX

Clarithromycin and azithromycin [11, 19] both have excellent activity against many strains of MAC, with clinical responses (decrease or elimination of bacteremia, resolution of fever and night sweats) demonstrated even with single-drug therapy. To avoid resistance, most clinicians treat disseminated MAC infections with clarithromycin or azithromycin plus ethambutol. In some situations, rifabutin, clofazimine, and/or a quinolone are added. Drug interactions and adverse drug reactions are common with multiple-drug regimens, necessitating drug discontinuation in ~50% of patients. Clinical improvement is expected in the first 1–2 months of treatment, with sterilization of blood cultures within 3 months of starting therapy. Treatment of MAC infection in HIV-infected individuals typically is lifelong. Isoniazid and pyrazinamide have no role in the treatment of MAC infection. Prophylaxis of MAC infection with clarithromycin or azithromycin should be strongly considered for HIV-infected persons whose CD4 count is <50/mm^3.

NEW DRUGS FOR TB

Within the last few years a new form of TB has emerged, extensively drug-resistant TB (XDR-TB). Whereas regular TB and even MDR TB progress relatively slowly, XDR TB progresses much more rapidly and can be fatal within months or even a few weeks. XDR-TB is defined as TB that has developed resistance to at least rifampin and isoniazid, as well as to any member of the flouroquinolone family and at least one of the aminoglycosides or polypeptides. The emergence of XDR-TB, particularly in settings where many TB patients are also infected with HIV, poses a serious threat to TB control [8]. Short course Direct Observation Therapy (DOTS) is a key component (2009) of the World Health Organization's campaign to stop TB. A DOT involves patient case management by trained health professionals who ensure that the patient is taking his/her TB drugs and DOTS provide incentives to ensure patients continue their treatment, such as transportation or free meals.

Although effective chemotherapy for TB has been in place for over 50 years, it was clear from the first clinical trials that mono therapy with any agent led to the development of resistance and clinical failure in 2-5 months. In the last ten years, there has been resurgence in interest in identifying new compounds that are effective against Mtb.

FUTURE TRENDS-CURRENT RESEARCH

Since the pathogen-host interaction of Mycobacterium tuberculosis is still unknown, much of the current research is geared towards the understanding of the mechanism of virulence. For example, one such research showed that prokaryotic and eukaryotic like iso-forms of the glycoxylate cycle enzyme iso-citrate lyase (ICL) are jointly required for fatty acid catabolism and virulence in Mycobacterium tuberculosis. This discovery provides insight such as drugs that are glycoxylate cycle inhibitors could be used to treat tuberculosis [10-18].

Another group of scientists found that a newly identified protein with carboxy-esterase activity is required for the virulence of Mycobacterium tuberculosis. They found that the gene MT2282 encodes a protein that is associated with carboxy-esterase. It hydrolyzes ester bonds of the substrate. When a strain containing a mutant of this gene was used to infect mice, the mice's life was prolonged as compared with those that were infected with the wild type strain [10-16].

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