New tuberculosis drug regimen slashes treatment time

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Medical illustration of drug-resistant Mycobacterium tuberculosis. Credit: CDC Public Health Image Library

Tuberculosis is an age-old respiratory scourge, with a new twist: growing resistance to multiple first- and second-line drugs. UF researchers and physicians report on using a novel treatment to slash treatment time—and cure—a patient with extensively drug-resistant TB.

Physicians and researchers with the Southeastern National Tuberculosis Center at the University of Florida, and the UF College of Pharmacy, used a novel treatment regimen to cure a patient of extensively drug-resistant tuberculosis in less than half the normal time. They reported their case study in the January issue of *Emerging Infectious Diseases*.

Tuberculosis is an ancient disease affecting the respiratory system that—like COVID-19—is spread by airborne droplets. But in the case of TB, it's an acid-fast bacterium, Mycobacterium tuberculosis, that rides in aerosols from one human host to another. Globally, TB disease is the leading cause of death from an infectious pathogen and is second only to COVID-19 in the number of deaths it causes.

TB has not been highly prevalent in the US for several decades, but cases occur regularly at low levels. Tuberculosis remains a large concern in many parts of the world, however, and drug-resistant strains are on the rise everywhere. As of 2017, at least 20% of TB cases globally were resistant to at least one first- or second-line drug, and around 10% of these multi-drug resistant cases were extensively drug-resistant against some second-line defense drugs—or all of them.

"The field of TB has been slow to improve since the first antibiotic effective against TB was recognized in the 1940s," says the report's first author, Connie Haley, M.D., M.P.H., who is an affiliate faculty member in UF's College of Medicine. "And tuberculosis patients who become infected with TB strains resistant to existing drugs have very limited treatment options."

Haley is also a medical consultant for the Southeastern National Tuberculosis Center, which is one of four Tuberculosis Centers of Excellence funded by the US Centers for Disease Control and Prevention's Division of Tuberculosis Elimination.

Some patients can't tolerate existing treatments, which can last up to two years, Haley notes. Others lose their hearing as a side effect, or can develop renal or liver toxicity. "In Africa, they have a saying, "Better deaf than dead,"' Dr. Haley says. "But as a clinician, I feel it's unacceptable to ask a patient to risk severe disability in exchange for a cure."

Haley worked with UF physicians, pharmacists, and researchers—along with David Ashkin, M.D., affiliate UF faculty, Medical Director of the SNTC and Medical Director of the Florida Department of Health—to cure a patient with extensively-drug resistant TB using a novel regimen recently

approved by the Food and Drug Administration.

The team says that, to the best of their knowledge, they were the first providers to use this new treatment regimen in the US outside of a clinical trial. Since this case, close to 40 patients in the US have undergone similar care.

"It took one-third of the normal time, with fewer side effects, and it saved her life," Dr. Haley says.

Drug-resistant TB

Patients who have drug-susceptible TB disease can typically be cured after six months using an effective regimen—as long as one drug, rifampin, can be used for the full duration.

"Rifampin is currently the most effective drug against TB, killing the bulk of organisms that are actively replicating as well as the harder-to-eradicate semi-dormant or 'persister' organisms that can cause recurrent TB," Dr. Haley says.

In multi-drug resistant TB, the infecting TB organisms are resistant to rifampin and isoniazid; and in extensively-resistant TB, there is also fluoroquinolone resistance and at least one injectable medication (such as amikacin, kanamycin, or capreomycin) which renders these patients very hard to cure.

"Without rifampin, TB can require treatment for 18-24 months, since other first-line drugs do not have the same sterilizing action," Dr. Haley says. "And currently recommended second-line drugs often have worse side effects, so we have clearly needed something else."

A clinical trial completed in 2019 found that a six-month oral regimen of three drugs—bedaquiline, pretomanid, and linezolid, known as BPaL—was effective in curing extensively drug-resistant TB in 90 percent of enrolled participants. Based on these results, the FDA approved the new BPaL regimen for use in the US in August 2019. All three drugs in the BPaL regimen work strongly against actively replicating M. tuberculosis organisms, but like rifampin, both bedaquiline and pretomanid can also kill perisisters, enabling a shorter treatment to cure the patient.

Test results had shown that samples of M. tuberculosis obtained from Dr. Haley's patient had mutations indicating that her strain was extensively drug-resistant.

Dr. Haley and her team received FDA clearance to use BPaL with their patient, who was also being treated for locally advanced cervical cancer when she was diagnosed with TB. The regimen was so new that the pretomanid was not available in the US and had to be shipped from overseas.

"Prior to this new regimen, a diagnosis of extensively drug-resistant TB meant that there were no drugs that were likely to be effective or tolerated by the patient," Dr. Haley says. "It's really a huge breakthrough."

Individualized drug therapy

A co-author to the case report, Charles Peloquin, Pharm.D., directs UF's Infectious Disease Pharmacokinetics Laboratory in the College of Pharmacy. The lab was critical to the team's success.

Peloquin, who is also a faculty member in UF's Emerging Pathogens Institute, specializes in therapeutic drug monitoring, or TDM. His lab uses an analytical chemistry technique called LC MS, or liquid chromatography with mass spectrometry. The method allows for a patient's drug regimen to be tailored individually. The lab monitors drug concentrations in the patient's serum and then recommends adjustments to the size or frequency of the doses.

This approach allows the clinicians to analyze how a patient absorbs, metabolizes and clears a drug, which allows them to find the right dose early during treatment and optimize outcomes.

One of the BPaL drugs, linezolid, is effective but carries a risk of concentration-related adverse drug reactions. TDM allows clinicians to balance the competing goals of giving enough of a drug to kill the bacteria that cause TB, but not so much drug that the patient is harmed.

Dr. Haley says the patient is the first in the US to receive the BPaL regimen in conjunction with therapeutic drug monitoring. The team published the case study to further clinical knowledge of how BPaL therapy can be individualized.

"BPaL is still so new that in another country, this patient would have had no cure," Dr. Haley says. "We wanted to share our work because if clinicians don't implement new scientific discoveries into practice, then the benefit is lost."

More information: Connie A. Haley et al. Novel 6-Month Treatment for Drug-Resistant Tuberculosis, United States, *Emerging Infectious Diseases* (2020). DOI: 10.3201/eid2701.203766

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