2 TB

a Bedaquiline: the first new drug in decades to treat TB is now available in South Africa

For the first time in 40 years a new anti-tuberculosis drug with a novel mechanism of action has become available. Bedaquiline (BDQ) is a diarylquinoline antimycobacterial drug and specifically inhibits mycobacterial adenosine triphosphate synthase. Clinical data has consistently shown faster mycobacterial sputum clearance in patients on BDQ than those on a background regimen. In one study at the end of an 8-week period, 48% were culture converted compared with 9% in those on placebo. The follow-up study showed a median time to sputum-culture conversion that was significantly shorter in the BDQ group than in the placebo group (83 days vs. 125 days; P<0.001). However, there was an imbalance in mortality between the 2 groups. Although it was difficult to biologically prove causality, it was sufficient enough to cause concern.

Based on these findings and following a risk-benefit review, BDQ received accelerated approval in December 2012 by the United States (US) Food and Drug Administration (FDA). As part of the Bedaquiline Clinical Access Programme (BCAP), approval was granted by the Medicines Control Council (MCC) of South Africa for a national programme to treat XDR- TB or pre-XDR TB patients (defined as MDR-TB with additional resistance to either a fluoroquinolone or a second-line injectable medicine) with BDQ in December 2012. This allowed pre-XDR or XDR-TB patients with limited treatment options safe access to this drug prior to registration.

Since October 2014, Sirturo (bedaquiline, BDQ) from Janssen Pharmaceutica, has been registered in South Africa for use in HIV-negative or HIV-infected, ART-naïve patients 18 years or older who have laboratory-confirmed MDR-TB. Additionally, the World Health Organization (WHO) has issued guidance on the treatment of MDR-TB with bedaquiline. The South African National Department of Health has developed a new draft policy framework for the introduction of new drugs and drug regimens for the management of drug-resistant TB in South Africa.

Surveillance for early detection of BDQ resistance is advised by the WHO and is incorporated into the South African policy framework. BDQ's action on mycobacterial ATP synthase is inhibited with mutations in the *atpE* gene. At this stage, the occurrence of this mutation is very low. Presently, definitive criteria for resistance have not been determined. However, all patient isolates with MIC values above 0.25 ug/ml and those with a 4-fold increase from baseline will be evaluated for the possibility of drug resistance.

The Centre for Tuberculosis incorporating the National TB Reference Laboratory at the National Institute for Communicable Diseases has recently participated in a multicentre project to validate test methodologies for BDQ resistance surveillance. Surveillance has now initiated on patients who have been started on BDQ treatment, submitting sputum samples at baseline, week 8 and week 24 for BDQ minimal inhibitory concentration (MIC) determination. To date, no isolates with an MIC >0.25 ug/ml have been identified.

The introduction of new drugs for TB treatment has been long overdue. However, the judicious use of BDQ following licensing is paramount, and practitioners are advised to consult the NDoH policy for introduction of new drugs once publically available (for an update contact NdjekO@health.gov.za or naziri@nicd.ac.za). BDQ and other new drugs soon to be introduced (including delaminid) are expected to change the dismal patient outcomes for drug-resistant TB.

Source: Centre for Tuberculosis, NICD-NHLS