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Pharmaceutical Sciences **REVIEW ARTICLE……!!!**

DRUG RESISTANCE OF TUBERCULOSIS

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ABSTRACT

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that one-third of the population of the world is infected with *Mycobacterium tuberculosis* and that more than 8 million new cases of active TB occur annually. The estimated global annual mortality from TB is close to 2 million people. Resistance to anti-TB drugs, a problem recognized in the very early days of the chemotherapeutic era has also emerged as a serious problem. TB drug resistance is characterized by both the types of drugs to which the bacteria lack susceptibility and the manner in which resistance was acquired. Resistance to single agents is the most common type; resistance to multiple agents is less frequent but of greater concern. By convention, "multidrug resistance" is defined as resistance to at least isoniazid and rifampin. Drug resistance is either acquired with the initial infection (from a host harboring resistant tubercle bacilli) or develops during treatment with anti-tuberculous chemotherapeutic agents because of poor patient compliance or inadequate/inappropriate treatment regimens. This review discusses the mechanism of drug resistance of tuberculosis, causes and treatment of drug resistance of TB.

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INTRODUCTION:

Tuberculosis (TB)

A disease caused by bacteria that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. In most cases, TB is treatable and curable; however, people with TB can die if they do not get proper treatment.

Drug-Resistant TB (DR TB)

Sometimes drug-resistant TB occurs when bacteria become resistant to the drugs used to treat TB. This means that the drug can no longer kill the TB bacteria.

DR TB Spread the same way that TB is spread. TB is spread through the air from one person to another. The TB bacteria are put into the air when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings.

People nearby may breathe in these bacteria and become infected.

CLASSIFICATION OF ANTI-TB DRUGS

FIRST LINE DRUGS:

All first-line anti-tuberculosis drug names have semistandardized three-letter and single-letter abbreviation.

Ethambutol is EMB or E

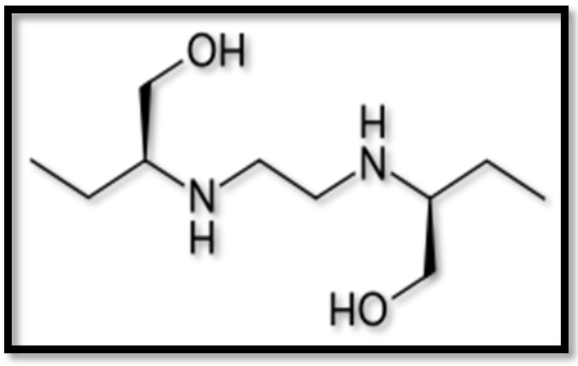

Figure 1:Structure of Ethambutol

MECHANISM OF ACTION

Ethambutol is bacteriostatic against actively growing TB bacilli. It works by obstructing the formation of cell wall. Mycolic acids attach to the 5'-hydroxyl groups of D-arabinose residues of arabinogalactan and form mycolyl-arabinogalactan-peptidoglycan complex in the cell wall. It disrupts arabinogalactan synthesis by inhibiting the enzyme arabinosyl

transferase. Disruption of the arabinogalactan synthesis inhibits the formation of this complex and leads to increased permeability of the cell wall.

Isoniazid is INH or H

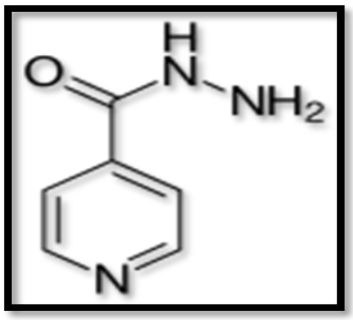

Figure 2: Structure of Isoniazid

MECHANISM OF ACTION

Isoniazid is a prodrug that is activated on the surface of M. tuberculosis by katG enzyme to isonicotinic acid. Isonicotinic acid inhibits the bacterial cell wall mycolic acid and thereby makes M. tuberculosis susceptible to reactive oxygen radicals. Isoniazid may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. The drug is active against susceptible bacteria only during bacterial cell division.

SECOND LINE DRUGS:

The second line drugs (WHO groups 2, 3 and 4) are only used to treat disease that is resistant to first line therapy (i.e., for extensively drug-resistant tuberculosis (XDR-TB) or multidrug-resistant tuberculosis (MDR-TB)).

Thioamide (Who Group 4): e.g. Ethionamide

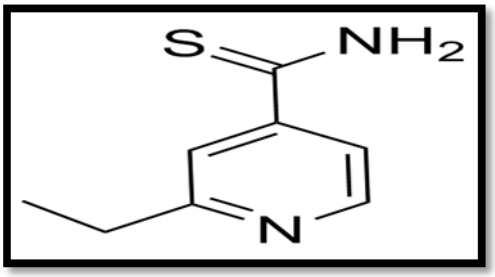

Figure 3: Structure of Ethionamide

MECHANISM OF ACTION

Ethionamide may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. Ethionamide, like prothionamide and pyrazinamide, is a nicotinic acid derivative related to isoniazid. It is thought that

ethionamide undergoes intracellular modification and acts in a similar fashion to isoniazid. Isoniazid inhibits the synthesis of mycoloic acids, an essential component of the bacterial cell wall. Specifically isoniazid inhibits InhA, the enoyl reductase from Mycobacterium tuberculosis, by forming a covalent adduct with the NAD cofactor. It is the INH-NAD adducts that acts as a slow, tight-binding competitive inhibitor of InhA.

Cycloserine (WHO group 4)

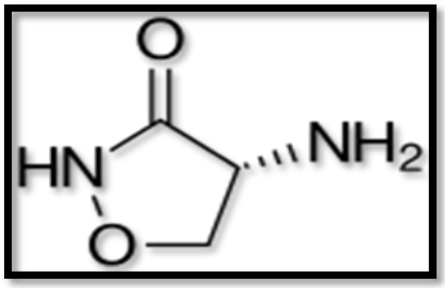

Figure 4: Structure of Cycloserine

MECHANISM OF ACTION

Cycloserine works as an antibiotic by inhibiting cell-wall biosynthesis in bacteria. As a cyclic analogue of D-alanine, cycloserine acts against two crucial enzymes important in the cytosolic stages of peptidoglycan synthesis: alanine racemase (Alr) and D-alanine: D-alanine ligase (Ddl). The first enzyme is a pyridoxal 5'-phosphate-dependent enzyme which converts the L-alanine to the D-alanine form. The second enzyme is involved in joining two of these D-alanine residues together by catalyzing the formation of the ATP-dependent D-alanine-D-alanine dipeptide bond between the resulting D-alanine molecules. If both of these enzymes are inhibited, then D-alanine residues cannot form and previously formed D-alanine molecules cannot be joined together. This effectively leads to inhibition of peptidoglycan synthesis.

THIRD LINE DRUGS:

Third-line drugs (WHO group 5) include drugs that may be useful, but have doubtful or unproven efficacy.

Rifabutin

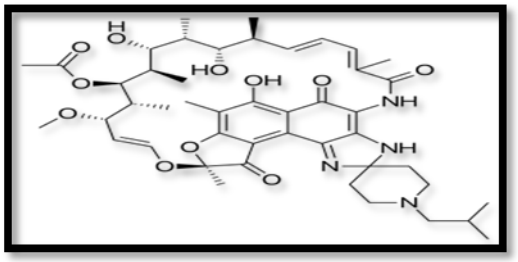

Figure 5: Structure of Rifabutin

Macrolides: e.g., Clarithromycin (CLR)

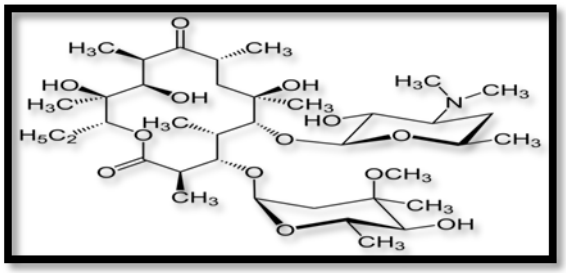

Figure 6: Structure of Clarithromycin

CLASSIFICATION OF DR TB TYPES

Mono-resistance: Resistance to one first-line anti-TB drug only**.**

Poly-resistance: Resistance to more than one first-line anti-TB drug, other than both Isoniazid and rifampicin.

Multi-Drug Resistance (MDR): Resistance to at least both isoniazid and rifampicin**.**

Extensive Drug Resistance (XDR): Resistance to any fluoroquinolone, and at least One of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance**.**

Rifampicin Resistance (RR): Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

Causes of DR TB

DR TB can occur when the drugs used to treat TB are misused or mismanaged. Examples of misuse or mismanagement include:

People do not complete a full course of TB treatment.

Health care providers prescribe the wrong treatment (the wrong dose or length of time).

Drugs for proper treatment are not available.

Drugs are of poor quality.

DR TB is more common in people who:

Do not take their TB drugs regularly.

Do not take all of their TB drugs.

Develop TB disease again, after being treated for TB disease in the past.

Come from areas of the world where drug-resistant TB is common.

Have spent time with someone known to have drug-resistant TB disease.

Mechanism of Drug-Resistance:

The TB bacteria have natural defenses against some drugs, and can acquire drug resistance through genetic mutations. Some mechanisms of drug resistance include:

Cell wall: The cell wall of M. tuberculosis (TB) contains complex lipid molecules which act as a barrier to stop drugs from entering the cell.

Drug modifying & inactivating enzymes: The TB genome codes for enzymes (proteins) that inactivate drug molecules. These enzymes usually phosphorylate, acetylate, or adenylate drug compounds.

Drug efflux systems: The TB cell contains molecular systems that actively pump drug molecules out of the cell.

Mutations: Spontaneous mutations in the TB genome can alter proteins which are the target of drugs, making the bacteria drug resistant.

Treatment of DR TB:

Treating and curing DR TB is complicated. Inappropriate management can have life-threatening results. Drug resistance is diagnosed by drug-susceptibility testing in the laboratory. However, since these tests can take several weeks, treatments start with an empirical treatment regimen based on expert advice, depending on the assumption that the person has DR TB. When the test results are out, the treatment regimen should be adjusted according to the results. Patients should be monitored closely throughout the treatment. Directly Observed Therapy (DOT) should always be used in the treatment of DR TB to ensure adherence.

SPECIAL CONSIDERATIONS:

PEOPLE INFECTED WITH HIV:

Although the treatment of drug-resistant TB in persons with HIV infection is similar to patients without HIV, management of HIV-related TB requires expertise in the management of both HIV and TB. Providers must monitor the interactions among many of the antiretroviral drugs. Rifampin (RIF) should not be used with most antiretroviral drugs. Rifabutin, which has fewer problematic drug interactions, may be used in place of RIF. As new antiretroviral agents and pharmacokinetic data become available, these recommendations are likely to be modified.

CHILDREN:

In case of suspected drug resistant TB in a child, specimens for microbiological evaluation should be obtained.

Initial treatment for children with suspected drug resistant TB disease (e.g., after exposure to a person with drug-resistant TB) should be guided by the source-case susceptibility results until the drug

susceptibility results for the child's isolate are available. If an isolate from the child under treatment is not available, drug susceptibilities can be inferred by the drug susceptibility pattern of isolates from the adult source case.

PREGNANT WOMAN:

Case management for pregnant women who have drug-resistant TB requires consultation with an expert because most second-line anti-TB drugs have unknown effects on the fetus.

In most cases, pyrazinamide (PZA) is not recommended as part of the treatment regimen for pregnant women. Counseling concerning risks to the fetus should be provided.

NEW DR TB DRUGS

BEDAQUILINE

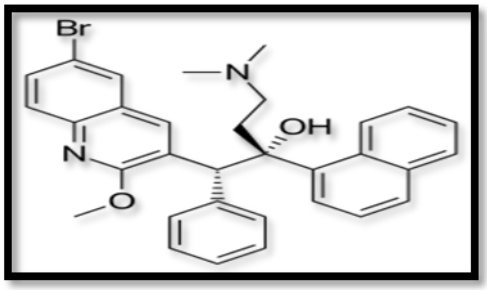

Figure 7: Structure of Bedaquiline

DELAMANID

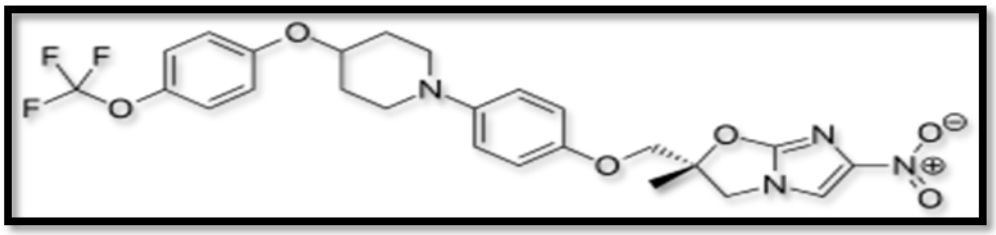

Figure 8: Structure of Delamanid

PRETOMANID

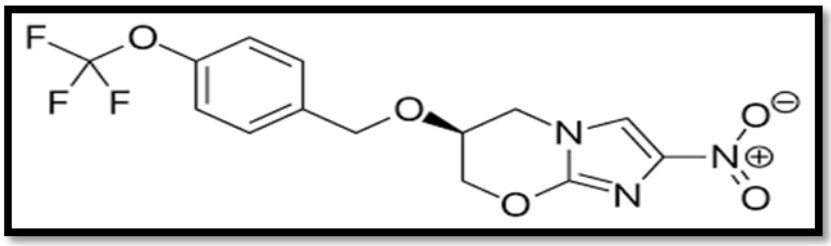

Figure 9: Structure of Pretomanid

CONCLUSION

Drug resistance is a worldwide problem that threatens to undermine effective control of TB. As shown by the recent report of WHO/IUATLD (International Union against Tuberculosis and

Lung Disease), hot spots of MDR-TB have appeared in regions with weak TB-control programs and misuse of anti-TB drugs. Prevention of drug resistance depends on appropriate treatment of all patients with TB with combination drug regimens and early detection of resistance followed by treatment with second-line agents. In countries with low levels of MDR-TB, efforts should be concentrated on preventing acquired MDR-TB by endorsing and widely implementing the WHO DOT strategy. In regions with high levels of MDR-TB, although concentration on detecting and treating new susceptible TB cases remains critically important, MDR-TB management efforts should adapt treatment by performing drug susceptibility testing. In countries with limited resources, more operational research is needed to define the best cost-effective strategies for individual versus standardized patient management of MDR-TB under national program conditions. The development of better and more rapid diagnostic assays and new classes of anti-TB drugs are urgent priorities for the containment of MDR-TB.

REFERENCES:

1. Definition @https://www.cdc.gov/tb/topic/drtb/default.htm
2. Lambert M P, "Mechanism of D-cycloserine action: Alanine racemase from Escherichia coli W". Journal of Bacteriology, Edition - 1972, Volume 3, Pages - 978–987.
3. Anti-TB Drugs @https://en.wikipedia.org/wiki/Tuberculosis_management#Drugs
4. Ethambutol Uses @https://www.webmd.com/drugs/2/drug-8082/ethambutol-oral/details
5. Prosser, Gareth; de Carvalho, Luiz Pedro S, "Kinetic mechanism and inhibition of Mycobacterium tuberculosis d-alanine: D-alanine ligase by the antibiotic d-cycloserine", Edition – 2013, Volume 4, Pages - 1150–1166.
6. Ethambutol MOA @en.wikipedia.org/wiki/Ethambutol
7. Isoniazid uses @https://www.webmd.com/drugs/2/drug-8665/isoniazid-oral/details
8. Ethionamide MOA @https://www.drugbank.ca/drugs/DB00609
9. Cycloserine Uses @https://www.webmd.com/drugs/2/drug-1054/cycloserine-oral/details
10. Jean B. Nachega Richard E. Chaisson, *Clinical Infectious Diseases*, Edition - 2003, Volume 36, Pages - S24–S30
11. Drug resistance of TB Types @https://www.who.int/tb/areas-of-work/drug-resistant-tb/types/en/
12. Causes @https://www.cdc.gov/tb/topic/drtb/default.htm
13. Mechanism @https://en.wikipedia.org/wiki/Multi-drug-resistant_tuberculosis
14. Treatment @https://www.cdc.gov/tb/publications/factsheets/treatment/drugresistanttreatment

15. Bedaquiline @https://www.tbfacts.org/bedaquiline/

16. Delamanid @https://www.tbfacts.org/delamanid/

17. R.V. Patel, S.D. Riyaz, S.W. Park, Bedaquiline: a new hope to treat multi-drug resistant tuberculosis, Edition – 2014, Pages – 1866-74

18. Delamanid synthesis @https://newdrugapprovals.org/2016/07/27/delamanid-deltyba

19. Pretomanid @https://en.wikipedia.org/wiki/Pretomanid

20. Pretomanid synthesis @https://www.researchgate.net/figure/Scheme-1-Synthesis-of-pretomanid