Editorial

Bedaquiline: An Effective Anti-tuberculous Drug with Novel Mechanism of Action

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There were 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB) and 100,000 new patients with rifampicin-resistant tuberculosis (RR-TB) in 2015. Mortality was common in Asia with 250,000 deaths in the same year.[1] Treatment was successful in 52% of the MDR/RR-TB patients whereas 17% mortality and 9% treatment failure were reported. Extensively drug-resistant TB (XDR-TB) have acquired in 9.5% of MDR-TB cases with 117 countries have reported for XDR-TB in the world.[1] Treatment success rate was only 26% in XDR-TB cases.[1] Drug sensitive strains of TB need treatment duration of 6 months whereas MDR-TB and XDR-TB requires more than 20 months of treatment.[2] The burden of MDR-TB is increasing in various regions of the world. In the last 40 years after rifampicin has been started to be used in 1970s, no new anti-tuberculous drug was introduced.[2] The research for the development of new anti-tuberculous drugs is expensive and slow because the replication rate of tubercle bacilli takes time and the pharmaceutical manufacturers which are present in well-developed countries without TB burden have no much interest.[2]

There was an increasing interest in the development of novel drugs with a different mechanism of action which can combat both drug-sensitive as well as drug-resistant strains of *M. tuberculosis* in last 10 years after global plan has been launched to stop TB.[2] Andries and co-workers at Janssen Pharmaceutical Company discovered bedaquiline, a new anti-tuberculosis (TB) drug and was approved by the US FDA in 2012 to treat MDR-TB as part of combination therapy.[2] Bedaquiline was known to have a novel mechanism of action with the effect on the metabolism of *M. tuberculosis*.[2] It inhibits mycobacterial ATP synthetase and is effective against both replicating and dormant organisms because ATP is still essential in dormant organisms for the survival. Although it has long half-life, early bactericidal activity of bedaquiline at the dose of 400 mg daily was nearly the same to 600 mg rifampicin and 300 mg isoniazid from 4th day onwards in the course of 7 days.[2] Phase II trials indicated that bedaquiline has been well tolerated by the patients and efficacy was good when it is used in combination with background regimen (BR) to treat MDR-TB.[2] Time of sputum conversion was shorter and percentage of sputum conversion was higher in both two months and six months phase trials.[2] Two black boxes were observed with bedaquiline, which are prolonged QT interval and higher mortality when compared with the placebo treatment[3]. Currently Phase III trials are on the way to verify its safety and effectiveness.[2, 3]

Drug resistance mechanisms occur usually by means of horizontal transfer of plasmids or transposons carrying resistance genes between bacteria.[4] For antibiotics, it is feasible to identify resistance in bacteria only after market release.[4] However, drug resistance in the *Mycobacterium tuberculosis* emerged by chromosomal mutations.[4] The methods for detecting resistance mechanisms include identifying drug-resistant mutants *in-vitro*, *in-vivo* animal models and clinical trials.[4] Mutations in the ATP synthase associated with bedaquiline resistance have been found to emerge in the next-generation sequencing approach. Drug resistance was known 8 years after the mechanism of bedaquiline was well understood.[4] Subunit c of

ATP synthase was encoded by *atp*E gene. Five single nucleotide polymorphisms namely A28V, A28P, G61A, A63P and I66M were associated with bedaquiline-resistance.[3] However, 28% of the bedaquiline-resistant *Mycobacterium tuberculosis* harboured these mutations and the remaining 72% did not have such mutations.[3] The mutational upregulation of an efflux pump was observed to be other mechanism of bedaquiline-resistance and the cross resistance to clofazimine can occur because of this mechanism.[3] As a consequence, regimens including both drugs need to be reconsidered as the combination of these two drugs has significant effects on reduction of treatment success.[3]

A standardised shorter MDR-TB regimen was recommended by World Health Organization for the treatment of MDR/RR-TB patients who are still sensitive to fluoroquinolones or second-line injectable agents such as kanamycin, amikacin or capreomycin.[1] Currently, bedaquiline has been started to be used in 70 countries together with BR. Furthermore, the important information is addition of bedaquiline to BR has advantages of decrease in disability-adjusted life years and reduced total healthcare costs when compared with BR.[5] The significance was observed remarkably in high TB burden countries.[5]

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