Use of combination drug regimen for treating TB may represent an effective treatment option

April 12 2011

In patients with newly diagnosed tuberculosis (TB), use of a combined 4-drug fixed-dose regimen was found to have comparable outcomes to drugs administered separately, according to a study in the April 13 issue of *JAMA*, a theme issue on infectious disease and immunology.

Christian Lienhardt, M.D., M.Sc., Ph.D., of the World Health Organization, Geneva, Switzerland, presented the findings of the study at a *JAMA* media briefing at the National Press Club. Dr. Lienhardt conducted the study while heading the Clinical Trial Division at the International Union Against Tuberculosis and Lung Disease.

"Despite the availability of a highly effective 6-month chemotherapy regimen, worldwide control of tuberculosis is severely impeded by poor treatment completion rates that threaten the emergence of multidrug resistance," according to background information in the article. "Fixed-dose combinations (FDCs) of drugs have been advocated as a way of preventing the emergence of drug resistance attributable to inappropriate drug intake. In addition, they can reduce the risk of incorrect dosage, simplify drug procurement, and aid in ensuring adherence."

Dr. Lienhardt and colleagues conducted a multicenter randomized controlled trial to evaluate the efficacy and safety of a 4-drug FDC for the treatment of tuberculosis. The study was conducted at 11 sites in Africa, Asia, and Latin America between 2003 and 2008 and included

1,585 adult patients with newly diagnosed smear-positive pulmonary tuberculosis. Patients were randomized to receive daily treatment with 4 drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) given as an FDC (n = 798 patients) or separately (n = 787) in the 8-week intensive phase of treatment. A favorable treatment outcome was defined as a negative culture result at 18 months post randomization and not having already been classified as unfavorable. The FDC was assessed for noninferiority (no worse than the separate drug regimen) via several measures.

The researchers found that, in the per-protocol analysis 18 months after the start of treatment, 555 of 591 patients (93.9 percent) in the FDC group vs. 548 of 579 (94.6 percent) in the separate-drugs group had a favorable outcome. In two different models of a modified intention to treat analysis, the researchers found that 570 of 684 patients (83.3 percent) in the FDC group had a favorable outcome, compared with 563 of 664 (84.8 percent) in the separate-drugs group; and 591 of 658 assessable patients (89.8 percent) in the FDC group had a favorable outcome, compared with 589 of 647 (91.0 percent) in the separate-drugs group, respectively.

"The results of this trial show, using a strict definition of noninferiority, that a 4-drug FDC regimen may be noninferior to a regimen of separately administered drugs in terms of efficacy for treatment of tuberculosis," the researchers write. They add that one of the main advantages of FDCs is that patients have to take considerably fewer pills (3-4 instead of 9-16 per day in the intensive phase), thus making treatment easier, aiding adherence, and potentially eliminating the risk of developing drug resistance attributable to selective drug intake.

"FDCs are a full part of the recently revised World Health Organization treatment guidelines. The uptake of FDCs in tuberculosis control programs globally is gaining momentum, but challenges remain," the authors write. "The uptake and acceptance of FDCs is primarily affected

by doubts about the efficacy of FDCs, questions of access and quality, advantages over other formulations or packaging, lack of political will at the country level, and the conflicting policies of funders."

"For efficient tuberculosis control worldwide, it is essential that quality-assured FDCs are made available. While new regimens or drugs are being developed for the treatment of tuberculosis, it is essential that strategies are developed for their introduction in national tuberculosis control programs, which includes the protection of these new drugs within established and quality-assured FDCs."

More information: *JAMA*. 2011;305[14]1415-1423.

Provided by JAMA and Archives Journals