New TB drug regimen may not work against TB meningitis

Researchers demonstrated in a recent paper that the FDA-approved regimen of three antibiotics, bedaquiline, pretomanid, and linezolid (BPaL), used to treat TB of the lungs caused by MDR strains, is ineffective in treating TB meningitis because bedaquiline and linezolid are restricted in their ability to cross the blood-brain barrier, a network of cells that prevents the entry of pathogens and toxins into the brain. This was observed in animal models.

An international hazard to public health is TB, which is brought on by the bacterium Mycobacterium tuberculosis. It is one of the most lethal infectious agents, according to the World Health Organization. The deadliest type of TB, TB meningitis, develops in about 1%–2% of cases and results in an infection in the brain that increases fluid and inflammation. The BPaL regimen was authorised by the FDA in 2019 to treat MDR TB strains, particularly those that cause pulmonary TB. On how successfully these antibiotics penetrate the blood-brain barrier, there is, however, little information.

The study team created a pretomanid antibiotic that was imageable and chemically equivalent to learn more. They performed research employing direct drug assessments in mouse brains and positron emission tomography (PET) imaging to noninvasively assess pretomanid penetration into the central nervous system in mouse and rabbit models of TB meningitis. According to experts, PET imaging showed good pretomanid brain

or central nervous system penetration in both animals. Pretomanid levels in the cerebrospinal fluid (CSF) that surrounds the brain, however, were significantly lower than in mouse brains.

The effectiveness of the BPaL regimen was next evaluated in comparison to the usual TB treatment, which consists of rifampin, isoniazid, and pyrazinamide, an antibiotic cocktail used to treat drug-susceptible types of TB. Results revealed that after six weeks of therapy, the BPaL regimen in the mouse model was around 50 times less effective at killing germs in the brain than the conventional TB regimen.

Current research, however, points to trials using modest amounts of a medicine as a valid indicator of the drug's biodistribution.

Journal article: Mota, F., et al., 2022. Dynamic 18F-Pretomanid PET imaging in animal models of TB meningitis and human studies. *Nature Communications*.