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Pretomanid For Tuberculosis: A systematic review

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ABSTRACT:

Tuberculosis (TB) is a bacterial infection caused by Mycobacterium tuberculosis that primarily affects the lungs, but can also affect other parts of the body. It is a contagious disease that can be spread through the air when an infected person coughs, sneezes, or talks. TB is typically treated with antibiotics, and early diagnosis and treatment can cure the disease. However, drug-resistant strains of TB have emerged, making treatment more challenging. TB is a significant public health concern, particularly in low-income countries, where access to healthcare and diagnostic resources may be limited. The World Health Organization (WHO) estimates that TB affects over 10 million people worldwide each year, resulting in approximately 1.5 million deaths.

Pretomanid is a prodrug which is metabolically activated by a nitroreductase enzyme, known as Ddn, producing various active metabolites that are responsible for its other therapeutic actions, particularly the induction of nitric oxide. The nitroreductase enzyme which activates pretomanid is deazaflavin dependent and relies on reduced cofactor F420. Reduction of F420 occurs via the enzyme glucose-6-phosphate dehydrogenase.Reduction of pretomanid's imidazole ring at the C-3 position causes the formation of the metabolites, which include a des-nitro derivative. The formation of this derivative leads to increased levels of nitric oxide, leading to bactericidal activities under anaerobic conditions via its action as a bacterial respiratory poison.Bactericidal activity against anaerobes is reported to be associated with a shortened duration of antibiotic treatment.

Pretomanid exerts aerobic bactericidal effects through its inhibitory actions on bacterial cell wall mycolic acid biosynthesis. This allows for the killing of actively replicating Mycobacterium tuberculosis bacteria, resulting in the treatment of active tuberculosis infection. The molecular mechanism of the above bactericidal effects is poorly understood at this time, but may involve effects exerted on various genes that affect the cell wall, including the false and fasII as well as the efpA and iniBAC operons. Other possible targets include the genes of the cyd operon. The clinical effects of the above target relations are unknown at this time.

Key words : Linezolid, 4. XDR-TB (Extensively Drug-Resistant TB),5. MDR-TB (Multi-Drug Resistant TB), DprE1 inhibitor, Bedaquiline, Bactericidal activity, Bactericidal activity, Tuberculosis, Pretomanid

Introduction:

Tuberculosis (TB) was the leading cause of death by a single infectious agent in 2019 TB treatment regimens contain an active core drug with high bactericidal and high sterilizing activity to drive its efficacy For rifampicin-resistant (Rr) TB treatment regimens fluoroquinolones and bedaquiline (Bdq) act as core drugs. High early bactericidal activity (EBA) is important to prevent resistance against the core drugs.

Since 2019, pretomanid (Pa) can be used under operational research conditions with Bdq and linezolid (Lzd) for Rr-TB with fluoroquinolone resistance Pa is an oral nitroimidazole with in vitro and in vivo activity against Mycobacterium tuberculosis (MTB) Pa kills active MTB through inhibition of mycolic acid biosynthesis, blocking cell wall production. In anaerobic or hypoxic conditions, Pa acts against non-replicating bacilli Coronavirus disease (COVID-19) pandemic heavily impacted on the diagnosis and management of tuberculosis (TB) with an estimated global decrease of TB case detection of 18%, and the first increase year-over-year of TB-related deaths since 2005 reported in 2021 (Dheda et al., 2022). Moreover, the economical effects of the COVID-19 pandemic are expected to increase the catastrophic costs for TB treatment in high-burden, limited resources settings (Dheda et al., 2022). If immediate action is not undertaken a 10-years delay in TB control programs has been estimated (Dheda et al., 2022).

Mechanism of Action of Pretomanid :

1. inhibition of Mycobacterial Cell Wall Synthesis: Pretomanid inhibits the synthesis of the mycobacterial cell wall, which is essential for bacterial growth and survival.
2. Binding to DprE1: Pretomanid binds to the enzyme DprE1 (Decaprenylphosphoryl-β-D-ribose 2'-epimerase), which is involved in the biosynthesis of the mycobacterial cell wall.
3. Inhibition of Arabinan Synthesis: By binding to DprE1, Pretomanid inhibits the synthesis of arabinan, a key component of the mycobacterial cell wall.
4. Disruption of Cell Wall Integrity: Inhibition of arabinan synthesis disrupts the integrity of the mycobacterial cell wall, ultimately leading to bacterial death.

5. Bactericidal Activity: Pretomanid has bactericidal activity against Mycobacterium tuberculosis, meaning it kills the bacteria rather than just inhibiting their growth.

Pharmacokinetics:

1. Absorption: Pretomanid is well absorbed after oral administration, with a bioavailability of approximately 55%.
2. Distribution: It is widely distributed throughout the body, with a volume of distribution of approximately 1,200 L.
3. Metabolism: Pretomanid is metabolized by the liver enzyme CYP3A4, with minor contributions from CYP2C19 and CYP2D6.
4. Elimination: It is eliminated primarily through the feces (70%), with a smaller amount excreted in the urine (20%).
5. Half-life: The terminal half-life of Pretomanid is approximately 20-30 hours.

PA needs phase I and II biotransformation by several metabolic pathways. The elimination half-time is estimated at 16–20 h. The mean Tmax is 4–5 h and the steady state is achieved in 5–6 days. The drug diffuses into the body with a Vd/F of 92–180 L and is modestly bound to albumin (86.3–86.5%). A single daily dose posology is possible due to the good tissue absorption and to the long half-life of this drug. PA crosses the blood-brain barrier due to its lipophilic nature Pretomanid exhibits linear absorption and clearance processes at a given dose, but the absorption rate and bioavailability change with dose. Clearance and volume of distribution scale allometrically with body weight. Apparent clearance is 18% lower in females compared to males. Bioavailability is about 50% higher when pretomanid is administered with a high-fat, high-calorie meal compared to fasting conditions.Bioavailability decreases with increasing dose under fasted conditions, but not for doses up to 200 mg under fed conditions.Concomitant use of CYP3A4-inducing antiretrovirals like efavirenz and lopinavir/ritonavir can reduce pretomanid exposure by 46% and 17%, respectively.

Pharmacodynamics:

1. Mechanism of action: Pretomanid inhibits the enzyme DprE1, which is essential for the synthesis of the mycobacterial cell wall.
2. Bactericidal activity: Pretomanid has bactericidal activity against Mycobacterium tuberculosis, with a minimum inhibitory concentration (MIC) of 0.06-0.12 mg/L.
3. Synergy with other drugs: Pretomanid has been shown to have synergistic activity with bedaquiline and linezolid, enhancing its bactericidal activity.
4. Resistance: Resistance to Pretomanid has been observed in vitro, primarily through mutations in the dprE1 gene.
5. Pharmacodynamic targets: The pharmacodynamic targets for Pretomanid are not fully established, but it is believed to require sustained exposure above the MIC to achieve optimal bactericidal activity.

Pretomanid is part of defined multidrug regimens being evaluated for treatment of drug-resistant TB, such as BPaL, BPaCL, BPaML, and BPaMZ.
The population pharmacokinetic model developed can help characterize the dose-exposure-response relationship of pretomanid and support further clinical development.
In summary, pretomanid exhibits complex pharmacokinetics, with factors like food effect, drug-drug interactions, and body weight influencing its exposure. Understanding these pharmacokinetic properties is crucial for optimizing the use of pretomanid in the treatment of drug-resistant tuberculosis.
Pretomanid has shown novel pharmacodynamic mechanism in combating both the replicating Mycobacterium tuberculosis (M. tb) as well as the anaerobic nonreplicating MTb. In actively replicating MTb, this drug works by inhibiting mycolic acid biosynthesis and killing the mycobacterium by blocking its cell wall production.

Risk Factor :

Patient-related risk factors:

1. Hepatic impairment: Pretomanid is metabolized by the liver, so patients with pre-existing liver disease or impairment may be at risk of increased toxicity.
2. Renal impairment: Patients with severe renal impairment may require dose adjustments.
3. Diabetes: Pretomanid may increase the risk of hypoglycemia in patients with diabetes.
4. Electrolyte imbalance: Patients with pre-existing electrolyte imbalances (e.g., hypokalemia, hypomagnesemia) may be at risk of exacerbation.
5. Older adults: Older adults may be more susceptible to adverse effects due to age-related decline in renal and hepatic function.

Drug-related risk factors:

1. CYP3A4 inhibitors: Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) may increase Pretomanid levels and toxicity.
2. CYP3A4 inducers: Concomitant use with strong CYP3A4 inducers (e.g., rifampicin, efavirenz) may decrease Pretomanid levels and efficacy.
3. Bedaquiline: Concomitant use with bedaquiline may increase the risk of QT prolongation.
4. Linezolid: Concomitant use with linezolid may increase the risk of myelosuppression.

Other risk factors:

1. Pregnancy and lactation: Pretomanid is not recommended during pregnancy or lactation due to limited data.
2. Pediatric patients: Safety and efficacy in pediatric patients have not been established.

Adverse effects

Severe hepatotoxicity (life-threatening liver damage)
Severe allergic reactions (anaphylaxis, angioedema)
Blood disorders (aplastic anemia, agranulocytosis, pancytopenia)
Severe electrolyte imbalance (life-threatening)
QT prolongation (abnormal heart rhythm)
Hepatotoxicity (elevated liver enzymes, liver damage)
Increased creatinine levels (kidney function impairment)
Anemia (low red blood cell count)
Neutropenia (low white blood cell count)
Thrombocytopenia (low platelet count)
Hypoglycemia (low blood sugar levels)
Allergic reactions (mild to moderate)
Electrolyte imbalance (low sodium, potassium, or magnesium levels)
Nausea, Vomiting, Abdominal pain Diarrhea, Headache, Fatigue, Muscle pain, Joint pain, Rash

Conclusion :

Evidence suggests an important role for pretomanid in rifampicin-resistant and highly resistant tuberculosis. Trials comparing pretomanid to existing core and companion drugs are needed to further define that role.
In conclusion, Pretomanid is a novel oral antibiotic used to treat drug-resistant tuberculosis, specifically extensively drug-resistant (XDR) and multi-drug resistant (MDR) tuberculosis. Here are the key takeaways:
Pretomanid is a valuable addition to TB treatment regimens Effective against XDR and MDR TB Used in combination with bedaquiline and linezolid Shortens treatment duration and improves outcomes Has a unique mechanism of action, inhibiting mycobacterial cell wall synthesis Generally well-tolerated, but monitoring for liver and electrolyte abnormalities is necessary Available as tablets and in fixed-dose combinations Generic formulations may be available in some countries Overall, Pretomanid represents a significant advancement in the treatment of drug-resistant tuberculosis, offering hope for improved outcomes and reduced treatment duration. However, it should only be used under the guidance of a healthcare professional and as part of a comprehensive treatment plan.

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