Access sought to tuberculosis drug from nutraceutical company

Early last year, after struggling for months with a severe case of drug-resistant tuberculosis, Gary, a 39-year-old Californian, was transferred to the care of tuberculosis specialist Caitlin Reed. She sent his samples to the US Centers for Disease Control and Prevention (CDC) for analysis. "I remember how shocked I was when I first saw his test results from the CDC lab. His tuberculosis was resistant to every drug that the CDC lab tested," Reed, a medical director at the UCLA Medical Center in California, told *Nature Medicine*. She put Gary on an intensive new drug regimen, which included the new medication bedaquiline, and by August he was discharged and sent home, to continue treatment as an outpatient.

Gary's story, unfortunately, didn't end with his return home. Because of severe complications, Gary landed back in the hospital this fall. Doctors continue to fear his tuberculosis will ultimately develop resistance to bedaquiline if another new drug is not added to his regimen. To this end, Reed has urgently been trying to get him access to a medication called delamanid.

Delamanid, only the second tuberculosis drug approved in 40 years by European regulators, uses a new mechanism of action to treat the disease by inhibiting the synthesis of a cell-wall component of *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis. But patient advocates worry that the new drug may not reach the patients who need it because, according to these advocates, the developer of the drug has failed to aggressively study and market the medication in regions that need it most.

Early clinical trials of delamanid, marketed as Deltyba by the Japanese pharmaceutical and nutraceutical company Otsuka, suggests that it can produce cure rates over 45% when used in conjunction with an optimal background drug regimen that includes a medication known as pyrazinamide and a set of four second-line drugs. "In essence, the use of delamanid doubles the proportion of patients with no signs of the TB bacterium in their spit, after two months of treatment—a standard way to tell the patient is [tuberculosis] free," says Giovanni Migliori, director of the World Health Organization (WHO) Collaborating Centre for Tuberculosis and Lung Diseases in Tradate, Italy. "This is a very promising result," he adds.

Clinical support for the efficacy of delamanid, however, is still in its infancy, with only a small phase 2b trial under its belt, explains Mario Raviglione, director of the Global TB Programme at the WHO. "Phase 3 trials have not yet been completed and it will take another few years before we have those results," Raviglione says.

As a consequence, the use of this new drug is only permitted according to a strict set of guidelines established last year by the WHO. Raviglione explains that the drug should not be used on its own as that would promote drug resistance "within weeks." Yet delamanid treatment offers promising outcomes, says Raviglione, for people with multidrug-resistant tuberculosis (MDR-TB). "If one follows strictly these recommendations, delamanid could be used, roughly, in one-third of MDR-TB patients emerging yearly," he says. Notably, the WHO has declined to support use of delamanid with bedaquiline, citing a lack of clinical data backing this combination.

Reaching the next phase

Delamanid was approved by regulators in Japan and South Korea as well as by the European Medicines Agency (EMA) in 2014. The drug is part of the wide product portfolio of Otsuka, which also makes sports drinks—one of which it hopes to send to the moon as part of a marketing campaign. According to Marc Destito, communications director at Otsuka, the company has plans to submit delamanid for approval in China, Indonesia and the US later this year. He adds that a 400-person, multicenter phase 3 trial started in November with sites in places ranging from Peru and the Philippines to South Africa and Latvia, and it is set to last for about 30 months.

According to WHO estimates, countries such as South Africa, India, Russia and China are among those with the highest incidence of MDR-TB. However, approval is likely to take significant time in these countries, as they depend entirely on the specific regulatory requirements of each country. Destito says that the company has been in contact for several years with various advocacy groups and has been reaching out to see how they can ensure that high-burden countries are prepared to use new drugs rationally and to harmonize their regulatory processes.

Yet, according to Raviglione, the WHO was still waiting to hear from Otsuka as *Nature Medicine* went to press. "At the moment, the WHO is not aware of the intentions of Otsuka concerning the registration in [more] countries and strategies for providing access to the drug," he says, adding that the WHO is willing to work with Otsuka to facilitate access to delamanid for all patients in need.

Otsuka declined to provide sales figures for delamanid, which is only approved for sale in Europe, Japan and South Korea. The drug is available on a more limited basis worldwide under Otsuka's compassionate use program, which offers the drug free of charge to those in need who qualify. According to Destito, the program has so far received about a dozen requests, most of which he says have been granted, with the exception of those in which patients were following a bedaquiline regimen. Patients who have used bedaquiline may still qualify if they can remain bedaquiline-free for at least six months.

Unfortunately for Gary, he was among the denied requests. "Each time his appeals were denied because the drug had not yet been studied in combination with bedaquiline," Reed says. "Patients like Gary [are] perfect candidates for compassionate use. [They] face death from extensively drug-resistant TB or severe permanent disability from the toxicities of their treatment," she adds.

Destito says that owing to patient confidentiality they cannot comment on specific compassionate request cases, but Otsuka recognizes the difficult situation that MDR-TB patients like Gary are facing. However, they have to put safety first, he says. "The US [National Institutes of Health] is working on a study to evaluate the safety of delamanid and bedaquiline when used together," he adds. "Until this evidence is available, we cannot put other patients and both drugs at risk. Should an adverse event occur in a compassionate use framework, there is a risk that it could lead to a contraindication for these two compounds."

But Erica Lessem, assistant director of the TB/HIV Project at the New York–based Treatment Action Group, thinks Otsuka needs to do more to get the drug approved swiftly in more countries. "Otsuka claims to have a compassionate use program, but there is nothing compassionate about only allowing a handful of patients to access delamanid," Lessem says. "In contrast, bedaquiline, the other new drug developed for tuberculosis, has reached hundreds of patients with MDR-TB in urgent need."

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