

RESEARCH

CBTBR member: Prof Diacon in USA news - 27 October 2008

ICAAC-IDSA: Novel Drug Shows Power in MDR-TB by Michael Smith, North American Correspondent, MedPage Today Published: October 27, 2008

WASHINGTON, Oct. 27 -- An investigational compound aimed at tuberculosis is safe and well tolerated, Dr Diacon said. Moreover, the compound TMC207 (Tibotec) appeared to cause a sharp increase in the number of patients who became culture-negative after eight weeks of therapy, according to Andreas Diacon, M.D., of the University of Stellenbosch in South Africa. The apparent efficacy is impressive because the phase II study was designed mainly to look at safety and dosing levels, Dr. Diacon told the Interscience Conference on Antimicrobial Agents and Chemotherapy, held jointly with the Infectious Diseases Society of America meeting. While TB remains a major public health problem in many parts of the world, no new drugs to treat it have been developed in several decades. At this meeting, however, there are reports of at least two, of which TMC207 is most advanced. The drug is a highly targeted molecule that interferes with synthesis of adenosine triphosphate (ATP) in *Mycobacterium tuberculosis* cells. Interestingly, Dr. Diacon said, the drug does not affect the ATP molecules of even closely related bacteria. The effect of inhibiting ATP, researchers think, is to reduce the energy available to the TB bacteria. In this study, Dr. Diacon and colleagues were looking at the safety and tolerability of the drug, as well as its pharmacodynamics, in 47 patients with multi-drug resistant TB, defined as a strain resistant to the first-line drugs isoniazid (Nydrazid) and rifampin (Rifadin). They were treated with a five-drug background regimen (which varied from patient to patient) and randomized to placebo or TMC207, which was given daily at 400 mg for two weeks, followed by 200 mg three times weekly for six weeks. Adverse events were evenly distributed between the groups, except for a slight increase in nausea among those getting TMC207, Dr. Diacon said, and grade 3 and 4 adverse events also occurred at similar rates -- 26% for TMC207 and 21% for placebo. No serious adverse events were related to the study drug and there were no discontinuations owing to adverse events, he said. A secondary endpoint was the rate of culture conversion, defined as two consecutive negative cultures in liquid medium collected at least a week apart, Dr. Diacon said. After eight weeks of treatment, 8.7% of those getting placebo (and background therapy) had negative cultures, compared with 47.5% of those on TMC206. The difference was significant at $P=0.003$. Also, serial sputum colony counting was performed in 22 patients in overnight sputum collections, with the result that none of the nine TMC207 patients had any colony forming units by week four. In contrast, nine of 13 placebo patients had colony forming units at week four and one remained positive at eight weeks, he said. "The most important thing (about the study) is that it is breaking the logjam of a complete lack of new drugs for TB," said Andy Pavia, M.D., of the University of Utah in Salt Lake City, who was not part of the study. Dr. Pavia, who heads the IDSA's public health committee, cautioned that it is early days for the drug and more research is required. "In early phase II (studies) we get the good news," he said. Bad news -- such as lack of safety or efficacy -- will come later, if at all, he said. But he said new drugs for TB couldn't have come at a better time, as more and more countries are reporting cases of extensively drug resistant TB -- strains that are even harder to treat than multi-drug resistant disease. While most of those cases are seen in the developing world, he said, "nobody's immune -- it will reach developed countries."

Source reference: Diacon AH, et al "Interim Analysis of a Double-Blind, Placebo-Controlled Study with TMC207 in Patients with Multi-Drug Resistant (MDR) Tuberculosis" ICAAC-IDSA 2008; Abstract B-881b.