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CHALLENGES IN THE DEVELOPMENT OF DRUGS FOR THE TREATMENT OF TUBERCULOSIS – A REVIEW

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Abstract:

A significant hazard to human health is tuberculosis infection, and in the early 21st century, the disease's prevalence has dramatically increased worldwide. Mycobacterium tuberculosis is the organism that causes tuberculosis, and it uses a number of tactics to thrive in different host lesions. Due to these survival strategies, the infection is immune to currently available medications, which is a significant reason why tuberculosis cannot be effectively controlled. There are numerous medications that can be used in therapeutic settings, and a number of prospective substances are also being screened, produced, or tested in preclinical or clinical research. Effective and long-lasting progress in the creation of anti-tuberculosis medications will primarily depend on an accurate comprehension of the complicated the pathogen's interactions with the host human. There is a lot of information to support the characteristics of tuberculosis. In this work, we emphasized the difficulties in creating innovative medications with strong bacteriostatic or bactericidal activity that shorten the minimal amount of time needed to treat tuberculosis infection.

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INTRODUCTION:

Robert Koch discovered Mycobacterium tuberculosis, the organism that causes tuberculosis (TB) infection, in 1882. The global TB epidemic has not abated, meanwhile, and in 2010 there are projected to be more new cases than ever before (9,8 million). Over one-third of these additional TB cases—or around 80%—will be identified in China and India, two of the 20–25 countries with the greatest burdens. An analysis of the TB only 35 of the 134 nations that reported cases between 1998 and 2007 had per capita drop rates that exceeded 5% annually[1].The total incidence of TB per person is, however, falling at an estimated rate of 1% per year, according to mathematical modelling and surveillance data. This finding suggests that the global incidence rate will decline by 2015. The total number of new TB cases continues to climb, despite the fact that the global population is increasing at a rate of roughly 2% annually[2]. This research highlights the relative ineffectiveness of current TB management regimens and the ineffectiveness of public health systems, particularly in developing nations. Despite the availability of anti-TB medications created during the past five decades, one-third of the global population still has tuberculosis. Latent or dormant M. tuberculosis. These groups are typically asymptomatic but continue to have a high lifetime risk of the disease reactivating and pose a serious threat to the propagation of the illness. Since at least three effective drugs must be used in combination to effectively treat the disease while preventing the development of further drug resistance, the existence of multidrug resistant (MDR) and extremely drug resistant (XDR) TB strains and declining treatment options is currently exacerbating the TB epidemic[3].Combination dosage of isoniazid (INH) and rifampicin, which uses a new mechanism of action, was the final medication identified and licensed for the treatment of TB (RIF). But MDR-TB is immune to both INH and RIF. MDRTB and XDR-TB cases are the consequence. either an initial bacterial illness caused by a drug-resistant strain or subpar treatment durations or methods. Lower cure rates for MDR-TB have been noted, ranging from 50 to 70%[4], despite the concurrent chemicals' widespread introduction for usage in TB treatment many years ago. INH and RIF, all fluoroquinolones, and at least one of the second-line anti-TB injectable medications such as amikacin, kanamycin, and/or capreomycin are all ineffective against XDR-TB. The fatality rates from these resistant TB infections are extremely high[3]. Additionally, the presence of drug-drug interactions precludes the simultaneous administration of certain existing anti-TB treatments and other drugs for chronic conditions[5]. It is necessary to create numerous efficient treatments that accomplish multiple goals, including. Reduced duration of therapy, effectiveness against MDR-TB and XDR-TB strains, less complicated dosing schedules, and medicines that can be delivered with drugs for other chronic conditions. As many of the upcoming compounds are either derivatives of currently used compounds or affect the same cellular processes as medications currently in use, it is challenging to match the range of expectations for this desired target product profile[5,6]. The analogues and derivatives under development may also be hindered by cross-resistance, poor economics surrounding the development of TB drugs, a lack of enough funding, and other factors. government incentives. The goal of this study was to assess if there are enough promising drugs in the TB pipeline to successfully manage the epidemic on a worldwide scale. To improve the focus of research and development efforts, we described a mechanism of action against tuberculosis infection, offered a perspective, and noted the fundamental knowledge gaps and technical challenges in the creation of TB drugs.

Mechanisms of Mycobacterium tuberculosis drug resistance

The current state of affairs regarding the expanding number of TB patients who are drug-resistant is extremely unsettling and shows a huge weakness in the ability to control disease on a worldwide basis[5,6].Any viral infection that compromises the human immune system can create the possibility of developing new TB cases by reactivating the TB infection. According to recent research, the proportion of MDR cases exhibiting resistance to different antibiotic classes ranged from 0 to 22.3%. 6 A projected 40.000 new cases of XDR-TB will appear annually worldwide[5,7]. Understanding the processes through which mycobacterial cells withstand anti-tuberculosis medications is crucial. The development of novel anti-tuberculosis medications and techniques for preventing the emergence of such drug resistance will be made possible by an understanding of the mechanism[7].

Very soon after the first drug, streptomycin, was introduced, TB drug resistance started to develop. Genetic mutations result from chromosomal mutations that happen between 106 and 108 mycobacterial replications. resistance to a prescribed antibiotic[5].The benefit of utilizing a multidrug regimen is that there is no correlation between the chromosomal regions responsible for medication resistance. As a result, the likelihood of building resistance to three medications taken at the same time drops to 1018 to 1020, which is

an exceedingly unlikely or improbable scenario[8]. It has taken a tremendous amount of work to pinpoint the molecular mechanisms behind medication activity and resistance in the TB virus. For the purpose of highlighting the need for novel drug design that could shorten treatment times and prevent the development of drug resistance in the treatment of tuberculosis infections, the drug action and the bacterial resistance mechanism of a few commonly used drugs have been briefly summarized.

Resistance to anti-TB medications

Isoniazid (INH)

Isoniazid (INH) has been the most popular treatment for TB and associated latent infections since it was first introduced as an anti-TB medicine in 1951[9,10]. INH enters the cell as a pro-drug that has been activated by the katG gene, which codes for catalase-peroxidase. In order to activate INH and enable its interactions with numerous hazardous reactive species in the bacterial cell, this enzyme's peroxidase activity is crucial[11]. The reactive species—typically oxides, hydroxyl radicals, and organic moieties—degrade cell wall constituents, leading to a loss of cellular integrity and, ultimately, bacterial mortality[12]. INH has a substantially greater resistance frequency of 10[5,6] than the majority of anti-tuberculosis medications[13] . Enoylacyl carrier protein reductase, or InhA, is an enzyme that aids in the elongation of fatty acids in radicals.

Rifampicin(RIF)

Rifampicin (RIF) Rifampin, rifapentine, and rifabutin are first-line treatments frequently combined with other medications for the treatment of tuberculosis infections. Short therapy courses were created as a result of the usage of RIF in conjunction with PZA/INH, cutting the length of typical TB treatment from a year to six months. RIF is thought to prevent bacterial DNA-dependent RNA polymerase from functioning. Four distinct subunits make up RNA polymerase and, and the genes that code for each of these subunits are located at the loci rpoA, rpoB, rpoC, and rpoD, respectively. RMP stops transcription by attaching to the RNA polymerase subunit, which prevents RNA synthesis and causes the organism to perish. Missense mutations in the gene cause RIF resistance. In M. RIF resistance in tuberculosis occurs between 10^{-7} and 10^{-8}, [5] times per year. The 81-base-pair (bp) (27-codon) core region of the gene that codes for the RNA polymerase -subunit is where the resistance in RIF originates from[19].The 81-bp core region of the gene, which contains 96% of all mutations, is located between codons 507 and 533. The most frequent mutations are found in the codons Ser531Leu, His526Tyr, and Asp516Val[20].

Pyrazinamide (PZA)

The first-line medication PZA is essential for the treatment of tuberculosis. PZA has a superior sterilizing impact on tubercle bacilli that are semi-dormant. PZA, INH, and RIF make up the core of contemporary TB treatment therapy because they destroy dormant bacilli in an acidic environment. In PZA contributed a significant part in bringing down the length of TB treatment from the prior 9–12 months to the present 6 months[21]. Prodrug PZA is transformed by the mycobacterial enzymes pyrazinamidase and nicotinamidase into its active form, pyrazinoic acid (POA). PZA is generated intracellularly, passively diffuses into the tuberculosis infection, and is then changed into POA by the pyrazinamidase enzyme within the cell. Massive POA buildup in the bacterial cytoplasm is made possible by the mycobacterial cell's ineffective efflux system, which disrupts the membrane potential[22,23]. PZA resistance's precise mechanism is still unknown. It is understood that pyrazinamidase activity is typically lost in PZA-resistant bacterial strains[24], both cloning72–97% of all PZA-resistant clinically isolated specimens possess a mutation, either in the structural gene or in the putative promoter region of the gene, according to sequencing investigations of the pyrazinamidase gene[25].

Ethambutol (EMB)

EMB, a first-line medication, is used with INH, RIF, and PZA in order to stop the development of mycobacterium-specific drug resistance. Although it has little effect on bacilli that are not reproducing, EMB is an active bacteriostatic agent for growing bacteria. Through a synthetic mechanism, EMB disrupts the mycobacterial cell wall and prevents the enzyme arabinosyl-transferase from participating in the formation of the cell wall[26]. Arabinogalactan synthesis is aided by this gene, which is encoded by arabinosyl-transferase. It has been suggested that the target of EMB activity within the TB organism is arabinosyltransferase [27]. According to studies, resistance to EMB results from random spontaneous genetic mutations that happen about 1 in 10^7 times in organisms. These mutations typically lead to an increase in the production of the enzyme arabinosyl-transferase, which outweighs the inhibitory effects of EMB. ATG-GTG, ATG-CTG, ATG-ATA, ATG-ATC, and ATG-ATT are five codon 306 mutations that, in EMB-resistant strains, cause three distinct amino acid changes (Val, Leu, and Ile)[28,29].Seventy to ninety

percent of all isolates that are EMB resistant have these five mutations[29]

CURRENT CHALLENGES IN THE TREATMENT

The recently found anti-TB medications developed through a series of clinical trials that lasted through the 1980s, especially in the 1950s to 1970s[30]. The subsequent 30 years, up until around 2000, were a fallow time for TB drug research and development. This gap greatly contributed to the significant difficulties currently faced by the community of drug developers working to improve active MDR-TB and XDR-TB treatments. Only four of the medications currently used to treat MDR-TB were created specifically to treat TB, and therapy for MDR-TB currently last 18 to 24 months[31].Nearly 30% of MDR-TB patients experience treatment failure as a result of subpar therapy[32]. There are very few therapy options for XDR-TB because the bacilli are resistant to both INH and RIF, as well as fluoroquinolones, which include injectable medications such aminoglycosides. The majority of MDR-TB and XDR-TB medications also have substantial adverse effects, such as nephrotoxicity and ototoxicity when aminoglycosides are used, hepatotoxicity when ethionamide is used, and dysglycemia when gatifloxacin is used[33].The great majority of TB cases and fatalities take place in developing nations, and around one in four of the deaths include HIV-positive individuals. According to reports, 11-2 percent of the 9,4 million people diagnosed with TB in 2009 also tested positive for HIV, with 80% of these morbidities occurring only in Africa[34]. Due to decreased compliance with therapeutic regimens brought on by more pills and limited access to healthcare, overlapping harmful side effects, burden, and drug-drug interactions. RIF-induced upregulation of the hepatic cytochrome (CYP P450) oxidase system is the main interaction between HIV and anti-TB therapy drugs[35]. According to studies, CYP accelerated the pharmacokinetic rate and reduced the effectiveness of a number of co-administered drugs, including HIV protease inhibitors[36]. It is highlighted that typical trench levels of several kinds of protease inhibitors cannot be attained when CYP450 inhibitors, such as ritonavir, are used. They have thus been demonstrated to engage in intracellular phosphorylation competition with rifampicin. As a result, these medications shouldn't be taken together. However, ritonavir with a cocktail of proteases raises the serum levels ofrifabutin, hence raising the toxicity that comes with it[37].For the majority of second-line TB medications, such as ethionamide, cycloserine, kanamycin, amikacin, capreomycin, and para-amino salicylate, which have been used for treating HIV patients with MDR- or XDR-TB strain co-infections for the past ten years, there aren't many studies on multiple drug interactions[38].In order to specifically target HIV-infected people and the interactions between anti-retroviral and already available second-line TB medications as well as those that are currently in clinical development, active case-finding procedures must be developed. Diabetes is known to triple the chance of acquiring active TB and, like HIV, is linked to the reduction of cell-mediated immunity[39]. In 2000, studies found that in India, diabetes-related smear-positive TB cases accounted for almost 20% of all cases[40]. In the interim, 42% of smear-positive TB cases in India by 2030 will be attributed to diabetes if the expected increase from 25 million diabetes patients in 2000 to 80 million in 2030 materializes and the risk ratio stays the same. Each diabetes-related TB case could also result in the infection of more people, increasing the overall TB burden in the neighborhood[41]. It is unclear what biological factors contribute to diabetics' poor anti-TB drug response and higher risk of MDR-TB development. However, it's thought that diabetes suppresses cell-mediated immunity, which leads to greater rates of tuberculosis infection.

Future TB infection resistance

There has been a dearth of medicine development for decades to treat TB and other pandemic diseases. The traditional strategy for developing anti-TB medications calls for replacing each approved drug in the present multi-drug regimen, but only after the new medication has been given the go-ahead for use as a single agent. The testing of multiple novel drugs simultaneously under the TB control initiative programme could significantly accelerate the research cycle, however ethical considerations should be taken into account while finding a workable approach to implement such clinical trial designs[5,6].

Adenosine Triphosphate (ATP) Synthase Inhibitors

Accessibility to the TB pathogen's genomic sequence has largely influenced the choice of novel TB therapeutic targets. However, research on the development of novel medications has demonstrated that target- and genome-derived techniques typically have only marginal therapeutic impact in the field of antibiotics[42].Studies have also demonstrated that the effectiveness of TB medications is significantly enhanced by switching the selection strategy from single-enzyme targeting to the level of the entire bacterial cell. The whole-cell screening method is however constrained by a lack of knowledge regarding the mode of action and the identification of the

pertinent ligands for internal infections[43]. The discovery of novel TB therapeutic agents like TMC207, a diarylquinoline that prevents ATP synthesis, and BTZ043, a benzothiazine that prevents arabinan synthesis[44,45], highlights recent successes utilising the whole-cell approach. TMC207 (R207910 or the J' compound) is effective against isolates of M. tuberculosis that are both drug-sensitive and drug-resistant[46,47].Additionally to having bactericidal effects on latent (non-replicating) tubercle bacilli, it may shorten the course of treatment[48]. In a mouse tuberculosis model, TMC207 exhibited the same inhibitory effects that would have been caused by the combination of isoniazid, rifampin, and pyrazinamide. However, employing TMC207 combined with a triple-drug regimen and the synergistic interaction with pyrazinamide resulted in a significantly higher rate of bacilli clearance[49]. Additionally, it has been shown that TMC207 increases the efficiency of a second-line medication combination in a mouse model of drug sensitivity[50].Additionally, TMC207 has been examined in a phase II dose range trial carried out for seven days in individuals with drug-resistant tuberculosis The findings show that clinically meaningful bactericidal activity was only obtained with a delayed beginning of response at the maximum dose (400 mg). The side effects of this treatment were manageable[51].In addition, a controlled trial with an 8-week treatment phase and a 24-week proof-of-efficacy phase was conducted to assess TMC207's effectiveness in treating patients with newly diagnosed, smear-positive pulmonary infections brought on by multidrug-resistant M. tuberculosis. The conversion to a negative sputum culture was faster with TMC207. These illustrations show how new TB therapy scaffolds can be found by using multi-dimensional signaling pathway blockage as the foundation

Protein Synthesis Inhibitors

Redesigning current regimens is another effective tactic for accelerating the pipeline for developing antibiotics and finding novel treatment scaffolds to utilize against resistant bacterial species. Different members of each antibiotic class have a similar core structure, and when an antibiotic is modified synthetically, its functional groups are rearranged while maintaining the antibiotic's core structure to increase the drug's activity. New structures like PNU-100480 and AZD-5847, which have been discovered to increase antibiotic activity, have been made possible by the customized forms of oxazolidinones (linezolid against Gram-positive infections)[44]. A novel class of antibacterial agent called 4-amino-1,2-oxazolidin-3-one (cycloserine) was applied for the first time. A broad-spectrum drug is cycloserine. antibiotic that has been used since 1955 as a second-line treatment for tuberculosis[52,53]. Linezolid (Zyvox), which was introduced by Upjohn in 2000, is the only medication in the class that has been approved by the Food and Drug Administration (FDA) for the treatment of nosocomial pneumonia and skin and soft tissue infections brought on by Gram-positive bacteria in the modern era when many bacterial strains are developing antibiotic resistance. [52]. Linezolid was the first oxazolidinone to be used off-label to treat MDR-TB, but its prolonged use has not been recommended due to several side effects, including thrombocytopenia, anaemia, peripheral neuropathy, and optic neuropathy.[54]. The minimum inhibitory concentration (MIC) for M. tuberculosis is between0,125-1,0g/mL; for better in vivo activity and less toxicity, PNU-100480 (Sutezolid), a linezolid analogue developed by Pizer with comparable MICs for M. tuberculosis, replaced it due to its severe side effects. [52,55,56]. PNU-100480 demonstrated more strong bactericidal effect in contrast to linezolid in a research comparing the mouse model of tuberculosis, even at lower drug doses. [44]. In addition, PNU-100480 increased the bactericidal activity of regimens containing several first-line medications by a specific factor, suggesting that it might be useful for cutting the length of treatment for drug-susceptible TB by 1-2 months[57]. An earlier study examined its pharmacokinetics, pharmacodynamics, safety, and tolerability in people by administering PZA was added to the various doses on days 27 and 28, i.e., 100, 300, or 600mg twice daily; 1200mg once day for 14 days; or 600mg twice daily for 28 days. A sixth cohort received linezolid at a dose of 300 mg per day for four days. All of the doses were well tolerated and had no fatal side effects. In healthy volunteers who received 600 mg or 1200 mg of PNU twice daily or once daily, respectively[58] . The Cmax level was 0,94 or 2,01g/mL, and the half-life was 2,92 or 3,38h. Concentrations at the trough were kept at or above the MIC. An EBA analysis recommends 14 days of daily testing at 600 mg and 1200 mg. AstraZeneca uses the lead-containing drug AZD-5847 (posizolid) to treat tuberculosis. It has a MIC equivalent. linezolid and PNU100480 for treating M. tuberculosis, and has demonstrated great efficacyexperiment involving a mouse model of TB[53]. Although the test organism experienced nausea with the 600 mg oral dose, the Cmax was 2,60 g/mL in fasting participants and 5,66 g/mL in fed subjects, with a half-life of nearly 8 hours[53].In healthy volunteers, a daily oral dose of 800, 1600, and 2400mg for 14 days was well tolerated and increased Cmax by up to 10g/mL, but the rise was not dose-proportional[53].Similar to this,

cephalosporins like cefaclor and ceftazidime permeate the bacterial membrane more effectively and are more resistant to being destroyed by the resistance enzyme lactamase. Third-generation cephalosporins can also be broken down by novel -lactamases. Consequently, less sensitive fourth-generation compounds like cefepime were created. by -lactamase to cleave[45] 64% of the new chemical scaffolds that were registered between 1981 and 2005 are found in cephalosporins and other semi-synthetic antibiotics[59].

Delaminid(OPC 67683), Nitromidazole (PA-824)

Prodrug PA-824, which is made from metronidazole, has demonstrated potent efficacy against anaerobic bacteria and protozoa (trichomoniasis, amoebiasis). With a MIC90 of 0,125g/mL against both drug-resistant and non-drug-resistant strains of M. tuberculosis, PA-824 has shown significant sterilizing and anti-tuberculosis activity[60]. Both latent (non-replicating or slowly reproducing) and actively replicating TB bacteria are susceptible to it. Because of its antibacterial properties, it prevents aerobic includes preventing the synthesis of certain proteins and lipids needed for the survival and reproduction of bacterial species. Nitric oxide gas is released during enzymatic nitro-reduction, poisoning the respiratory system, killing the latent bacteria[61]. In TB murine models, PA-824 showed bactericidal action both during the initial phase and the continuation phase, where it eliminated the bacteria that had survived for the first two months[62]. When administered individually, PA-824 exhibited bactericidal properties similar to those of isoniazid and moxifloxacin[63].Results from the assessment of PA824 in combination therapy with first-line medications to reduce the length of treatment were favourable. Its daily consumption is combined with PZA and moxifloxacin has made a significant contribution to an exceptional sterilising regimen, indicating the ability to speed up the healing process[64].When compared to the first-line combination of rifampin, INH, and PZA, a study that replaced isoniazid with PA-824 resulted in much fewer lungs CFU after 2 months of treatment as well as a rapid conversion to culture-negative[65]. It has been proposed that it could replace rifampin as the first-line medication during the intensive phase of therapy, thereby reducing the need for treatment of multidrug-resistant tuberculosis[66]. Compared to the control, TB patients received various dosages of PA-824 orally (standard first-line TB treatments). The findings supported PA-824's potential bactericidal abilities, indicating that it will soon be incorporated into a regimen for prompt and efficient therapy. drug-resistant and drug-susceptible TB[67].

DNA gyrase Inhibitors

Fluoroquinolones are a class of antibiotics that kill M. tuberculosis by binding to DNA gyrase and causing double-stranded breaks in the organism's DNA. The gyrase A (gyrA) and gyrase B (gyrB) genes, respectively, encode two A and two B subunits of DNA gyrase[68]. The nalidixic acid compounds moxifloxacin and gatifloxacin, which are presently being researched for DS-TB, were previously used instead of ofloxacin and levofloxacin. In a Phase III trial, gatifloxacin by the Oflotub Consortium (NCT00216385) and moxifloxacin by Bayer and the TB Alliance (NCT00864383) were assessed as first-line treatments to replace ethambutol (gatifloxacin, moxifloxacin) with isoniazid (moxifloxacin) to accelerate DS-TB treatment [69]. Moxifloxacin and gatifloxacin have been demonstrated to have potential in vitro, in mice models of TB, as well as in humans, according to a number of studies[70,71,72,69]. Additionally, the toxicities that may be associated with these medications tend to vary by group. However, gatifloxacin has been linked to disturbances in the metabolic state of glucose in diabetic and elderly people [73]. In contrast, treatment with moxifloxacin did not result in this kind of side effect [74]. The fact that gatifloxacin and moxifloxacin are not powerful CYP enzyme system inhibitors or inducers and are also not extensively metabolised has also been proven in studies to decrease drug-drug interactions [75]. RIF is a first-line TB treatment that reduced cases by 30%. According to the pharmacokinetic and dynamic conditions of moxifloxacin, RIF induce glucuronidation or sulphation which decreased moxifloxacin plasma level in 18 out of 19 patients. Plasma concentrations of moxifloxacin. [76,77]. By 2015, a 4-month fluoroquinolone-based treatment for drug-susceptible TB might be implemented in clinics to treat the disease. We anticipate that the Phase III trials will provide more information on the treatment's safety and effectiveness.

CONCLUSION:

Examples of prolonged TB transmission and increased susceptibility of large populations to infection and sickness are described in this paper. It is evident that the amount of resistance to all currently licensed anti-TB medications is controlled by particular genetic abnormalities in the bacterium that causes mycosis. As bacterial resistance rises, prolonged usage of a particular antibiotic causes it to lose effectiveness. In order to prevent the emergence of serious bacterial resistance issues, the appropriate medication should be administered at the appropriate time. This study also outlined potential promising bactericidal treatments

for both drug-susceptible and drug-resistant TB that can be used to quickly prevent the disease and treat it effectively. The WHO also recommends adjusting the medicine dosage on a regular basis according to a set schedule. 78 In addition to these strategies, it's critical to create new medications that prevent the development of drug resistance in bacterial cells. We concluded that control initiatives have been less successful than anticipated in preventing TB transmission, mainly because due to the slow diagnosis and treatment of patients. We sincerely expect that improving antibiotic properties will contribute to the creation of better TB control methods. If TB is to be eradicated as a global public health concern, these TB control initiatives will need to be strengthened and increased. Maintaining the fundamentals of chemotherapeutic treatment, including the use of drugs like moxifloxacin and gatifloxacin, should now be the top focus.

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