



Bedaquiline in Pediatric Drug Resistant Tuberculosis: Is this the Next Big Answer?

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Editorial

Definitive diagnosis of tuberculosis has always been more challenging when it comes to paediatric population. On top of that crisis, increase in multidrug resistant and extremely drug resistant strains of *Mycobacterium tuberculosis* bacilli is now an emerging problem globally. In 2016, World Health Organisation (WHO) stated that during 2015-16, nearly half a million people got infected with multidrug-resistant (MDR) tuberculosis (TB) globally [1]. Among these, nearly 32,000 cases were found to have occurred in "less than 15-years-age" population [2]. Extremely drug-resistant (XDR) TB (MDR TB additionally resistant to a fluoroquinolone and a second-line injectable drug) statistics were not very clear in paediatric population due to very limited data. More than 33% MDR TB cases were estimated to be resistant against fluoroquinolone, a second-line injectable drug or both [3].

Worldwide among all the age groups, overall favourable outcomes were observed in 48% patients with MDR-TB and only 22% patients XDR TB in 2011 [4]. MDR-TB poses several difficulties for treating paediatricians as they are dealing with infants, children and adolescents. First, treatment options are quite limited. Even if a promising drug comes in use its evaluation in adult patients beforehand takes lot of time. Second, among the disease burdened countries access to appropriate laboratories and effective treatment regimens is still a big problem. Third, drugs used in combination for MDR TB often causes adverse reactions (example: Injectable drug causing deafness in more than 25% children in one cohort) [5].

As the need of newer more effective and less toxic anti TB drugs was felt, researchers started experimenting with several molecules. Among them oxazolidinones, diarylquinolines, nitroimidazopyrans, ethylenediamines and benzothiazinones showed promising results [6]. Bedaquiline or Sirturo (developed by Janssen Therapeutics under the name R207910 or TMC207) is the first novel drug that was approved by US Food and Drug Administration in 2012 and also in Europe in 2014, almost about 40 years after approval of rifampicin [7].

Bedaquiline belongs to group diarylquinolines which is very much close to quinolones but instead of inhibiting DNA gyrase, this novel group of drugs inhibit mycobacterial adenosine triphosphate (ATP) synthase. They disrupt energy production and intracellular metabolism of both intra and extracellular mycobacterium by interfering with proton transfer chain [8-10]. This action of bedaquiline is more or less specific for mycobacterial ATP synthase activity as human mitochondrial ATP synthase is 20,000 times less sensitive to it [11].

Bedaquiline has activity against both drug sensitive and drug resistant TB bacilli. Minimum inhibitory concentration (MIC) studies showed better potency against drug sensitive strains than isoniazid or rifampicin. It acts in similar fashion against bacilli resistant to first line drugs (all five included) and moxifloxacin [8].

This is an oral drug, has good absorption from the gut, metabolised by hepatic CYP3A4 (also with help of CYP2C8 and CYP2C19), excreted

in faeces, is highly protein bound (>99.9%), has a long terminal half-life owing to redistribution from different tissue compartments [12]. It has got no significant drug interactions with isoniazid, pyrazinamide, ethambutol, kanamycin, ofloxacin or cycloserine [13]. Dose adjustment should be considered while co-administering with lopinavir or ritonavir [14].

Bedaquiline is currently in phase III trial [15]. As per WHO interim guidelines, it may be considered when there is difficulty to construct an effective 4-drug regimen using other drugs or in case of fluoroquinolone resistance. But limited data about the drug prompted WHO to declare that it should not be currently used in case of paediatric population [16].

Bedaquiline has shown to increase hepatic transaminase like many other first line antitubercular drugs. Prolongation of QT interval and need for regular ECG monitoring for corrected QT is another issue to consider. Although some studies have reported increase mortality in bedaquiline group compared to placebo there is considerable doubt whether this increase is directly attributed to bedaquiline use itself [17]. We have to wait for completion of phase III trial and its outcome for this. In low-resource settings, the higher cost of the drug is also a concern for its routine use (24 weeks course costing US\$ 28,400 in an adult case) [18].

There are reasons that we are getting hopeful about this drug. Up to 66% of all patients in a large retrospective cohort study have been shown to be benefited from addition of bedaquiline or delamanid to their regimen [19]. The US CDC stated that bedaquiline may be an alternative for children and adolescents when treatment options are limited due to resistance to second line drugs [13]. A recent study which collected data from children and adolescents with advanced resistance to second line drugs showed promising outcome with good compliance. This study concluded that bedaquiline is safe in children >12 years of age with proper monitoring. Although prolongation of QTcF was noted in handful patients with concomitant administration of other cardiotoxic drugs, no patient required bedaquiline cessation [20]. Increasing accessibility to bedaquiline, according to an international group of paediatric TB experts, may reduce the need of second line injectable drugs with resultant irreversible toxicity [21]. So, hopefully after phase III trial results are at hand and also the Janssen group study among <18 years patients publish their results, we may find a valuable drug to fight multidrug-resistant tuberculosis globally.

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