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Review Article

Mechanism and Treatment of Multi-Drug Resistance of Mycobacterium Tuberculosis: A Review

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ABSTRACT

Tuberculosis (TB) is the greatest common cause of infection which is related to death worldwide. Multi-drug-resistant tuberculosis (MDR-TB) is tuberculosis (TB) infection which is caused by bacteria that are resistant to medication with at least two of the most powerful first-line antituberculosis medications (drugs), isoniazid and rifampin and the tuberculosis which are resistant to second-line medications are called extensively drug-resistant tuberculosis (XDR-TB). The isoniazid resistance has been associated with mutations in numerous genes that include katG, ahpC, inhA, kasA and ndh. The rifampicin resistant to m.tuberculosis appear mutations in the gene rpoB which encodes the β-subunit of RNA polymerase and results in low affinity for the drug and develops resistances. Clofazimine, linezolid and bedaquiline is used in the treatment of multidrug resistance for m.tuberculosis. Pulmonary resection may be required in patients with tuberculosis (TB) due to in drug-resistant cases when medication regimen is failed. The multidrug resistant tuberculosis creates a risk to health care workers, doctors and other patients, which should be prevented such as nosocomial transmission. The miliary disease and tubercular (TB) meningitis are the first and most deadly complications of primary tuberculosis.

Keywords: tuberculosis, multidrug resistant, mechanism, treatment, bedaquiline, linezolid, prevention.

INTRODUCTION

Tuberculosis (TB) is the greatest common cause of infection which is related to death worldwide. Multi-drug-resistant tuberculosis (MDR-TB) is tuberculosis (TB) infection which is caused by bacteria that are resistant to medication with at least two of the most powerful first-line antituberculosis medications (drugs), isoniazid and rifampin and the tuberculosis which are resistant to second-line medications are called extensively drug-resistant tuberculosis (XDR-TB).

Mechanism of multidrug resistance for M.Tuberculosis:

Isoniazid:

Isoniazid is used as main drugs for the treatment of tuberculosis. Isoniazid contains modest structure which is a pyridine ring and a hydrazide group and these mechanisms are vital for the high activity against M. tuberculosis.

The process of isoniazid resistance is a complex. The isoniazid resistance has been associated with mutations in numerous genes that include katG, ahpC, inhA, kasA and ndh. Isoniazid is a prodrug which is activated by the catalase/peroxidase enzyme and encoded by katG (1). When isoniazid is activated it interferes with the synthesis of mycolic acids and it inhibits NADH-dependent enoyl-ACP reductase and which is encoded by inhA (2). The main two molecular mechanisms such as mutation in katG and inhA are main causes of isoniazid resistance (3, 4).

The mutations katG which is main cause of genetic alternation leads to decrease in or total loss of catalase/ peroxidase activity has been associated with isoniazid resistance (1).

The mutation S315T which is found in katG occurs more commonly in MDR than in isoniazid mono resistant strains due to extremely poor in forming the isoniazid –NAD adduct which is related to isoniazid antimicrobial activity.

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Isoniazid and tolerance:

Antibiotic tolerance is defined as the capacity of bacteria to stop cultivating in the occurrence of an antibiotic. Tolerance or phenotypic resistance arises in M.Tuberculosis due to changes in the metabolism or physiological status of the bacteria that make them momentarily resistance to a certain drugs. Isoniazid persuades both drug resistant and drug tolerant M.Tuberculosis strains due to alternations in the expression of numerous genes. Several genes belong to functional class of lipid metabolism and remaining fall into class of cell wall and cell processes or transporter (5).

M.TuberculosisiniA gene (RV0342), which is a part of the three gene operon (Rv0341, Rv0342, Rv0343) contributes in the development of isoniazid and ethambutol tolerance that willinduce in the presence of isoniazid (6).

Isoniazid also persuades numerous other genes that include an operon cluster of five genes that will code type II fatty acid synthase enzymes and fbpC and which encodes trehalose dimycolyl transferase. Some of other genes like efpA, fadE24, fadE23 and ahpC are linked to the toxicity of the drug and efflux mechanisms (7).

Rifampicin:

Rifampicin is a lipophylic ansamycin, due to its effective antimicrobial action; it is used as the short course treatment regimen for tuberculosis together with isoniazid (8).

Rifampicin in m.tuberculosis targets β-subunit of RNA polymerase that binds and inhibits the elongation of RNA messenger (9). Rifampicin is active against growing and slowly metabolising bacilli (10).

The rifampicin resistant to m.tuberculosis appear mutations in the gene rpoB which encodes the β-subunit of RNA polymerase and results in low affinity for the drug and develops resistances (11).

Rifampicin resistance is related with a hotspot (codon 507 to 533) core region called rifampicin resistance determining region (RRDR). The mutation in a hot-spot region of 81bp to rpoB has been found in 96% of rifampicin resistant m.tuberculosis (12).

The mutation A191C in Rv2629 is also associated with rifampicin resistance (13).

Pyrazinamide:

Pyrazinamide decrease the length of treatment from 9 to 6 months and has ability to inhibit semi-dormant bacilli residing in acidic environments (14).

Pyrazinamide is a structural analogue of nicotinamide.Pyrazinamide is a prodrug which should be converted into pyrazinoic acid in the presence of enzyme pyrazinamidase/nicotinamidase (PZase) (15). PZase is encoded by the gene pncA in m.tuberculosis (16). It is assumed that the mechanism of action of pyrazinamide has active moiety which helps in disrupting bacterial membrane energetics and also inhibiting membrane transport in the presence of pyrazinioic acid.

Pyrazinamide enters into M. tuberculosis by passive diffusion which is then converted into pyrazinoic acid by PZase and that isevacuated by a feeble efflux pump. The protonated pyrazinoic acid which is reabsorbed under acid conditions that accumulates inside the cell due to inefficient efflux pumps which results in cellular damage (17). Pyrazinoic acid with n –propyl ester inhibits synthesis of fatty acid type I in replicating bacilli (18).

The main mechanisms for pyrazinamide resistance in m.tuberculosis are mutations in pncA. Utmost alterations which occur in a 561 bp region of the open reading frame or in an 82 bpregion of its putative promoter (19, 20).

Streptomycin:

Streptomycin is an aminocyclitol glycoside antibiotic which is the first antibiotic that was used in the treatment of m.tuberculosis and its mechanism of action is to inhibit the instigation of translation by binding to the 16 rRNA (21).

In mycobacterium fortuitum, an aminoglycoside 3”-O-phosphotransferase is involved in streptomycin resistance (22). In m.tuberculosis, streptomycin resistance is due to mutation in rrs or rpsL. This will produce change in the streptomycin binding site (23).

The mutations in gidB, which encodes a preserved 7-methylguanosine methyltransferase specific for

the 16S rRNA, can deliberate a low level of streptomycin resistance (24, 25).

Ethambutol:

Ethambutol, 2, 2'-(1, 2-ethanediyldiimino) bis-1-butanol, which was first used in 1966 against m.tuberculosis and it is used together with isoniazid, rifampicin and pyrazinamide as the first-line drugs for treatment of the m.tuberculosis. Ethambutol interferes in the biosynthesis of cell wall arabinogalactan and is active against multiplying bacilli (26).

The genes embCAB were ordered as a 10 kbp operon encoding for mycobacterial arabinosyl transferase in m.tuberculosis. It was found that near to 50% which had mutation present in codon 306 of embB is ethambutolresistance to m.tuberculosis (27).

Fluoroquinolones:

Fluoroquinolones are bactericidal antibiotics and it is used as second-line drugs in the treatment of m.tuberculosis. moxifloxacin and gatifloxacin are used as first line antibiotics that will decrease duration of m.tuberculosis treatment (28,29,30). Type II topoisomerase (DNA gyrase) which is present in m.tuberculosis and hence fluoroquinoloneactivity only target on this (31). Type II topoisomerase which is a tetramer that is composed of two A and B subunits and is encoded by the genes gyrA and gyrB that catalyses the supercoiling of DNA (32, 33, 34).M. tuberculosis resistance to fluoroquinolones is due to amino acid exchanges in the putative fluoroquinolone binding region in gyrA or gyrB (34). This mutation so called quinolone resistance-determining region (QRDR) gyrA and gyrB.

The strain with an Asn-533-Thr mutation in gyrB was found to be resistant to moxifloxacin and gatifloxacin but susceptible to ofloxacin (35).

Kanamycin, amikacin, capreomycin and viomycin:

Kanamycin and amikacin are aminoglycoside antibiotics and capreomycin and viomycin are cyclic peptide antibiotics. These all are used as second line drugs in the treatment of multidrug resistance m.tuberculosis.

The mechanism of drug resistance in m.tuberculosis is associated with an A1401G mutation in the rrs gene coding for 16S rRNA. This mutation has high level resistance to kanamycin and amikacin (36).

The mutation in the gene tlyA has been found in resistance to capreomycin and viomycin. This gene codes an rRNAmethyltransferase specific for 2'-O-methylation of ribose in rRNA and when transmutatedit defines an absences of methylation activity (37).

Ethionamide:

Ethionamide is a prodrug which requires activation to form an adduct with NAD and later inhibits the NADH-dependent enoyl-ACP reductase InhA. Ethionamide activation occurs through ethA-encoded mono-oxygenase after that it yields ethionamide-NAD adduct (38).

The ethionamide resistance occurs by mutation in ethA and inhA(39).

Coresistance to isoniazid and ethionamide can be arbitrated by mutations that change the InhA target or it cause their overexpression, or by mutations in ndh that increase the intracellular concentration of NADH (40, 41).

p-Amino salicylic acid:

p-Amino salicylic acid in combination with isoniazid and streptomycin is used in treatment of m.tuberculosis and is also the first antibiotic to show the anti-TB activity (42). Its mechanism action is unknown but it may contest with para-amino benzoic acid for dihydropteroate synthase, an enzyme which is needed in folate biosynthesis.

p-amino salicylic acid-resistant in M. tuberculosis harboured mutations in thyA resulting in decreased enzyme activity (43). It is also found that thr202Ala most common mutation associated with p-amino salicylic acid resistance.

Treatment:

Clofazimine is used in multidrug resistant tuberculosis with total daily dose 100 mg for gram-positive organisms (44).

The diarylquinoline antimycobacterial, bedaquiline which is approved by the FDA in December 2012 as part of a 22 weeks multidrug regimen for pulmonary multidrug resistant tuberculosis.

Bedaquiline is also used in multidrug resistant tuberculosis with recommended dose is 400 mg a

day for two weeks and after that 200 mg taken three times a week (with at least 48 hours between doses) for the next 22 weeks(45).

Linezolid is also used in the treatment of multidrug resistant m.tuberculosis and it was well tolerated, had low rates of discontinuation and may have efficacy. The dose of linezolid was 600mg daily (47, 48, and 49).

Surgical Management of TB:

Pulmonary resection may be required in patients with tuberculosis (TB) due to in drug-resistant cases when medication regimen is failed. Surgical resection also required in patients when there is progressive disease with extensive caseation necrosis. Hemoptysis, though rare in children, may require surgical intervention. TB abscesses and bronchopleural fistulae should be surgically removed.

Prevention of transmission of MDRTB:

The multidrug resistant tuberculosis creates a risk to health care workers, doctors and other patients, which should be prevented such as nosocomial transmission (46). The patients should be kept in single room with negative pressure relative to the outside with six air exchanges per hour and the room to be exhausted to the outside, consideration of ultraviolet lamps or particulate filters to supplement ventilation, use of disposable particulate respirators for persons entering the room and during cough inducing procedures.

Complications of TB Disease:

The miliary disease and tubercular (TB) meningitis are the first and most deadly complications of primary tuberculosis. A great index of doubt is required for prompt diagnosis and management of these diseases. Pulmonary complications which include the growth of pleural effusions and pneumothorax. When caseous material extrudes into the lumen it leads to complete obstruction of a bronchus and also leads to atelectasis of the involved lung. Bronchiectasis, stenosis of the airways, bronchoesophageal fistula, and endobronchial disease which is caused by penetration through an airway wall and all these are other catastrophes that may develop with primary tuberculosis.

Perforation of the small bowel, obstruction, enterocutaneous fistula, and the development of severe malabsorption may obscure TB of the small intestine.

Pericardial effusion may be an acute complication or can look like chronic constrictive pericarditis.

Conclusion:

Multi-drug-resistant tuberculosis (MDR-TB) is tuberculosis (TB) infection which is caused by bacteria that are resistant to medication with at least two of the most powerful first-line antituberculosis medications (drugs), isoniazid and rifampin and the tuberculosis which are resistant to second-line medications are called extensively drug-resistant tuberculosis (XDR-TB). Bedaquiline is also used in multidrug resistant tuberculosis with recommended dose is 400 mg a day for two weeks and after that 200 mg taken three times a week (with at least 48 hours between doses) for the next 22 weeks. The main two molecular mechanisms such as mutation in katG and inhA are main causes of isoniazid resistance. The miliary disease and tubercular (TB) meningitis are the first and most deadly complications of primary tuberculosis. Pulmonary resection may be required in patients with tuberculosis (TB) due to in drug-resistant cases when medication regimen is failed.

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