Approval of Novel TB Drug Celebrated—With Restraint

On New Year’s Eve, the U.S. Food and Drug Administration (FDA) approved the first new tuberculosis drug in more than 40 years. But the celebration was tempered because sobering challenges face the drug’s widescale use.

FDA approved the drug, bedaquiline, for only patients who have multidrug-resistant tuberculosis (MDR TB), which can require up to 2 years of treatment. Mycobacterium tuberculosis easily develops resistance to drugs used alone, including bedaquiline, so FDA specifies that the pill must be part of a combination therapy. Recognizing the urgent need for better MDR TB drugs, FDA put bedaquiline, made by Janssen Therapeutics of Titusville, New Jersey, through an accelerated approval process, which relaxes efficacy data requirements, and approved it in 6 months. “This is indeed a major breakthrough,” says Nesri Padayatchi, a TB specialist at the Centre for the AIDS Programme of Research in South Africa in Durban. But Padayatchi, who works in a country with a high MDR TB burden, immediately adds, “I am skeptical about its use in our setting.”

In South Africa and many other countries, MDR patients often start treatment without having the results of drug-sensitivity tests—which are both costly and time-consuming—of their particular M. tuberculosis strains. As a result, patients sometimes receive drugs that they are resistant to, and adding bedaquiline would be essentially giving monotherapy—and breeding resistance to it. “Bedaquiline is indeed a great drug, but we have to just be careful about how we use it,” Padayatchi says. Clinician Andreas Diacon of Stellenbosch University, Tygerberg, in South Africa, who ran one of the clinical trial sites that tested bedaquiline, says its “major impact” may well be to “kick-start” the routine tailoring of drug regimens to each patient’s MDR strain.

Bedaquiline’s discovery was first reported in Science 8 years ago (14 January 2005, p. 223) by a team led by Koen Andries, who works at Janssen in Beerse, Belgium. The drug raised high hopes because it seemed extraordinarily powerful and worked by a unique mechanism: It inhibits an ATP enzyme that is specific for mycobacteria, which they need to convert energy for reproduction. Even so, Andries says it was a “rough ride” to develop, because there’s no attractive marketplace. Wealthy countries have scant tuberculosis and a minuscule scale of MDR TB cases—only 98 occurred in the United States in 2011. But he praises his bosses for sticking with it, and says Johnson & Johnson (J&J), which owns Janssen, plans to sell the drug at little profit in developing countries that approve it. (FDA regulates U.S. use.)

In 2011, 12 million people had active cases of TB, according to the World Health Organization (WHO). Relatively safe drugs can cure drug-sensitive TB in 6 months, but an estimated 630,000 people worldwide have the much harder to treat MDR TB. Nearly 1.4 million people died in 2011 from TB because they weren’t properly diagnosed, skipped drug doses, received ineffective second-line treatments, or had concomitant infections with HIV. By adding bedaquiline to existing regimens, researchers hope to replace the most toxic drugs, shorten the course of treatment, and cure more MDR TB cases. Ultimately, combinations of bedaquiline and other novel drugs in the pipeline may cure conventional TB cases more quickly.

Delighted as Spigelman is about bedaquiline on two studies that involved 440 MDR TB patients. Both added bedaquiline to standard regimens and evaluated how long it took patients’ sputum to clear M. tuberculosis, a surrogate marker for a cure. One trial found that patients given bedaquiline became sputum negative for the bacilli after 83 days versus 125 days in patients taking a placebo. In a second trial that did not have a placebo arm, sputum became negative after 57 days. Phase III studies in MDR TB patients just getting under way—which may take 5 years to complete—will evaluate whether adding bedaquiline to existing regimens indeed decreases disease and death.

Serious side effects included increased irregular heart rhythms and more deaths in the treated group of the placebo-controlled study (11.4% vs. 2.5%), which Janssen must note in the packaging of the drug. Andries doubts the drug harmed patients, however: Not only did the causes of death differ and have no connection to abnormal heart rhythms, but most occurred a year after people stopped receiving the compound. “It would be very weird and unusual that side effects would appear after 1 year of stopping bedaquiline treatment,” Andries says.

TB researcher Barry Bloom of the Harvard School of Public Health in Boston says several logistical questions loom large. Given the WHO estimate that 81% of the people who have MDR TB do not know it, how will suppliers determine how much bedaquiline to procure? How should clinicians best combine it with existing TB drugs? Will bedaquiline interfere with drugs to treat HIV or other diseases? “You have to take this a step at a time,” Bloom says.

As for bedaquiline’s future as a first-line treatment, J&J gave the Global Alliance for TB Drug Development (TB Alliance), a nonprofit based in New York City, a royalty-free license to develop and sell it worldwide for that use. Mel Spigelman, head of the TB Alliance, says tests in a highly predictive mouse model combined bedaquiline with two or three other new TB drugs in development and reduced the 6-month cure time to 6 weeks. “I think there’s a huge potential,” Spigelman says. They plan to launch human studies later this year.

Delighted as Spigelman is about bedaquiline’s approval for MDR TB, he cautions that this is just a first step. “The only downside of getting the approval now is people walk away and say, ‘Ah, it’s a new drug, the problem is solved,’ ” he says. “It’s not yet. This is the beginning.”

–JON COHEN