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Review

Access to new medications for the treatment of drug-resistant tuberculosis: Patient, provider and community perspectives

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) is on the rise, and is difficult to treat. The approval of two new drugs, bedaquiline and delamanid, and growing evidence for the use of linezolid, offer renewed hope for addressing MDR-TB. However, access to these medicines remains a significant challenge. These drugs have not been registered for TB in most settings; barriers to preapproval access persist; and high pricing and intellectual property restrictions limit access. Many unanswered research questions about optimal use of these drugs also limit access, particularly for vulnerable populations. This review outlines challenges in accessing drugs encountered from the perspective of clinicians, patients and affected communities, and offers potential solutions.

1. Introduction

Drug-resistant tuberculosis (TB) is common, and the extent of resistance rising, rendering cure and the interruption of transmission increasingly difficult.[1] Two new drugs, bedaquiline and delamanid, recently received conditional regulatory approval to treat multidrug-resistant (MDR) TB.[2,3] Mounting evidence also supports the repurposing of antibiotics, such as linezolid—approved for other indications—for MDR-TB.[4] These drugs offer renewed hope of curing those with MDR-TB and of achieving a world free of TB.[5] Access to these medications, however, remains a significant challenge. This article highlights some of these regulatory, financial, and scientific access challenges from the perspectives of patients, providers and programs, with a hope that understanding these barriers will help overcome them.

2. Pre-approval access barriers

Pre-approval access programs, including "compassionate use" (CU) and "expanded access" programs, allow patients with limited therapeutic options to access potentially lifesaving investigational drugs prior to formal regulatory approval.[6]

Janssen, the manufacturer of bedaquiline, initiated a pre-approval access program for bedaquiline in 2011, while the drug was in phase IIb trials. To date, Janssen has successfully provided nearly 500 patients with access to bedaquiline.

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Despite this relative success, early attempts to access bedaquiline in the United States were complicated by a lack of clearly defined mechanisms both for dealing with requests and providing the drug. A physician caring for a patient with extensively drug-resistant (XDR) TB applied for CU access to bedaquiline. Various delays, including the drug being held at U.S. customs, caused two months to pass before bedaquiline reached the patient. The delay was a significant barrier in drug access, and similar delays have been reported elsewhere. Later requests were fulfilled more rapidly.

Moldova, a country with a significant MDR-TB problem, lacks a legal framework for CU, which prevents access. Now, nearly two years after patients, activists and a World Health Organization (WHO) TB program review raised this issue,[7] it is understood that bedaquiline's European Medicines Agency (EMA) approval allows its import as "humanitarian aid". However, confusion over the legality of importing bedaquiline under CU means that Moldovan patients still have no access to bedaquiline, despite the efforts of civil society and the Moldovan National TB Program, and Janssen's willingness to provide the drug.

Pre-approval access to bedaquiline initially proved challenging for other country-specific reasons in South Africa, which has a large MDR-TB burden, with 15,419 cases reported in 2012 alone.[8]

> As one clinician diagnosed with MDR-TB in 2010 in South Africa noted: "I was immediately concerned about survival, as I knew the dismal cure rates globally—48% in 2012.[9] I heard of a new drug, bedaquiline, undergoing studies in South Africa and tried to gain access through a recently opened CU program. I was told I was not ill enough, as I did not have XDR-TB, despite the fact that the drug had only been studied in patients like me with MDR-TB.
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> After two months, I started losing my hearing from amikacin therapy. I was forced to choose between my hearing (and effectively, my career) and cure. I was extremely fortunate to gain access to bedaquiline after re-applying, so I could stop the amikacin therapy. I fully comprehended the risk of cardiac arrest associated with this, but facing MDR-TB, I was willing to take it. I was one of only four patients that gained access to the drug before the South African Medicines Control Council closed the CU program."

The South African Medicines Control Council closed this program, citing premature data and an initial preference for a clinical trial instead. Following the US Food and Drug Administration (FDA) approval of the use of bedaquiline to treat MDR-TB in December 2012, and lengthy discussions with the South African National Department of Health, the South African Medicines Control Council finally approved in 2012 a national "Clinical Access to Bedaquiline Programme", which has offered eligible patients in approved sites access to bedaquiline under safe conditions.[10]

Pre-approval access to delamanid has been much more limited. Otsuka initiated its CU program only in 2014—after EMA approval was assured and their phase III trial had completed enrollment, and has no expanded access. There are no clear procedures or eligibility criteria identified to guide application for delamanid under CU. To date, fewer than five patients have been enrolled, all of whom live in Europe, where the drug has been approved.

A recent case has elucidated that patients treated with bedaquiline are specifically excluded from consideration for delamanid due to Otsuka's concerns that both drugs may cause modest prolongation of the QT interval; the drugs have not yet been studied in combination.[11] CU access to delamanid was denied to a patient with the most drug-resistant TB isolate ever identified in the United States, confirmed susceptible only to linezolid and cycloserine, and presumed susceptible to bedaquiline. This patient had a very limited chance of survival without adding an additional effective drug to the regimen, and was being treated in a facility with intensive cardiac monitoring to reduce potential risk. Due to Otsuka's refusal to provide delamanid, this patient is suffering from permanent disabling side effects of a suboptimal regimen, including hearing loss and peripheral neuropathy. Patients like this have the most to gain from use of novel combinations of drugs, but are specifically excluded by the company's current policy. Notably, in the absence of data on simultaneous use, the WHO's recent guidance on delamanid does not issue a negative recommendation against its use together with bedaquiline.[12] By precluding seriously ill patients from accepting any potential risk of receiving novel drug combinations, Otsuka's restrictive pre-approval access policy leaves patients with a definite risk of dying from drug-resistant TB. This runs in stark contrast to the purpose and practice of compassionate use, designed to offer an otherwise unavailable treatment for the most desperate clinical cases.

A recent prospective study from South Africa showed the poor five-year prognosis for those receiving treatment for XDR-TB: only 11% of patients with XDR-TB had a favorable treatment outcome, and overall mortality was 73%.[13] These statistics highlight the dire and urgent need for new treatment regimens, but it will be years before these regimens are identified and available, as definitive research studies and new drug registration timelines are lengthy. It is therefore crucial to make pre-approval access available to patients now to give them a chance for survival. These access programs also provide countries with the framework to implement broader policy planning and roll-out of more effective MDR-and XDR-TB regimens at a national level.

3. Registrations, normative guidance and technical assistance barriers

Pre-approval access is critical for select urgent TB cases, but widespread registration of new drugs is required for broad uptake. Unfortunately, slow registration due to limited industry investment and regulatory challenges (such as a lack of harmonization across authorities requiring multiple onerous submission processes, and a lack of capacity among regulators to rapidly review drug applications) has stymied access. So far, bedaquiline is only approved by six regulatory authorities, with several more registrations in high MDR-TB burden countries pending. Otsuka has only filed for approval for delamanid in Europe, Korea, and Japan, home to very few people with MDR-TB; Otsuka has not registered the drug in most of the countries where it held clinical trials.[14] More registrations for both drugs, but especially delamanid, are urgently needed.

The regulatory approval of new drugs for the treatment of TB is just one step that must occur for medications to reach those who need them. In most high-burden TB countries—especially those that rely on external funding—the medication must also be recommended by the WHO; purchased through approved mechanisms and imported; and incorporated into a national plan consistent with the overall strategy of the TB program and that follows WHO recommendations.[15,16] In addition, countries need to develop updated clinical guidance for the use of new medications, train implementers, and set up systems needed for the monitoring and active pharmacovigilance that are essential parts of new drug introduction.[17–19]

These steps are crucial, but can be time-consuming and prolong the process of getting the medication to those most in need. The WHO has developed a more streamlined process for introducing new medications for TB under program conditions,[17] but significant hurdles remain. At this writing, although several countries have ordered bedaquiline for the treatment of MDR-TB, not a single patient in a high-burden setting has received bedaquiline or delamanid under program conditions. Most countries are also