Original Article

Development Of Pretomanids And Their Therapeutic Uses In The Treatment Of Tuberculosis

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Abstract

The most common infectious cause of death worldwide is tuberculosis (TB). Although new anti-tuberculosis medications have been developed, controlling resistant Mycobacteria remains difficult. New drug development and targeted drug delivery techniques have the potential to shorten treatment times, lessen side effects, and improve treatment outcomes. Pretomanid is the third drug authorised as a component of a novel therapeutic regimen for treating drug-resistant TB, following bedaquiline and delamanid. It is one of the promising medications that has the potential to change TB therapy and carry out the World Health Organization's End TB strategy. Pretomanid's efficacy has been documented in numerous observational and clinical trials. The pretomanid-based regimen is advised under an operational research framework, which forbids its wider and programmatic usage, although long-term safety data in humans are still lacking. Before pretomanid can be hailed as a promising candidate treatment for different types of TB and certain patients, in our opinion, further research must be done. Pretomanid development and its clinical use in the treatment of Mycobacterium tuberculosis are updated in this study. Pretomanid is administered orally, 200 mg once day with food, along with bedaquiline (200 mg three times weekly for 24 weeks after 400 mg once daily for two weeks), for a total of 26 weeks.

Keywords: - Mycobacterium tuberculosis, drug-resist tuberculosis, treatment of tuberculosis.

INTRODUCTION:-

The largest infectious cause of death worldwide is tuberculosis (TB), an infectious disease brought on by the bacteria Mycobacterium tuberculosis [1-3]. Particularly in low- and middle-income countries, it is still the main infectious cause of morbidity and mortality today [4, 3].Although there has been a concentrated effort on a global scale to reduce TB mortality, it is still difficult due to the massive public health burden and serious adverse health effects [4, 5]. According to the World Health Organization (WHO), 9.9 million new cases of TB are anticipated to be identified in 2020 [3]. Additionally, there were considerable regional differences in TB incidence rates. A substantial TB burden (>100,000 incident cases) was identified in thirty nations, particularly in low- and middle-income regions instances),making over 87% of all cases worldwide [3]. Despite tremendous advancement over time,The Sustainable Development Goals of the United Nations call for a world without TB or with an incidence of It is still difficult to attain a TB patient incidence of fewer than one per million persons [6, 7]. It has been concerning to see first-line anti-tuberculosis drugs (rifampin and isoniazid) developing resistance. Drug-resistant TB (DR-TB) has been identified in more patients over the past ten years [8, 9]. 71% (2.1/3.0 million) of those with bacteriologically confirmed pulmonary TB worldwide in 2020 underwent testing for 3 resistance to rifampicin. A total of 157, 903 patients—132, 222 MDR/RR-TB cases and 25, 681 preXDR-TB or XDR-TB cases—were found among them [3]. Additionally, MDR-TB was found in 2 million or more youngsters [10].

THE DEVELOPMENT AND CHALLENGES OF DRUG-RESISTANT TUBERCULOSIS (DR-TB):-

Given the complicated genetics of TB drug resistance, Mycobacterium tuberculosis's resistance to any antituberculosis treatment is not the result of a single molecular mechanism. However, factors related to biology, microbiology, and clinical practise generate opposition[11–13]. The fusion and accumulation of these unique and poorly understood developing Identified mutations transform the mechanisms underlying antibiotic resistance and increase the complexity of harmful resistant strains[14]. Whole-genome sequencing is one of the most reliable methods for identifying treatment resistance, genetic diversity, and evolutionary dynamics in Mycobacterium tuberculosis [15].The most prevalent mechanism of drug resistance has been found as mutations in target proteins [15].The rpoB gene is assumed to be the source of rifampicin resistance, while the rpoA and rpoC loci may also be involved [16].Exosomal noncoded RNAs (ncRNAs) may be useful functional indicators in the aetiology and diagnosis of tuberculosis because they serve as intercellular messengers [17]. The emergence of DR-TB presents difficulties for TB care, and the resources required to treat the illnesses are still in short supply [18, 19]. The global TB control programme 2030 has been seriously hampered by the emergence of treatment

resistance, particularly in countries with a high burden [20, 21]. Drug-resistant TB is becoming increasingly prevalent, necessitating longer and more expensive treatments [22, 23]. The spread of drug-resistant strains that cause high rates of morbidity and mortality is significantly facilitated by factors such as political instability, competing economic interests, and health inequities[24]. Limited therapy options are available for patients with TB that is very drug-resistant[25]. The proportion of poor outcomes is still very high, the standard treatment is longer, toxic, and expensive[26, 22, 23]. Additionally, patients from countries with a high incidence of TB were more likely to receive a typical standard regimen and experienced significant delays in receiving therapy, which quickly led to treatment failure[27]. Poorly managed medication resistance can derail worldwide TB reduction efforts if preventative and management methods are not implemented in a timely manner[28]. For the purpose of creating a regimen and managing DR-TB patients, a multi-disciplinary approach is required, involving active collaboration between various members of the healthcare team[29].

INTRODUCTION TO PRETOMANID:

Chemical Property And Mechanism Of Action:-

Pretomanid, formerly known as PA-824, was first discovered in 2000 in a batch of 100 nitroimidazopyran derivatives that had been produced and tested for their ability to inhibit mycobacterial growth[30, 31]. Pretomanid, a nitroimidazole derivative like azomycin and metronidazole, represents the class of nitroimidazopyrans. Additionally, it shares an antibacterial class with delamanid, a compound with a large number of bicyclic nitroimidazooxazole structures[32–34]. Compared to pretomanid, delamanid was more effective against MDR-TB and XDR-TB isolates in vitro [35].depicts a generalised perspective of the pretomanid's molecular structure. In order to activate components that limit bacterial mycolic acid and protein synthesis, the prodrug PA824 needs to be activated by a bacterial F420-dependent glucose-6-phosphate dehydrogenase and nitroreductas [31, 36, 30]. The reduced form of cofactor F420 serves as an electron donor for the bacterial deazaflavin-dependent nitroreductase [36].Pretomanid is then protonated, resulting in active des-nitro metabolite and nitrous acid, both of which further breakdown to create nitric oxide [32]. Pretomanid is activated within Mycobacteria in anaerobic (non-replicating bacteria) organisms to reactive nitro radical anion intermediates that interact with cellular constituents and interfere with cellular respiration, acting as respiratory poison [37, 36]. Pretomanid, however, suppresses protein and lipid biosynthesis while leaving nucleic acid synthesis unchanged in reproducing bacteria (under aerobic circumstances) [30]. This prevents the biosynthesis of the mycobacterial cell wall [37, 36, 38]. Furthermore, it suppresses the availability of keto mycolic acids, which make up the lipid bilayer that makes up the cell wall [30, 39]. Unlike other TB medications, Pretomanid also affects the pentose phosphate pathway, which results in phosphate buildup molasses [40].

Pharmacokinetics and pharmacodynamics:-

Pretomanid is a molecule that is expected to diffuse efficiently through lipid membranes because it is extremely lipophilic and has a low solubility[32, 41]. Compared to other animals, humans are exposed if pretomanid were administered in a fed condition as opposed to a fasting state. the giving of a 200 mg With a high-fat, high-calorie breakfast, pretomanid dosage increased mean Cmax by 76% and 70% Compared to the fasting condition, AUC increased by 88% [42]. In humans, it has a high bioavailability at doses between 50 and 1500 mg, and bioavailability disproportionately rises with dose [43,44], and when administered once daily, the highest plasma drug concentration has been well tolerated in people level is reached 4–5 hours after oral dosing[31, 36]. Pretomanid enters the central nervous system and is disseminated throughout the body. that drug varies between 86.3 and 86.5%[45, 46] and is only mildly protein-bound in human plasma, predominantly to albumin. Through a number of metabolic routes, it travels through phase I and phase II biotransformation, producing a range of metabolites. Up to 20% of the drug's metabolism is specifically contributed by the liver enzyme CYP3A4 [46, 47]. Pretomanid has the capacity to directly and time-dependently inhibit phase I metabolic pathways, which determines the degree of drug-drug interactions. However, pretomanid and cytochrome P450 did not interact significantly [48]. Pretomanid directly suppressed CYP3A4/5 by up to 91% at doses higher than those seen with normal dosage [46]. pharmacokinetics in the general population Participants using rifampin experienced reductions in the area under the curve (AUC) for pretomanid of 44.4% and 59.3% in comparison to those taking rifabutin or pretomanid alone in the population pharmacokinetic model [48]. However, when coadministered with the CYP3A4 inducers rifampin and efavirenz, pretomanid exposure is decreased in healthy volunteers by roughly 50% and 30%, respectively.However, it is anticipated that exposure will decrease by around 20% when paired with the mild inducer lopinavir/ritonavir [49, 50]. HIV patients should be assessed for concurrent antiviral therapy, and efavirenz should be avoided if at all possible due to lower pretomanid exposure. If pretomanid is given with food, the reduction is unlikely to reduce efficacy when combined with rifampicin. Pretomanid metabolites are eliminated in both urine (53%) and faeces (36%) (38). The elimination half-life is 17 hours, regardless of the dietary conditions [44, 47]. Pretomanid inhibits the renal tubular uptake transporter Organic Anion Transporter-3 (OAT3) at clinically relevant levels, potentially reducing the clearance of substrate medicines[46].

MECHANISM AND EMERGENCE OF RESISTANCE:-

Pretomanid's minimum inhibitory concentrations (MICs) for drug-susceptible, MDR, and XDR isolates of Mycobacterium TB range from 0.005-0.48 g/mL [41, 30]. Genes associated with pretomanid activation have shown spontaneous alterations in vitro, raising MIC >8 times from baseline [51]. Resistance to protenamid was demonstrated to be explained by sequence variations in the genes encoding deazaflavin-dependent nitroreductase, F420-dependent glucose-6-phosphate dehydrogenase, and proteins involved in F420 production [51, 52]. Functional or structural analogues of F420 proteins in Mycobacterium tuberculosis organisms contribute to redundancy, resulting in minimal mycobacterial

fitness loss despite gene disruption.6 [53, 51]. Protenamid is equivalent to other first-line regimens (isoniazid, ethambutol, and pyrazinamide) but has a higher mutation frequency (105 to 107) than rifampin [54].The exposure of the isolates to pretomanid concentration and the commencement ,The rates of spontaneous mutation appear to be influenced by mycobacterial inoculum [32]. models using animals Pretomanid resistance has also been characterised as developing in a dose-dependent manner[55, 56].n=21 papers were included in a systematic analysis of mutations linked to resistance to the new and Mycobacterium TB was reused for protomanid, and four studies found 106 distinct mutations in same genes (as well as in fbiB). 12 fdg1 mutations identified in five investigations, spread out between 230 and codons 43[52]. In one study, pretomanid resistance was linked to the identification of resistance mutations in five non-essential genes, ddn (29%), fbiC (26%), fbiA (19%), fgd1(7%), and fbiB (2%), in pretomanid laboratory-generated mutants. Although 17% of pretomanid resistant mutants lacked mutations in these genes, this suggests the existence of other resistance mechanisms [57]. The hypervirulent Beijing strain N0008 (which had not been exposed to pretomanid in the clinic) was predicted and found to be resistant to pretomanid in a study that examined 15,000 Mycobacterium TB genomes from clinical strains. This finding indicates that resistance to this drug has in this case developed through genetic drift rather than selective pressure. In this study, protein engineering was employed to disable the native menaquinone reductase activity of the deazaflavin dependent nitroreductase (DDN), but leave intact the prodrug activating activity, in order to find mutations that might lead to the development of antibiotic resistance [53]. According to a report, pretomanid and delamanid exhibit cross-resistance.But the documentation is sketchy [52]. Eight of the nine pretomanid-resistant Mycobacterium TB H37Rv strains were found to be delamanid-resistant, and one strain, according to a study by the TB alliance.it was resistant to pyrazinamide and kanamycin. But each of the nine isolates was sensitive.compared to other anti-TB drugs [32, 41]. A unique nonsynonymous mutation was found in Mycobacterium TB.The fbiA gene's (Glu249Lys) may be a factor in the high level of delamanid resistance and primitive [35]. Therapeutic targets and evolutionary factors may exhibit genomic differences. crucial for better comprehension and the development of possible inhibitors to combat resistance[15]. Before being treated to the medication, some strains are resistant to pretomanid. Accurate resistance prediction will be possible through the use of genome sequencing to track the mutations that give resistance in order to employ pretomanid treatment with knowledge. An increasing amount of Mycobacterium TB whole genome sequencing (WGS) data is being produced for first-line resistance detection and transmission 7 inference. Since its inception, WGS has become a part of clinical microbiology laboratories, promising quicker and more accurate drug detection resistance, as well as a thorough and current epidemiology of TB epidemics. The ultimate objective of WGS is to give patients with resistant TB more individualised antibiotic therapy [52]. The technology of next-generation WGS has shown outstanding potential for For Mycobacterium TB isolates, an accurate and thorough resistance prediction, allowing for accurate clinical decisions[57, 58]. We should be able to use antibiotics more wisely and reduce the emergence of resistance by evaluating probable resistant mutations in the lab prior to their widespread usage. The alterations found can be used to better understand how pretomanid should be used and to delay the formation of resistance [53]. enhancing knowledge of the resistance-causing mechanisms overall improving the results of treatment for pretomanid.

THERAPEUTIC EFFICACY AND CLINICAL ROLE APPROVAL FOR DRUG-RESISTANT TUBERCULOSIS:-

Pretomanid is the third drug recently licenced as a component of a new therapeutic regimen for treating drug-resistant TB, following bedaquiline and delamanid [59, 21]. It is an agent that may be taken orally and is active against both DS-TB and DR-TB with no notable cross-resistance to other antimycobacterial medications[60]. Pretomanid's in vitro activity against drug-susceptible Mycobacterium TB strains persists against drug-resistant bacteria as well [31]. Pretomanid enhanced bactericidal activity and prevented relapse in mice when combined with bedaquiline-linezolid (Bdq-Lzd) or bedaquiline-moxifloxacin-pyrazinamide (Bdq-Mfx-Z) [61]. The TB Alliance developed protomanid as a potential mainstay of present and future TB therapy regimens [41]. In the Nix-TB trial, the efficacy and safety of a 26-week course of treatment with the drug combination pretomanid-linezolid bedaquiline (BPaL) were assessed. l. 109 patients (65% XDR-TB and 35% MDR-TB; single-cohort, open-label study) who did not demonstrate an acceptable response or were unable to tolerate a second-line regimen were included (resulted in treatment discontinuation). In the intention-to-treat study, 10% of patients experienced an unfavourable outcome (treatment failure or relapse) at the 24-week post-treatment followup, while 90% did not[25]. The U.S. Food and Drug Administration (FDA) approved pretomanid (Pa) combined with bedaquiline and linezolid for treating adult patients with treatment-intolerant or unresponsive MDR-TB and XDR-TB on August 14, 2019, following the phase III Nix-TB trial. The treatment was given FDA clearance through the agency's limited population pathway for antibacterial and eight antifungal agents, which expedites the approval of antimicrobial drugs used to treat serious or life-threatening infections in a constrained population of patients with unmet needs [42]. For 26 weeks, a dose of 200 mg once daily is advised. Pretomanid was delivered alone or in combination with other TB medications in 19 clinical trials, which were done in 14 countries and involved more than 1,100 patients [41]. In MDR-TB patients with additional fluoroquinolone resistance (who have not previously received bedaquiline/linezolid treatment or have only recently been exposed to bedaquiline/linezolid for a period of two weeks or less), the WHO recommends using the BPaL regimen for a duration of 6–9 months [5, 21]. For patients with life-threatening diseases that exclude the use of prescribed treatment based on WHO guidelines, the regimen is regarded as "the last choice under contemporary ethical standards" [21]. Electrocardiographic QTc must be carefully monitored in XDR-TB patients receiving 6 months of BPaL, as was noted [62]. A recent clinical trial with 11 patients with RR-TB treated for 6 months with 200 mg of pretomanid, 400 mg of moxifloxacin, and 1500 mg of pyrazinamide(6Pa200MZ) found a 91% (95% CI: 59-100) favourable outcome [63]. A recent prospective cohort study comparing the bedaquiline (Bdq) and linezolid (Lzd)-based conventional 18-month

regimen to the oral three-drug regimen (BPaL) indicated that the latter had significantly worse outcomes than the former (89.9% vs. 65.1%; adjusted relative risk ratio=1.35; p0.001). Time to culture conversion and time to death were two areas where BPaL considerably outperformed Bdq-Lzd-based combinations (p=0.001 and p=0.03, respectively) [64]. Pretomanid's creation and approval process took time.

CLINICAL ROLES AND EFFICACY FOR DRUG SUSCEPTIBLE TUBERCULOSIS:-

The Global Alliance for TB Drug Development has undertaken a number of trials over the past ten years looking at different combinations of bedaquiline (B), pretomanid (Pa), moxifloxacin (M), and pyrazinamide (Z). Pretomanid has been testing in a phase 2b research to treat DS-TB (first 8 weeks). The daily change in colony-forming units (CFUs) at days 0-2, 0-56 in this NC-002 trial showed that moxifloxacinpretomanid-pyrazinamide (M200PaZ) was superior to conventional treatment (HR= 1.7; 95% CI: 1.1-2.7). The MPaZ regimen considerably outperformed the conventional four-drug therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE)) in terms of bactericidal activity and sputum culture conversion time [65]. The NC-003 phase 2a trial has determined that, among various combinations of the three medications, bedaquiline, pretomanid, and pyrazinamide (BPaZ) has the highest early bactericidal action, measured as daily rate of change in log10CFU days 0–14, and is 9-clofazimine compared to HRZE [66].Pretomanid-based regimens may be preferable to bedaquiline-based regimens in preventing acquired resistance because pretomanid early bactericidal activity (EBA) began more quickly than that of bedaquiline [67]. In the NC-005 phase 2b research, bedaquiline loading doses of 400 mg for 14 days, followed by 200 mg doses three times per week (BloadPaZ), and bedaquiline doses of 200 mg per day (B200PaZ) for BPaZ were compared to HRZE for eight weeks [68]. Both BPaZ doses considerably outperformed the control in terms of the daily rate of shift to sputum culture positivity, and both exhibited significantly higher cumulative percentages of culture negative sputum than B200PaZ but not BloadPaZ. This bedaquiline, moxifloxacin, pretomanid, and pyrazinamide regimen has promise for outcomes that are superior to the conventional therapy for DS-TB and MDRTB[68]. It can also simplify the dosage schedule. The phase 3 STAND/NC-006 research, which looked at the entire application of the MPaZ regimen throughout the 4-6 month treatment, was started because of the phase 2b NC-002 trial's successful results [63]. Participants were paired up with one of three groups at random.treatments: 100 mg pretomanid daily for 4 months in the same combination (4Pa100MZ); conventional DS-TB treatment for 6 months (200 mg pretomanid daily, 400 mg moxifloxacin, and 1500 mg pyrazinamide (Z) for 6 months (6Pa200MZ) or 4 months (4Pa200MZ). Results were unfavourable in 8.5%, 19.3%, 26.9 % and 1.9 % of patients on 6Pa200MZ,4Pa200MZ, 4Pa100MZ, and controls at 12 months post-randomisation, respectively. PaMZ failed this weakly powered study.The non-inferiority of the regimens was not realised [63]. Pretomanid displayed an early and prolonged bactericidal effect in rifampicin susceptible-TB (Rs-TB) and rifampicin-resistant (RR-TB) tuberculosis, according to data from a recent systematic analysis of the drug (n=8 clinical studies) [69].

SAFETY AND TOXICITY:-

Preclinical and in vitro research provide the majority of knowledge about the possible toxicity of protomanid. The approval for DR-TB was based on a discussion of the potential pretomanid toxicity depending on limited animal data and weighed against the risk of untreated TB infection [59]. Long-term safety data in humans are not yet available. Organ-specific safety signals from animal studies indicate the potential for hepatic, ophthalmologic, and reproductive harm (possibility of infertility through changes in spermatogenesis) at the exposure level that is most relevant to humans [46]. No major adverse effects happened when pretomanid was administered to healthy patients [70, 49]. Pretomanid has been linked to a number of negative side effects, including nausea, vomiting, acne, headaches, musculoskeletal pain, and transaminase increase [25, 38]. headaches could happened more frequently in patients receiving pretomanid alone compared to control patients (31.5% vs. 22.9%), suggesting that pretomanid was to blame. In contrast, 6.1% of the isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) control group had nausea, compared to 4.1% of the pretomanid alone group [41, 32]. The combination regimen of BPaL induces severe anomalies in cardiac rhythm, neuropathy, myelosuppression, and liver enzymes in the Nix-TB study [25]. Pretomanid is more likely to be the cause of lens problems, hepatic enzyme increases, dermatitis, gastrointestinal distress, and severe cutaneous adverse events in patients undergoing the BPaL regimen, according to professional opinion. Linezolid is more likely to be the cause of peripheral neuropathy and myelosuppression, whereas bedaquiline is connected to cardiac problems. [41, 25, 21] ,While moxifloxacin-containing regimens had more arthralgias and gastrointestinal issues, pretomanid-containing regimens had more neurological and hepatic abnormalities [68, 69]. Pretomanid alone (n=411) causes only modest liver damage (2.2%) compared to combination regimens comprising pretomanid (5.6–11.7%) and control regimens (6.5%) [41].Additionally, both the intervention and control groups in phase 2b's comparison of MPaZ for 8 weeks showed equal rates of adverse events. Arthralgia was primarily responsible for the higher frequencies of grade 3/4 treatment-emergent adverse events in the intervention arms (MPaZ) [65]. The STAND study, which compared PaMZ to the recommended course of treatment (HRZE), discovered more than a two-fold increase in the frequency of gastrointestinal and pulmonary side effects. This research was 4% (95% CI: 2-8) of the treatment was stopped due to significant hepatotoxic side events, including three fatalities. PaMZ patients [63]. When pretomanid-induced serious liver damage was more prevalent,pyrazinamide and moxifloxacin, two medications linked to liver damage [71].Pretomanid alone does not appear to significantly extend QTc or produce cardiotoxicity. Despite a good exposure-response association was discovered with bedaquiline [47], a 10 ms At maximal plasma concentrations, a rise is anticipate [72]. QTc modifications related to PaMZ were Cardiotoxicity is typical throughout pregnancy and was not clinically significant according to Tweed et al. [63, 68].Use of moxifloxacin [71].

AVAILABLE GAPS AND RELEVANT ONGOING STUDIES:-

The introduction of new medications presents an opportunity to enhance treatment in a time of growing resistance.results and lessen the toxicity as a complement to the current anti-TB arsenal agents. The rapid global spread of antibiotic resistance has prompted the creation of the stop this threat to the public's health, new standalone and combined therapies are needed. In spite of 11 the creation of new anti-tuberculosis medications, and the ongoing management of resistant Mycobacteria challenging. For TB treatment to be successful, shorter, more powerful, and target-based regimens are needed. One of the promising drugs with a better updated efficacy and safety profile is the recently licenced and advised pretomanid. According to the most recent studies, pretomanid might also be able to reduce the length of DS-TB treatment. The most recent information on the effectiveness and safety of pretomanid-based combinations should be incorporated into updated recommendations and guidelines. Individualization of the regimen for each patient taking biological, medication, patient, and illness aspects into account is also vital when taking all the factors into account. Future research will focus on QT prolongation, reproductive consequences, myelosuppression, peripheral and optic neuropathy, hepatotoxicity, and lactic acidosis. Innovative short-term oral-based regimens and advanced molecular-based diagnostics are possible directions for DR-TB therapeutic advancement. However, patients with DR-TB still have fewer.better results than those who received DS-TB treatment. Additionally, TB therapy research is Considering the TB pathophysiology can be helpful because more is occurring than ever in the history of the disease. used to create more effective and precise treatments. It is crucial to check several prominent names on the pretomanid label. monitoring physiological indicators often to evaluate the regimen's effectiveness and safety However, it routinely evaluate blood indicators for liver damage would be crucial to increase the knowledge about this allegedly efficient regimen. testing liver function (alanine) alkaline phosphatase, bilirubin, aspartate aminotransferase, and) at least at A baseline, at two weeks, and then once a month throughout treatment are required. Furthermore, for QT lengthening, getting an ECG before starting BPaL therapy, and at least 2, 12, and 24 weeks must pass following the beginning of treatment. Rapid phenotypic or genotypic drug susceptibility testing integrated into individualised drug-resistant treatment with innovative and repurposed drugs can improve treatment outcomes [9]. This can be accomplished with the aid of customised host-directed therapy, therapeutic drug monitoring, and biomarker-guided regimen personalization, among other methods. The patient's preferences, medical history, clinical characteristics, disease severity, geographic location, findings of medication susceptibility tests, and pathogen microbiology should all be taken into account when deciding on an appropriate regimen. For therapy individualization, it is necessary to comprehend antagonistic interactions, synergistic interactions, and cross-resistance for a number of potential combination regimens. Only pretomanid, bedaquiline, and linezolid were approved by the FDA for the treatment of a small number of patients with life-threatening drug-resistant TB, including XDR-TB, which precludes the use of WHO guidelines-based recommended treatment. the origin TB-Nix phase Ill, The trial's single-arm (uncontrolled), nonrandomized, and inclusion of a limited study population, which increased the generalizability and difficulties with representativeness Despite the approval being for TB with a significant treatment resistance, numerous phase According to studies from 2b, pretomanid can treat both medication interactions and A novel and promising treatment for TB that is susceptible and drug-resistant. more information information is required on the security and effectiveness of pretomanid-containing regimens for particular types of the patients as this unique treatment plan might possibly be advantageous for certain patients. The WHO report from 2021 supported additional research on pretomanid-based combinations.for the treatment of tuberculosis, both drug-sensitive and drug-resistant [3]. Right now, there areMany clinical trials are ongoing and some are recruiting participants (https://clinicaltrials.gov/).waiting for the enrollment of study subjects) to fill the openings. several of the phase I investigation of pretomanid's pharmacokinetics in humans is part of clinical studies.comparison of single-dose immediate-release and for individuals with renal impairment (NCT03896750)single-dose dispersible formulations of pretomanid in adults with hepatic dysfunction(NCT04309656) Pretomanid safety with regard to the male reproductive system impairment(NCT02422524) Phase III safety and effectiveness studies of various dosages and treatment durations(NCT04179500) Efficacy, safety, and tolerability of the BPaMZ regimen in DS and DR-TB(NCT03086486). Economic evaluation of the novel MDR-TB regimens in patients(NCT03338621) ,(PRACliCAL-EE) ,(NCT04207112).

CONCLUSIONS:-

The cost and difficulty of treating drug-resistant tuberculosis (DR-TB) are frequently higher. The third drug recently approved as a component of a cutting-edge treatment regimen for treating drug-resistant TB is protomanid. It was created by the TB Alliance and given FDA approval as a potential pillar of the ongoing and upcoming TB treatment regimen. The WHO conditionally recommends the use of the 6–9-month regimen within an operational research context, which forbids its wider and programmatic usage. By shortening the presently suggested lengthy and challenging to stomach and adhere to regimen, this regimen offers a new perspective on DR-TB therapy. The regimen also has a low risk of drug-drug interactions and is practical for oral administration. Despite the need for more research, the most recent data suggests that pretomanid is one of the innovative medications with the potential to influence TB treatment and produce the WHO's plan to end TB. Several clinical investigations on the best dosage, effectiveness, and safety in various demographics, various drug combinations, and the ideal time frame to reach an a mycobacterial reaction The introduction of fresh substances into the TB drug pipeline opens the a means of conducting thorough pharmacokinetic and pharmacodynamic research. In the future, many combinations of various innovative and reused medications for the majority of patients with drug-resistant TB, shorter or better tolerated regimens should be investigated. Alongside the continued development of reliable and fast TB detection methods .The need for medication resistance is also anticipated. More significantly, a

rigorous cost analysis, Health programmes will be made possible by the efficacy of novel and existing tests in resource-constrained environments to decide on long-term viability and implementation in a well-informed manner.

REFERENCES:-

1. Cooper CJTL. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. 2018;392(10159):1789-858.
2. Collaborators G, Roth G, Abate D, Abate K, Abay S, Abbafati C et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: A systematic analysis for the Global Burden of Disease Study 2017. 2018;392(10159):1736-88.
3. World Health Organization. Global Tuberculosis Report 2020. World Health Organization, Geneva. 2022.
4. Kyu HH, Maddison ER, Henry NJ, Mumford JE, Barber R, Shields C et al. The global burden of tuberculosis: Results from the Global Burden of Disease Study 2015. 2018;18(3):261-84.
5. World Health Organization. Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. WHO, Geneva. 2019.
6. United Nations. Transforming our World: The 2030 Agenda for Sustainable Development. 2015.
7. World Health Organization. The end TB strategy. World Health Organization. 2015. 8. Pontali E, Visca D, Centis R, D'Ambrosio L, Spanevello A, Migliori GB. Multi and extensively drugresistant pulmonary tuberculosis: advances in diagnosis and management. Current opinion in pulmonary medicine. 2018;24(3):244-52.
8. Lange C, Dheda K, Chesov D, Mandalakas AM, Udwadia Z, Horsburgh Jr CR. Management of drugresistant tuberculosis. The Lancet. 2019;394(10202):953-66.
9. Dodd PJ, Sismanidis C, Seddon JAJTLID. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. 2016;16(10):1193-201.
10. Rubin EJ. TB diagnosis from the Dark Ages to fluorescence. Nature microbiology. 2018;3(3):268-9.
11. Koch A, Cox H, Mizrahi V. Drug-resistant tuberculosis: challenges and opportunities for diagnosis and treatment. Current Opinion in pharmacology. 2018;42:7-15.
12. Iacobino A, Fattorini L, Giannoni F. Drug-Resistant Tuberculosis 2020: Where We Stand. Applied Sciences. 2020;10(6):2153.
13. Mnyambwa N, Kim D-J, Ngadaya E, Kazwala R, Petrucka P, Mfinanga S. Clinical implication of novel drug resistance-conferring mutations in resistant tuberculosis. European Journal of Clinical Microbiology & Infectious Diseases. 2017;36(11):2021-8.
14. Khan MT, Ali S, Khan A, Kaushik AC, Irfan M, Chinnasamy S et al. Insight into the drug resistance whole genome of Mycobacterium tuberculosis isolates from Khyber Pakhtunkhwa, Pakistan. Infection, Genetics and Evolution. 2021;92:104861.
15. Khan AS, Phelan JE, Khan MT, Ali S, Qasim M, Napier G et al. Characterization of rifampicinresistant Mycobacterium tuberculosis in Khyber Pakhtunkhwa, Pakistan. Sci Rep. 2021;11(1):1-10.
16. Kaushik AC, Wu Q, Lin L, Li H, Zhao L, Wen Z et al. Exosomal ncRNAs profiling of mycobacterial infection identified miRNA-185-5p as a novel biomarker for tuberculosis. Briefings in Bioinformatics. 2021.
17. Dheda K, Cox H, Esmail A, Wasserman S, Chang KC, Lange C. Recent controversies about MDR and XDR-TB: G lobal implementation of the WHO shorter MDR-TB regimen and bedaquiline for all with MDR-TB? Respirology. 2018;23(1):36-45.
18. Brigden G, Hewison C, Varaine F. New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid. Infection drug resistance. 2015;8:367.
19. World Health Organization. Global Tuberculosis Report 2021. World Health Organization, Geneva. 2021
20. World Health Organization. WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. WHO, Geneva. 2020.
21. Park M, Satta G, Kon OM. An update on multidrug-resistant tuberculosis. Clinical Medicine. 2019;19(2):135.
22. Miotto P, Cirillo DM, Migliori GB. Drug Resistance inMycobacterium tuberculosis: Molecular Mechanisms Challenging Fluoroquinolones and Pyrazinamide Eff ectiveness. Chest. 2015;147(4):1135- 43.
23. Günther G. Multidrug-resistant and extensively drug-resistant tuberculosis: a review of current concepts and future challenges. Clinical medicine. 2014;14(3):279.
24. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM et al. Treatment of highly drug-resistant pulmonary tuberculosis. New England Journal of Medicine. 2020;382(10):893-902.
25. Grüber G. Introduction: Novel insights into TB research and drug discovery. Progress in biophysics and molecular biology. 2020;152:2-5.
26. Günther G, Van Leth F, Alexandru S, Altet N, Avsar K, Bang D et al. Clinical management of multidrug-resistant tuberculosis in 16 European countries. American journal of respiratory and critical care medicine. 2018;198(3):379-86.
27. Pontali E, Matteelli A, Migliori GB. Drug-resistant tuberculosis. Current opinion in pulmonary medicine. 2013;19(3):266-72.
28. Migliori GB, Tiberi S, Zumla A, Petersen E, Chakaya JM, Wejse C et al. MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Network. Int J Infect Dis. 2020;92:S15-S25.
29. Stover CK, Warrener P, VanDevanter DR, Sherman DR, Arain TM, Langhorne MH et al. A smallmolecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature. 2000;405(6789):962-6.
30. Manjunatha U, Boshoff HI, Barry CE. The mechanism of action of PA-824: novel insights from transcriptional profiling. Communicative & integrative biology. 2009;2(3):215-8.
31. Stancil SL, Mirzayev F, Abdel-Rahman SM. Profiling Pretomanid as a Therapeutic Option for TB Infection: Evidence to Date. Drug Design, Development and Therapy. 2021;15:2815. 33. Zhang J, Ba Y, Wang S, Yang H, Hou X, Xu Z. Nitroimidazole-containing compounds and their antibacterial and antitubercular activities. European journal of medicinal chemistry. 2019;179:376-88.
32. Thompson AM, Bonnet M, Lee HH, Franzblau SG, Wan B, Wong GS et al. Antitubercular nitroimidazoles revisited: synthesis and activity of the authentic 3-nitro isomer of Pretomanid. ACS medicinal chemistry letters. 2017;8(12):1275-80.
33. Jing W, Zhang T, Zong Z, Xue Y, Shang Y, Wang F et al. Comparison of in vitro activity of the nitroimidazoles delamanid and pretomanid against multidrug-resistant and extensively drug-resistant tuberculosis. European Journal of Clinical Microbiology & Infectious Diseases. 2019;38(7):1293-6.
34. Singh R, Manjunatha U, Boshoff HI, Ha YH, Niyomrattanakit P, Ledwidge R et al. PA-824 kills nonreplicating Mycobacterium tuberculosis by intracellular NO release. Science. 2008;322(5906):1392- 5.
35. Pstragowski M, Zbrzezna M, Bujalska-Zadrozny M. ADVANCES IN PHARMACOTHERAPY OF TUBERCULOSIS. Acta poloniae pharmaceutica. 2017;74(1):3-11.
36. DEB U, BISWAS S. Pretomanid: the latest USFDA-approved anti-tuberculosis drug. Indian Journal of Tuberculosis. 2020.
37. Yuan Y, Barry CE. A common mechanism for the biosynthesis of methoxy and cyclopropyl mycolic acids in Mycobacterium tuberculosis. Proceedings of the National Academy of Sciences. 1996;93(23):12828-33.
38. Baptista R, Fazakerley DM, Beckmann M, Baillie L, Mur LA. Untargeted metabolomics reveals a new mode of action of pretomanid (PA-824). Sci Rep. 2018;8(1):1-7.
39. TB Alliance. Pretomanid sponsor briefing document for the antimicrobial drugs advisory committee. TB Alliance. 2019.
40. Food and Drug Administration. FDA approves new drug for treatment-resistant forms of tuberculosis that affects the lungs. . FDA. 2019.
41. Winter H, Ginsberg A, Egizi E, Erondu N, Whitney K, Pauli E et al. Effect of a high-calorie, high-fat meal on the bioavailability and pharmacokinetics of PA-824 in healthy adult subjects. Antimicrobial agents and chemotherapy. 2013;57(11):5516-20.

42. Ginsberg AM, Laurenzi MW, Rouse DJ, Whitney KD, Spigelman MK. Safety, tolerability, and pharmacokinetics of PA-824 in healthy subjects. Antimicrobial agents and chemotherapy. 2009;53(9):3720-5.
43. Shobo A, Bratkowska D, Baijnath S, Naiker S, Somboro AM, Bester LA et al. Tissue distribution of pretomanid in rat brain via mass spectrometry imaging. Xenobiotica. 2016;46(3):247-52.
44. Center for Drug Evaluaton and Research. Multidisciplinary review for application number 212862Orig1s000. FDA. 2019.
45. Keam SJ. Pretomanid: first approval. Drugs. 2019;79(16):1797-803.
46. Ignatius EH, Abdelwahab MT, Hendricks B, Gupte N, Narunsky K, Wiesner L et al. Pretomanid Pharmacokinetics in the Presence of Rifamycins: Interim Results from a Randomized Trial among Patients with Tuberculosis. Antimicrobial agents and chemotherapy. 2021;65(2).
47. Winter H, Egizi E, Erondu N, Ginsberg A, Rouse DJ, Severynse-Stevens D et al. Evaluation of pharmacokinetic interaction between PA-824 and midazolam in healthy adult subjects. Antimicrobial agents and chemotherapy. 2013;57(8):3699-703.
48. Dooley KE, Luetkemeyer AF, Park J-G, Allen R, Cramer Y, Murray S et al. Phase I safety, pharmacokinetics, and pharmacogenetics study of the antituberculosis drug PA-824 with concomitant lopinavir-ritonavir, efavirenz, or rifampin. Antimicrobial agents and chemotherapy. 2014;58(9):5245-52.
49. Haver HL, Chua A, Ghode P, Lakshminarayana SB, Singhal A, Mathema B et al. Mutations in genes for the F420 biosynthetic pathway and a nitroreductase enzyme are the primary resistance determinants in spontaneous in vitro-selected PA-824-resistant mutants of Mycobacterium tuberculosis. Antimicrobial agents and chemotherapy. 2015;59(9):5316-23. 52. Kadura S, King N, Nakhoul M, Zhu H, Theron G, Köser CU et al. Systematic review of mutations associated with resistance to the new and repurposed Mycobacterium tuberculosis drugs bedaquiline, clofazimine, linezolid, delamanid and pretomanid. Journal of Antimicrobial Chemotherapy. 2020;75(8):2031-43.
50. Lee BM, Harold LK, Almeida DV, Afriat-Jurnou L, Aung HL, Forde BM et al. Predicting nitroimidazole antibiotic resistance mutations in Mycobacterium tuberculosis with protein engineering. PLoS pathogens. 2020;16(2):e1008287.
51. McGrath M, Gey van Pittius N, Van Helden P, Warren R, Warner D. Mutation rate and the emergence of drug resistance in Mycobacterium tuberculosis. Journal of Antimicrobial Chemotherapy. 2014;69(2):292-302.
52. Rifat D, Li S-Y, Ioerger T, Shah K, Lanoix J-P, Lee J et al. Mutations in fbiD (Rv2983) as a novel determinant of resistance to pretomanid and delamanid in Mycobacterium tuberculosis. Antimicrobial agents and chemotherapy. 2020;65(1):e01948-20.
53. Li S-Y, Tasneen R, Tyagi S, Soni H, Converse PJ, Mdluli K et al. Bactericidal and sterilizing activity of a novel regimen with bedaquiline, pretomanid, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. Antimicrobial agents and chemotherapy. 2017;61(9):e00913-17.
54. Dookie N, Khan A, Padayatchi N, Naidoo K. Application of Next Generation Sequencing for Diagnosis and Clinical Management of Drug-Resistant Tuberculosis: Updates on Recent Developments in the Field. Frontiers in Microbiology. 2022;13.
55. Cohen KA, Manson AL, Desjardins CA, Abeel T, Earl AM. Deciphering drug resistance in Mycobacterium tuberculosis using whole-genome sequencing: progress, promise, and challenges. Genome Medicine. 2019;11(1):1-18.
56. Food and Drug Administration. FDA approves new drug for treatment-resistant forms of tuberculosis that affects the lungs. . FDA. 2019.
57. Tyagi S, Nuermberger E, Yoshimatsu T, Williams K, Rosenthal I, Lounis N et al. Bactericidal activity of the nitroimidazopyran PA-824 in a murine model of tuberculosis. Antimicrobial agents and chemotherapy. 2005;49(6):2289-93.
58. Xu J, Li S-Y, Almeida DV, Tasneen R, Barnes-Boyle K, Converse PJ et al. Contribution of pretomanid to novel regimens containing bedaquiline with either linezolid or moxifloxacin and pyrazinamide in murine models of tuberculosis. Antimicrobial agents and chemotherapy. 2019;63(5):e00021-19.
59. Caminero JA, García-García J-M, Caylà JA, García-Pérez FJ, Palacios JJ, Ruiz-Manzano J. Update of SEPAR Guideline "Diagnosis and Treatment of Drug-Resistant Tuberculosis". Archivos de Bronconeumología (English Edition). 2020;56(8):514-21.
60. Tweed C, Wills G, Crook A, Amukoye E, Balanag V, Ban A et al. A partially randomised trial of pretomanid, moxifloxacin and pyrazinamide for pulmonary TB. The International Journal of Tuberculosis and Lung Disease. 2021;25(4):305-14.
61. Oelofse S, Esmail A, Diacon A, Conradie F, Olayanju O, Ngubane N et al. Pretomanid with bedaquiline and linezolid for drug-resistant TB: a comparison of prospective cohorts. The International Journal of Tuberculosis and Lung Disease. 2021;25(6):453-60.
62. Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drugsusceptible or drug-resistant pulmonary tuberculosis. The Lancet. 2015;385(9979):1738-47.
63. Diacon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. American journal of respiratory and critical care medicine. 2015;191(8):943-53.
64. Diacon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. The Lancet. 2012;380(9846):986-93.
65. Tweed CD, Dawson R, Burger DA, Conradie A, Crook AM, Mendel CM et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drugsusceptible or drug-resistant pulmonary tuberculosis: a multicentre, open-label, partially randomised, phase 2b trial. Lancet Respir Med. 2019;7(12):1048-58.
66. Gils T, Lynen L, de Jong BC, Van Deun A, Decroo T. Pretomanid for tuberculosis: a systematic review. Clinical Microbiology and Infection.
67. Ginsberg AM, Laurenzi MW, Rouse DJ, Whitney KD, Spigelman MK. Assessment of the effects of the nitroimidazo-oxazine PA-824 on renal function in healthy subjects. Antimicrobial agents and chemotherapy. 2009;53(9):3726-33.
68. Lan Z, Ahmad N, Baghaei P, Barkane L, Benedetti A, Brode SK et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2020;8(4):383-94.
69. Li H, Salinger DH, Everitt D, Li M, Del Parigi A, Mendel C et al. Long-term effects on QT prolongation of pretomanid alone and in combinations in patients with tuberculosis. Antimicrobial agents and chemotherapy. 2019;63(10):e00445-19.
70. Diacon AH, Dawson R, Hanekom M, Narunsky K, Maritz SJ, Venter A et al. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrobial agents and chemotherapy. 2010;54(8):3402-7.
71. Diacon AH, Dawson R, du Bois J, Narunsky K, Venter A, Donald PR et al. Phase II dose-ranging trial of the early bactericidal activity of PA-824. Antimicrobial agents and chemotherapy. 2012;56(6):3027-31.