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Drug Resistant Tuberculosis: Gold, Glitter and Hope

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Dear Editor,

Tuberculosis represents a leading cause of morbidity and mortality worldwide. In 2012, tuberculosis was the 12th leading cause of death, with 0.9 million deaths (1) and ranking as the second leading cause of death from infectious disease, after human immunodeficiency virus (2). In 2013, 9 million new tuberculosis cases occurred, of which 550,000 were among children (2).

In previous issues of your journal, Moyo et al. (3) pointed out the outcomes in adolescent tuberculosis, especially focusing on drug-resistant tuberculosis. The authors studied 71 adolescents with tuberculosis and reported a treatment success of only 36.4% and a mortality rate of 9.1%. Multidrug-resistant tuberculosis (MDR-TB) accounted for 18.5% of the cases, but all four deaths occurred in patients with extensive drug-resistant tuberculosis (XDR-TB).

MDR-TB (as well as XDR-TB) challenges World Health Organization (WHO) efforts to tackle tuberculosis. Nearly 3.5% of new cases diagnosed in 2013 were MDR-TB, with a wide variation between different countries (2). Cases in China, India, and the Russian Federation accounted for 60% of the 480,000 MDR-TB cases that occurred in 2013 (4). Mortality in this patient population is higher than that in populations with drug-sensible tuberculosis, reaching up to 11% (4).

This discouraging picture provides a rationale for one of the WHO strategies against tuberculosis, that is, the support of the development of new drugs to fight disease, mainly MDR-TB and XDR-TB. After more than 50 years without drug discovery in this area, recently two drugs have become the hope in this distressing landscape, namely bedaquiline (Sirturo, Janssen) and delamanid (Deltyba, Otsuka), both with approved indication for pulmonary MDR-TB as a part of an appropriate combination regimen for adult patients when an effective treatment regimen cannot otherwise be administered because of resistance or tolerability (5, 6).

The efficacy of both drugs has been studied in phase II and III clinical trials. Bedaquiline (400 mg/day on weeks 1 and 2, followed by 200 mg three times per week on weeks 3 - 24) shortens time to conversion based on a negative sputum culture result at week 24 to 78 days, compared with 129 days in the placebo arm. It offers a curative rate of 57.6%, compared with the 31.8% with placebo (number needed to treat, 5; 95% confidence interval, 3 - 18) (4). Delamanid at a dose of 100 mg/12 hour converts sputum in 45.4% of patients, compared with 29.6% in the placebo arm (number needed to treat, 7; 95% confidence interval, 4 - 24) (7).

However, caution must be taken when these (and all) drugs are put in a clinical context and the balance between benefits and harms is considered. Although delamanid is usually well tolerated, except for a QTC prolongation in nearly 10% of patients (7), trials of bedaquiline have revealed a mortality higher than that in placebo by 8% (number needed to harm, 14; 95% confidence interval, 7 - 334). By using these data, we could calculate the LHH (likelihood of being helped versus being harmed and the possibility of being helped against being harmed), defined as the quotient of NNT and NNH inverses (1/NNT)/(1/NNH) (8). For bedaquiline, this value would be given by (1/4)/(1/14) = 3.5, that is, for every 3.5 patients cured with bedaquiline, one death occurs (4).

From the perspective of drug evaluation, it is beyond doubt that "not all that glitters is gold." Medical journals have reported promising and innovative drugs withdrawn from the market shortly after licensing because of a misbalanced harm-to-benefit ratio. Maybe bedaquiline or delamanid does not represent a real solution for MDR-TB, but new tuberculostatic drugs are awaiting approval and could warrant future effective findings.

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Authors' Contributions

Both authors equally contributed to the design, discussion, and redaction of this letter.

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