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Editorial

Pretomanid- A new drug in the fight against drug-resistant tuberculosis

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The management of tuberculosis (TB), one of the most primitive diseases known to mankind, is a challenge even in the modern world.[1] The disease has become a public health issue.[2] And has resulted in large scale morbidity and mortality.[3] The disease has burgeoned into a severe and drug-resistant (DR) form due to mutations.[4] These mutations have forced the scientific community to look for newer and better drugs with good patient compliance and higher success rates.[5] In over four decades the management of TB was based mainly on the drugs classified in the WHO classification for anti-TB drugs.[3] However, with the introduction of new drugs like Bedaquiline and Delamanid there has been a remarkable development in the management of TB especially the severe form of it i.e., DR-TB.[6,7] The fight against TB especially the DR-TB has become even more feasible with the introduction of the latest drug namely Pretomanid.[8]

Pretomanid was known as 'PA-824' in its earlier stages, is a nitroimidazole, a class of novel anti bacterial agents with a bactericidal action against both replicating and static M. tuberculosis.[2,9] The drug has been developed by TB Alliance a nonprofit organization and is approved by the US FDA on 14th August 2019 to treat extensively drug-resistant TB (XDR-TB) or treatment-intolerant/non-responsive multi-drug resistant TB (MDR-TB).[8] The drug is to be used with Bedaquiline and Linezolid, with all three constituting the BPaL regimen.[8] This BPaL regimen using three drugs is based on the Nix-TB trials conducted in South Africa which showed a successful treatment outcome of 89% (in 95 of the first 107 patients) after six months of treatment and further six months of post-treatment follow-up.[8] The BPaL regimen will be an all- oral, six-month-long treatment regimen using the three drugs i.e., Pretomanid, Bedaquiline and Linezolid.[8]

The WHO reports the success rate in XDR-TB as abysmal 34% and 55% in MDR-TB.[10] Besides, the management till date involved the use of anti-TB drugs for a duration ranging from six months to two years or longer.[6,8] The frequent and severe adverse drug reactions, large pill burden on the patients, issues related to injectable drugs, and long treatment duration had led to many deaths and loss to follow-up cases.[6]

The Pretomanid based all oral BPaL regimen is thus indicated in all adults who are either diagnosed as XDR-TB or in treatment-intolerant/non-responsive MDR-TB.[8] And its use is not indicated in patients with: drug-sensitive TB; latent TB infection; extra-pulmonary TB or in MDR-TB that is not treatment-intolerant or non-responsive to standard therapy.[8] However, the approval of the Pretomanid based regimen is based on limited clinical safety and efficacy data.[8]

Currently, the major contraindications of Pretomanid are the same as those of Bedaquiline and Linezolid.[8] The drug can lead to hepatic adverse effects, myelosuppression,

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peripheral and optic atrophy, QT prolongation, lactic acidosis, etc.[8] The drug has also led to testicular atrophy resulting in reduced fertility in animal models and thus the patients need to be counseled about the same till the availability of large scale data in human subjects.[8] Besides, a number of other adverse drug reactions($\geq$10%) have been reported like peripheral neuropathy, rash, acne, anemia, nausea, vomiting, headache, increased transaminases, hyperamylasemia, decreased appetite, pruritus, dyspepsia, abdominal pain, pleuritic pain, increased gamma- glutamyl-transferase, lower respiratory tract infection, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea.[8]

New drugs, with shorter, better-tolerated anti-TB regimens are needed to grapple with the high global burden of TB complicated by drug resistance and HIV. The development of Pretomanid only the third drug in four decades to be developed is a significant improvement and progress towards the goal of TB elimination. The drug will have a greater impact in high-burden, lower-income countries like in Asia, Africa, and some former Soviet Union countries, where there is higher prevalence of DR-TB. However, large scale human trials related to the drug and its further interactions with other drugs are imperative for achieving the targets of TB elimination.

Conflicts of interest

None

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None

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