Antibiotic shows promise in treating extensively drug-resistant tuberculosis

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When tested in patients hospitalized with extensively drug-resistant tuberculosis (XDR-TB) unresponsive to previous treatment, linezolid, an antibiotic used to treat severe bacterial infections, proved largely effective when added to the patients' ongoing TB treatment regimen. Also, few patients developed resistance to the drug. These promising findings were tempered, however, by the fact that 82 percent of the patients who received linezolid experienced significant adverse events that may have been related to the drug. Findings from the study appear in the October 18th issue of the *New England Journal of Medicine*.

XDR-TB is a form of tuberculosis that is resistant to at least four of the drugs most often used to treat TB. Although XDR-TB is rare, 77 countries worldwide reported at least one case by the end of 2011, according to the World Health Organization. In the United States, at least 57 cases of XDR-TB were reported between 1993 and 2010. Patients infected with XDR-TB typically have very poor clinical outcomes, and with no effective drugs available for their treatment, they often die.

Led by Clifton E. Barry, III, Ph.D., of the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and Sang-Nae Cho, D.V.M., Ph.D., professor of infectious diseases at Yonsei University, South Korea, researchers enrolled at two South Korean hospitals patients with chronic XDR-TB who had failed to respond to any treatment during the six months before enrolling into the study. The patients, predominantly men (72 percent) ranging in age from

20 to 64, were randomly assigned either to immediately begin 600 milligrams (mg) of linezolid once daily as part of their existing treatment regimen (19 patients) or to start the drug after a two-month delay (20 patients). After no longer testing positive for the bacterium or after four months of therapy, whichever came first, participants were then randomly assigned for the next 18 months to continue taking either a daily 600-mg dose of linezolid or a daily 300-mg dose. The patients were regularly monitored for any adverse effects.

After four months, 15 of the 19 patients (79 percent) in the immediate-start group, and 7 of the 20 (35 percent) patients in the delayed-start group no longer tested positive for TB. After six months of treatment with the drug, 87 percent (34 of 39 patients) no longer tested positive for the bacterium.

Adverse effects associated with long-term linezolid use included bone marrow suppression and peripheral and optic neuropathy. In the study, 31 patients (82 percent) experienced clinically significant adverse events that were likely related to the use of drug, but most of these events resolved quickly after briefly stopping the drug or using the lower 300-mg dose, the authors note. Only 3 of those 31 patients permanently discontinued use of the drug because of side effects. Additionally, only 4 of the 38 patients (11 percent) who used the drug for six months or more acquired resistance to linezolid. Thirteen patients completed treatment and have not had a relapse in the 12 months after treatment ended. All of the patients continue to be watched for long-term outcomes.

The authors conclude that linezolid may become an important therapeutic option for XDR-TB cases in the future. It also may form part of a regimen to treat MDR-TB in periods shorter than the two years of therapy standard for such patients now. Yet in both instances, additional clinical trials are needed to identify a dosage that is sufficiently potent yet does not cause significant adverse events.

More information: M Lee et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *New England Journal of Medicine* DOI: 10.1056/NEJMoa1201964 (2012).