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Review Article

Mechanism and management of antibiotic drug resistance tuberculosis

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ABSTRACT

Drug resistance in tuberculosis has been shown to result from spontaneous mutation in several chromosomal genes of M.Tuberculosis. Mutation may reduce the medications' capacity to bind to the target genes. In many patients polydrug resistance, multidrug resistance, rifampicin resistance (RR) and extensive drug resistance (XDR) were seen. The diagnosis of drug-resistant TB in HIV-positive persons is more difficult and may be confused with other pulmonary or systemic infections. Management of patients with mono- or poly-resistant TB will be done with standard first line chemotherapy. Treatment of latent infection for people suffering from multidrug resistant bacilli is problematic because the only cure by isoniazid and rifampicin. In the recent cases of severe hepatotoxicity associated with preventive treatment comprising either pyrazinamide and rifampicin or pyrazinamide and fluoroquinolone. The use of dilatory fluoroquinolones, such as moxifloxacin, remarkable improved treatment outcomes of XDR-TB.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium Tuberculosis. One of the epidemics that seriously harmed public health around the world is tuberculosis (TB). The "World Health Organization" declared tuberculosis to be a top priority after the worldwide breakout of the disease in 1993.[1] WHO projected that approximately 10 million people had the diseases in 2017 and that 6.4 million people developed TB for the primary time. Additionally, it had been stated that nearly 1.3 million individuals defunct due to tuberculosis each year. The death rate from tuberculosis is higher than that from HIV/AIDS among all infectious diseases in the world. Due to mutation in Mycobacterium genomes and other structural changes in it can resist the typical inhibitory medicines.[2] The emergence of resistance has complicated illness management strategies and treatment, particularly when a patient also co-infected HIV. Tubercle bacillus genetic mutant selection plays a critical part in the emergence and development of the resistant strain. The two primary categories that are frequently observed are both genetic and phenotypic resistances. Changes in bacteria's genetic structure that end in antibiotic resistance are also caused by chromosomal gene mutation. Drug-resistant TB is on the increase due to a combination of host genetics, mycobacterial virulence, HIV infection, and inadequate patient care. Single nucleotide polymorphisms, chromosomal gene rearrangements encoding the drug target, and therefore the metabolization of prodrugs by enzymes to their active forms all contribute to the development of drug resistance in Mycobacterium. Drug resistance also can result from mutations that reduce drug

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accumulation in the bacterium medicines inactive. Mutation may reduce the medications' capacity to bind to the target genes.[3] Resistance can arise within the bacterium when the target genes' expression is boosted by mutation to the point that the medications are no longer able to inhibit the target.

2. Types of Drug-Resistance TB

1. Monoresistance: Resistance to any one first-line anti-TB drug only.
2. Polydrug resistance: Resistance to more than one first-line anti-TB drug.
3. Multidrug resistance: (MDR): Resistance to both isoniazid and rifampicin.
4. Rifampicin resistance: (RR): Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.
5. Extensive drug resistance (XDR): Resistance to any fluoroquinolone, and at least one of second-line injectable drugs like capreomycin, kanamycin, and amikacin in addition to multidrug resistance.

3. Causes of Drug Resistance

Drug resistance may be a biological phenomenon that has been observed in Mycobacterium tuberculosis since the invention of the first anti-TB drug, streptomycin.[4] Many patients who were injected with streptomycin as first line anti-TB drug were brought from the dying and their sputum became temporarily beyond M. tuberculosis. But despite continuing to receive treatment, they soon began to excrete bacilli that were immune to streptomycin in the laboratory.[5]

With the arrival of Thioacetazone and para-amino salicylic acid in 1948 and isoniazid in 1952, it had been clear that combination chemotherapy was the key to preventing the development of resistance. Initial combination regimens required 18 months of treatment, but the invention of rifampicin in 1957, the foremost powerfully sterilizing anti-TB drug, precede for development of the shorter and simpler more effective isoniazid and rifampicin containing regimens known as short-course shorter and more effective isoniazid and rifampicin containing regimens known as short course chemotherapy.[6] As a part of the worldwide TB control strategy called DOTS (Directly Observed Treatment Short-course), these regimens became the standard of care even in resource limited settings starting in 1993.

Outbreak of MDR-TB was initially thought to be driven by Nosocomial transmission particularly among HIV-positive patients. As DST laboratory capacity improved in resource-limited settings and global drug-resistant TB surveillance efforts grew, it became clear that MDR-TB was even more common throughout the world and a growing threat to the general public health.[7]

The causes of the worldwide spread of MDR-TB include the following:

- Chaotic treatment before the deceased 1980s, many countries weren't using standard protocols for the treatment of TB and did not have systems in place to support patients. Furthermore, TB treatment wasn't provided for free, contributing to poor adherence.[8] Even today, drug-resistant TB was often created very quickly during times of socioeconomic instability if there are unavailable of anti-TB drugs or other structural weakness in the health care system.

- Amplifier effect of short-course chemotherapy. Once drug resistance has been created, the DOTS strategy can curiously exacerbate the matter. In figure, the initial strain has poly-drug resistance, but as a result of repeated use of short-course chemotherapy, it becomes resistant to all first-line anti-TB drugs.[9] Amplification of drug resistance patterns through repeated courses of DOTS short-course chemotherapy continues to be a serious major epidemic in many parts of the world that do not have the resource to diagnose or treat drug-resistant TB correctly.

- Community transmission within the 2000s, it had been believed that resistance mutations conferred a loss of fitness; therefore, the transmission of resistant strains would be self-limit. This has not turned out to be the case. Current models indicate that in most countries, the majority of TB patients were infected initially with MDR-TB strains, instead of slowly acquiring resistance caused by inadequate or irregular treatment.[10]

3.1. Molecular Mechanisms

Antibiotics resistance in M.tuberculosis has been shown to result from spontaneously mutations in several chromosomal genes, and this common mutation provides the necessary interaction between each anti-tuberculosis drug and its specific specified target. Known to alter interactions.[11]

4. Treatment of Drug Resistant Tuberculosis

4.1. Treatment of rifampin resistance TB

If rapid molecular testing for tuberculosis drug resistance detects rifampicin-resistant tuberculosis, starts treatment with recommended regimen and wait for drug susceptibility test results are available.[12] If drug susceptibility testing shows susceptibility to all drugs, assess the risk of resistance on a case by case basis.[13] Low-risk patients should, starts with a baseline regimen and continue for 6 months, regardless of how long the MDR-TB regimen has been used. MDR-TB regimens should be maintained in high-risk patients (eg. Re-treatment cases, contacts of MDR-TB patients, of alcohol and drug users).

4.2. Treatment of isoniazid resistant TB

Isoniazid one of the most important first-line drugs for the treatment of tuberculosis, isoniazid has potent bactericidal

activity against M. tuberculosis. However, single-drug resistance to isoniazid is recurring worldwide, with an estimated 8% of tuberculosis patient being accepted.[14] A recent methodology analysis and meta-analysis compared the treatment outcomes of isoniazid-resistant and drug-susceptible tuberculosis and found that treatment of isoniazid-resistant tuberculosis with first-line drugs had a higher rate of treatment failure and recurrence. Furthermore, this in addition, the study found that standardized empirical treatment of new isoniazid-resistant TB cases may have contributed to the increased rates of obtained drug resistance. Previous ATS, CDC and IDSA guidelines approved treatment with a standard four-drug regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) for 6 months, with isoniazid treatment discontinued after DST results became known and if isoniazid resistance was detected.[15]

The addition of a fluoroquinolone to this regimen significantly increased treatment success compared to rifampin, ethambutol, and pyazinamide administered daily for 6 months (with or without isoniazid). When evaluating the effect of shortening the duration of pyazinamide administration (ranging from 1-3 months) in regimen containing fluoroquinolones, the treatment success rate was very high, with 117 of 118 patients successfully treated. On the other hand, there was no significant difference in results when comparing shorter pyrazinamide regimens with regimens containing both fluoroquinolone and pyrazinamide for > 6 months did not show significant difference results.[16] Similar results were obtained when the correlation was restricted to patient receiving the next generation fluoroquinolones, namely moxifloxacin, levofloxacin and gatifloxacin.

5. Management of Drug Resistance TB

5.1. Management of mono and polydrug resistance TB

Patient with single and multi-drug resistant strains of M. tuberculosis is not classified as MDR or XDR-TB. Single-resistance is described to two or more first-line drugs other than rifampicin and isoniazid. Routine screening for single- and multidrug-TB in all the TB patients is not recommended because the majority of patients with ingle and multidrug-resistance TB will be cure with standard first-line chemotherapy.[17,18]

Treatment of patients with single- and multidrug-resistant TB given the oddity of streptomycin, definitive randomized or controlled clinical trials have not been controlled to determine the best treatment options for some resistance TB medicine. Evidence-based advice from the pre-rifampicin era, observational studies, conventional principles of microbiology and TB treatment, extrapolated from anecdotal evidence and expert opinion.[19] The design of treatment regimens for single and multidrug resistant TB should be experimental and should be done under the supervision of the provincial TB clinical trial panel. Treatment history, DST pattern, and the possibility that strains of M. tuberculosis have acquired additional resistance should be considered before an appropriate treatment regimen is determined.

Some of the specific issues that need consideration when designing a desirable regimen include:

5.1.1. Timing of DST results

4044 Due to the delay in culture time and the absence of DST, a DST result resulting in a change of treatment may not be accurately reflect the 4044 bacterial population at the time of reporting as it reflects the bacterial population at the time of reporting.[20] sputum sampling point. single- and multidrug-resistant TB assume that the concept of resistance does not change during this time period and should not be applied if further resistance to any drugs is suspected.

5.1.2. Use of Pyrazinamide DST Results

DST results for pyrazinamide are unreliable and resistance to pyrazinamide should be inferred based on the treatment history; in this case an alternative diet should be used.[21] However, the inclusion of pyrazinamide in the diet should be considered under certain circumstances, as a significant proportion of patients may still carry strains susceptible to pyrazinamide.

5.1.3. Development of further resistance

Additional resistance should be suspected if the patient receives only one or two functionally equivalent drugs for a one month or more.[22] For example, pyrazinamide is not considered a good companion drug to prevent resistance. If the patient is tolerating only rifampicin and pyrazinamide (due to isoniazid and ethambutol resistance), stabilization of rifampicin may develop. Therefore, it is important to determine which functional drugs the patient received from the time of sample collection to the time of initiation of the treatment regimen.[23]

5.2. Management of patients with MDR-TB

Multidrug resistant tuberculosis-which occurs when strains of the TB bacteria are least resistant to isoniazid and rifampicin-is clinically important because it significantly increases the likelihood of treatment failure, further acquired resistance, and death.[24] Its prevalence is highly variable and often reflects poorly organized treatment or nursing homes) where there has been an outbreak of resistant strains. Initially treatment of patient with suspected multi-drug resistant tuberculosis may reasonably use extended empiric regimens, particularly if the patient has extensive pulmonary disease or other forms of tuberculosis. Dangerous lung diseases such as millet or meningococcal disease.[25] For patients who already have the diseases,

it is important to give at least four drugs to which the mycobacteria are sensitive, usually three oral drugs and one injectable. Typically, an injectable drug such as an aminoglycoside is given for three to six months after the first the sputum cultures changes from the test positive for M tuberculosis to testing negative, and the patient continues on the antimicrobial. Orally for the next 15 to 18 months last positive sputum culture.

The treatment of the underlying infection for people with multi-drug resistant bacilli was a dilemma because the only cures were isoniazid and rifampicin. The combination of pyrazinamide and ciprofloxacin was considered as appropriate.[26] Experimentally, the combination of pyrazinamide and ciprofloxacin was considered appropriate. There was a favorable outcome for an antimicrobial effect in phagocytosis. In recent cases of severe hepatotoxicity associated with prophylaxis including pyrazinamide and rifampicin or pyrazinamide and fluoroquinolone, deficiency data on long term effectiveness of these treatments.

5.3. Management of patients with XDR-TB

The concept of broad-based drug-resistant TB management is similar to that of MDR-TB. However, the design of a broad-based drug-resistant TB regimen is more complex and referral to an expert are recommended. Although, DSTs for ethambutol, pyrazinamide, and second-line anti-tuberculosis drugs do not have high capacity or reliability, they appear to provide clinically useful information to guide TB regimen. MDR and XDR TB. Any drug for which the distinction is selective to class1 and any remaining drugs available from class 3 or 4 are added to the regimen. class 5 drugs are also often required for dietary intake to make a regimen as well. The optimal number of drugs and the duration of treatment remain uncertain. Treatment success was highest if at least six drugs were used in the enhancement phase and four in the continuation phase.[20] The recommended rate is maximum when the duration of enhancement phase is 6.6to9.0 months and the total duration of treatment is 20.1 to 25.0 months.[27] These results suggest that optimal treatment of XDR-TB requires a similar but more drugs-intensive time than the treatment for non-prolonged MDR-TB.

The use of a dilating fluoroquinolones, such as moxifloxacin, markedly improved treatment outcomes for of widespread drug-resistance tuberculosis, even when a DST showed resistance to the illustrated fluoroquinolone.[28] Linezolide may also be a valuable drug for the treatment of widespread drug-resistant tuberculosis. New drugs, such as bedaquiline and delamanid, and new combination regimens 55 are expected to improve cure rates for widespread drug-resistant TB. Adjuvant surgery should be considered in limited cases, and strict respiratory infection control measures are also important.

6. Conclusion

Tuberculosis is a infectious diseases caused by the M. Tuberculosis which can be treated by1st and 2^{nd} line anti-TB drugs but genetic mutation in M. Tuberculosis results in development of resistance towards anti-TB drugs. The death rate from tuberculosis is higher than that from HIV/AIDS among all infectious diseases in the world. Resistance can arise in the bacterium when the target genes' expression is boosted by mutation to the point that the medications are no longer able to inhibit the target, it can be a monodrug resistance, polydrug resistance, multiple drug resistance, rifampicin resistance & extensive drug resistance. for treatment of isoniazid resistance TB with 6 months of daily rifampin, ethambutol, and pyrazinamide (with or without isoniazid), adding a fluoroquinolone to this regimen was associated with significantly major treatment success. HIV is a powerful risk factor for development of all forms of TB including DR-TB. Management of mono and poly resistance can be done by DST and use of pyrazinamide. Patient with XDR-TB occurs when tuberculosis strains are resistant to at least isoniazid and rifampicin. The use of dilatory fluoroquinolones, such as moxifloxacin, remarkable improved treatment outcomes of XDR-TB even when a DST demonstrated resistance to an illustrative fluoroquinolone.

7. Source of Funding

None.

8. Conflict of Interest

None.

References

1. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City Turning the tide. *New Engl J Med*. 1995;333(4):229–33.
2. Gohil CJ, Patel PR, Gohil JJ. Antibiotic Drug Resistance TB in India. *Int J Pharm Chem Anal*. 2021;8(4):145–51.
3. Keshavjee S, Farmer PE. Tuberculosis drug resistance and the history of modern medicine. *New Engl J Med*. 2012;367(10):931–6.
4. Lin H, Shin S, Blaya JA, Zhang Z, Cegielski P, Contreras C. Assessing spatiotemporal patterns of multidrug-resistant and drug-sensitive tuberculosis in a South American setting. *Epidemiol Infect*. 2011;139(11):1784–93.
5. Kochi A, Vareldzis B, Styblo K. Multi-Drug resistant tuberculosis and control. *Resistant Microbiol*. 1993;144:104–10.
6. Gohil CJ, Noolvi MN. Types of p53/MDM2 Interaction Inhibitors. *Eur J Bio Med Pharm Sci*. 2018;5(11):143–7.
7. Damtie D, Woldeyohannes D, Mathewos B. Review on Molecular mechanism of first line antibiotic resistance in Mycobacterium tuberculosis. *Mycobact Dis*. 2014;4(6):1–4.
8. Gohil CJ, Noolvi MN. p53 Protein: Master Regulator of Apoptosis and its Application in Cancer Therapy. *Int J Pharm Bio Arch*. 2019;10(3):154–64.
9. De Vos M, Muller B, Borrell S, Black PA, Van Helden P. Putative compensatory mutations in the rpoC gene of rifampin-resistant Mycobacterium tuberculosis are associated with ongoing transmission. *Antimicrob Agents Chemother*. 2013;57(2):827–32.

10. Telenti A, Imboden P, Marchesi F, Lowrie D, Cole S. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. *Lancet*. 1993;341(8846):647–50.
11. Gohil CJ, Noolvi MN. Non peptidic small molecular inhibitors of the p53-MDM2 interaction. *Int J Pharm Chem Anal*. 2019;6(4):104–9.
12. Brandis G, Hughes D. Genetic characterization of compensator evolution in strains carrying rpoB Ser531Leu, the rifampicin resistance mutation most frequently found in clinical isolates. *J Antimicrob Chemother*. 2013;68(11):2493–7.
13. Zhang Y, Heym B, Young AB, Cole D. The catalase-peroxidase gene and isoniazid resistance of Mycobacterium tuberculosis. *Nature*. 1992;358(6387):591–3.
14. Munir A, Kumar N, Ramalingam SB, Tamilzhalagan S, Shanmugam SK, Palaniappan AN. Identification and Characterization of Genetic Determinants of Isoniazid and Rifampicin Resistance in Mycobacterium tuberculosis in Southern India. *Sci Rep*. 2019;9(1):10283.
15. Gohil CJ, Noolvi MN. Solvent-free Synthesis of Amide: A Novel Technique of Green Chemistry. *Asian J Pharm Clin Res*. 2021;14(5):99–102.
16. Zhao X, Yu H, Yu S, Wang F, Sacchettini JC, Magliozzo RS. Hydrogen Peroxide-Mediated Isoniazid Activation Catalyzedby Mycobacterium tuberculosis Catalase-Peroxidase (KatG) and Its S315T Mutant. *Biochemistry*. 2006;45:4131–40.
17. Shi W, Zhang X, Jiang X, Yuan H, Lee JS. Pyrazinamide inhibits trans-translation in Mycobacterium tuberculosis. *Science*. 2011;333(6049):1630–2.
18. Takayama K, Kilburn JO. Inhibition of synthesis of arabinogalactan by ethambutol in Mycobacterium smegmatis. *Antimicrob Agents Chemot*. 1989;33(9):1493–9.
19. Ahmad S, Jaber AA, Mokaddas E. Frequency of embB codon 306 mutations in ethambutol-susceptible and -resistant clinical Mycobacterium tuberculosis isolates in Kuwait. *Tuberculosis*. 2007;87(2):123–9.
20. Safi H, Sayers B, Hazbon MH, Alland D. Transfer of embB codon 306 mutations into clinical Mycobacterium tuberculosis strains alters susceptibility to ethambutol, isoniazid, and rifampin. *Antimicrob Agents Chemot*. 2008;52(6):2027–34.
21. Safi H, Lingaraju S, Amin A, Kim S, Jones M, Holmes M, et al. Evolution of high-level ethambutol-resistant tuberculosis through interacting mutations in decaprenylphosphoryl-β-D-arabinose biosynthetic and utilization pathway genes. *Nat Genet*. 2013;45:1190–7.
22. Gohil CJ, Noolvi MN, Patel CN, Sen DJ. Review of Design Approaches and Clinical Progress of MDM2 Inhibitors. *Int Res J Pharm*. 2021;12(11):1–7.
23. Crofton J, Mitchison DA. Streptomycin resistance in pulmonary tuberculosis. *Br Med J*. 1948;2:1009–1015.
24. Finken M, Kirschner P, Meier A, Wrede A, Bottger EC. Molecular basis of streptomycin resistance in Mycobacterium tuberculosis: Alterations of the ribosomal protein S12 gene and point mutations within a functional 16S ribosomal RNA pseudoknot. *Mol Microbiol*. 1993;9:1239–1246.
25. Okamoto S, Tamaru A, Nakajima C, Nishimura K, Tanaka Y, Tokuyama S, et al. Loss of a conserved 7-methylguanosine modification in 16S rRNA confers low-level streptomycin resistance in bacteria. *Mol Microbiol*. 2007;63:1096–1106.
26. Gohil CJ, Noolvi MN, Patel CN, Sen DJ. Chemical Classification of MDM2 Inhibitors. *Int J Pharm Chem Anal*. 2021;8(2):41–44.
27. Goss WA, Deitz WH, Cook TM. Mechanism of action of nalidixic acid on Escherichia coli. II. Inhibition of deoxyribonucleic acid synthesis. *J Bacteriol*. 1965;89:1068–1074.
28. Fàbrega A, Madurga S, Giralt E, Vila J. Mechanism of action of and resistance to quinolones. *Microb Biotechnol*. 2009;2:40–61.

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