ACTA SCIENTIFIC PHARMACEUTICAL SCIENCES

Volume 3 Issue 7 July 2019

Editorial

Tuberculosis: Are there New Drugs for this Old Disease?

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Received: April 16, 2019; **Published:** June 01, 2019

DOI: 10.31080/ASPS.2019.03.0295

Tuberculosis or TB has overtaken HIV/AIDS as the number one cause of death from a single infectious agent. According to WHO, approximately 10 million people contracted TB in 2017 with an estimated 1.3 million deaths across the globe. The emergence of drug-resistant tuberculosis has made this serious health problem much more daunting. Over half a million people developed rifampicin-resistant tuberculosis (RR-TB), 82% of which have multidrug resistant tuberculosis (MDR-TB), which is resistant to rifampicin and isoniazid, the two most effective first-line drugs. Incidentally, an estimated 8 of 100 MDR-TB cases have extremely drug resistant TB (XDR-TB), which is resistant to first-line drugs, any fluoroquinolone, and at least one of the injectable second-line drugs such as kanamycin, amikacin, or capreomycin. Indeed, tuberculosis remains a dreadful public health threat that latently infected roughly 1.7 billion people worldwide. The seriousness of this malady has prompted the world leaders to hold, for the first time, a high-level meeting in 2018 to tackle the tuberculosis problem and to summon all efforts to hit the Sustainable Development Goal (SDG) of ending the TB epidemic by 2030.

Although the pipeline for new drugs against TB has relatively expanded in recent months and now includes 20 compounds in clinical development, it is still very limited considering that only six of them are innovative, that is, they belong to a new class of compounds, have a new drug target or mode of action, or have no cross resistance to other class of antibiotics. The limited investment in TB drug discovery and development weakens the "intensified research and innovation" pillar of the WHO End TB Strategy and derails the accelerated efforts towards much aspired technological breakthrough by 2025. To date, only two new anti-TB drugs have reached the market after 60 years. In particular, Bedaquiline was approved for medical use in 2012. The interim policy guidelines on its use for treatment of MDR-TB were then issued by WHO in 2013. In the same year, the European Medicines Agency issued a conditional approval to use Delamanid in adults with MDR-TB. However, these newly licensed TB drugs are not readily accessible in many high-burden countries due primarily to issues of registration and cost.

As of third quarter of 2018, the global clinical development pipeline for new anti-TB drugs and regimens include 11 new compounds: contezolid (an oxazolidinone), GSK-303656 (an oxaborole), Macozinone (a benzothiazinone), OPC-167832 (a carbostyril), Q203 (imidazopyridine), TBA-7371 (an azaindole), and TBI-166 (a riminophenazine) in Phase I; delpazolid (an oxazolidinone), SQ109 (a 1,2-ethylene diamine), and sutezolid (an oxazolidinone) in Phase II; and pretomanid (a nitroimidazole) in Phase III. Additionally, seven approved drugs are also repositioned as anti-TB drugs and are currently in various stages of clinical development. For example, the leprosy drug clofazimine is now in Phase III clinical trial for MDR-TB. The other repurposed drugs include nitazoxanide, linezolid , levofloxacin, moxifloxacin, rifampicin (high-dose), and rifapentine. Moreover, new regimens or combination of drugs are being tested for the treatment of drug-susceptible and drug-resistant TB.

Although these ongoing clinical development programs bring new hope to a quarter of human population infected with TB, the number of compounds in the pipeline is still practically inadequate, given the fast development of mycobacterial resistance. There is an urgent need to reinvigorate the field of TB drug discovery and development. Without new druggable targets, new chemical architectures, and new drug combinations, the goal of better, safer, and shorter TB drug regimens will remain out of reach.

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