New drug for the treatment of multidrug-resistant TB shows promising results in Phase II clinical trial

Promising results to be published in the June issue of the *New England Journal of Medicine* were reported for the treatment of multidrug-resistant (MDR) TB with a new compound, TMC207, developed by Tibotec, a subsidiary of Johnson & Johnson. On addition of TMC207 to a drug cocktail to treat the life-threatening infection with MDR TB, the treatment was shown to be five-times more efficient.

MDR TB is a threat to life in many populations, and is extensively associated with long treatment regimes (up to 18 months) and high treatment costs.

Conducted in South Africa, this recent study is the first part of a randomized, placebo-controlled Phase II trial, including 47 hospitalized patients that were recently diagnosed with MDR-TB. The patients were randomized into two groups, one receiving TMC207 (23 patients) within a background regimen of five second-line anti-TB drugs, while the other group (24 patients) received placebo in the background regimen. TMC207 was administered at a dose of 400 mg/day for 2 weeks and subsequently at 200 mg three-times weekly for 6 weeks. Every day, patients gave a sputum sample, which was analyzed for TB bacteria. After 8 weeks, a total of 46.6% of patients were sputum culture-negative in the TMC207 group, while only 8.7% of patients achieved this result in the placebo group. Furthermore, TMC207 significantly reduced the time to culture conversion (positive to negative); the probability of a culture becoming negative was 11.8-times higher in the TMC207 group at any given day during the 8 weeks than in the placebo group. In addition, the mean colony-forming units count in sputum cultures reduced significantly faster in the TMC207 group. Adverse effects were reported to be mild-to-moderate, and only nausea was reported more frequently in the TMC207 group (26%) than in the placebo group (4%).

Peter Donald from Stellenbosch University in Capetown, South Africa, commented: "The results of this study are highly encouraging news for the treatment of tuberculosis. Not only is this an agent with a radically different means of action, but it shows potential to shorten the treatment of tuberculosis in the foreseeable future, something the tuberculosis community has been hoping for years."

The second part of the trial will prolong treatment with TMC207 to 24 weeks, and will be enrolled at sites in South Africa, Peru, Latvia and Russia. Results are expected later this year.

Source: Diacon AH, Pym A, Grobusch M et al. *The diarylquinoline TMC207 for multidrug-resistant tuberculosis.* N. Engl. J. Med. *360, 2397–2405 (2009).*

Promising trial results for maraviroc

Phase III clinical trials have demonstrated the efficacy of maraviroc, a member of a new class of antiretroviral agent, as a HIV treatment in patients with resistance to currently used antiretroviral medication.

Results from the double-blind, placebo-controlled, Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and 2 studies (of patients in Canada/USA, and Australia/Europe/USA, respectively) were published in the October issue of the *New England Journal of Medicine*. The study examined 1049 patients with R5 HIV-1 who had previously been treated with, or had already developed resistance to, three antiretroviral drug classes and who also had HIV RNA levels of more than 5000 copies per mm. Safety and efficacy were tested following 48 weeks of treatment. The mean change in HIV-1 RNA levels was significantly greater in maraviroc-treated patients, compared with placebo in both trials; -1.66 and -1.82 log10 copies per ml with the once-daily and twice-daily regimens of maraviroc, respectively, versus -0.80 with placebo in MOTIVATE 1, and -1.72 and -1.87 log10 copies per ml, respectively, versus -0.76 with placebo in MOTIVATE 2. CD4 counts were also significantly better in maraviroc-treated patients compared with controls in both studies. Furthermore, side effects were similar in both arms, suggesting that the use of maraviroc does not cause an increase in adverse effects.

These findings are of immense importance to the field of HIV therapy, as maraviroc is a member of a novel class of HIV drugs. Mararvoric is a CCR5 receptor antagonist. CCR5 is found on the surface of immune cells and is used by HIV as a coreceptor to enter and infect these cells. By blocking this interaction the drug inhibits viral entry and so prevents HIV replication. Due to the mutability of HIV, patients who take antiretrovirals for many years eventually develop resistance to the drugs. However, the demonstration that this novel class of drugs can be effective gives such patients renewed hope, as the virus has not had time to develop resistance.

Roy Gulick, of Weill Cornell Medical University (NY, USA) and lead author on the study, explains the significance of the results, "It is now possible to expect that a majority of treatment-experienced patients who experience failure on their current HIV drugs will regain control of their HIV infection with maraviroc combined with other newer antiretroviral drugs. This is an important step forward".

Sources: www.sciencedaily.com/releases/2008/10/081001181314.htm;
Gulick RM, Lalezari J, Goodrich J et al.*: Maraviroc for previously treated patients with R5 HIV-1 infection.* N. Engl. J. Med. *359, 1429–1441 (2008).*

Less is more: analysis shows that lower doses of an Alzheimer's drug may reduce the incidence of adverse events

It is often thought that administering higher doses of a drug results in more effective treatment of a disease. However, recent analysis has demonstrated that, relative to high doses, lower doses of an Alzheimer's drug, rivastigmine, can improve cognition while significantly reducing side effects. Rivastigmine is an acetylcholinesterase inhibitor manufactured by Novartis (Basel, Switzerland). It has been approved for use in 60 countries including all member states of the EU and the USA. Administration of rivastigmine between 6 and 12 mg improves cognitive functions, although a number of side effects are associated with it, including nausea, vomiting, diarrhea, abdominal pain and lack of appetite. Patients have also reported dizziness, fainting and weakness.

> "*This review has confirmed what we knew about the drug – that it provides cognitive improvements similar to other Alzheimer's medications.*"

Previous studies have suggested that lower doses of the drug administered more frequently may lead to a reduction in the number of adverse events. This preliminary evidence formed the basis of a new study that investigated the efficacy and safety of two doses of rivastigmine patch: 9.6 mg/day and 17.4 mg/day. The analyses included nine trials involving a total of 4775 patients. It appeared that patients receiving the 17.4 mg/day dose scored similarly on cognitive function tests compared with those taking the 9.6 mg/day dose. However, two thirds of patients taking the higher dose reported at least one adverse event compared with half of patients taking the lower dose. In addition, patients who were receiving the lower dose of rivastigmine patch had a reduced incidence of adverse events compared with those taking a 6–12 mg/day dose of rivastigmine capsules.

"This review has confirmed what we knew about the drug – that it provides cognitive improvements similar to other Alzheimer's medications", remarked Piero Antuono, a professor of neurology, pharmacology and toxicology at the Medical College of Wisconsin, WI, USA.

Source: Birks J, Grimley Evans J, Iakovidou V, Tsolaki M, Holt FE: Rivastigmine for Alzheimer's disease. Cochrane Database Syst. Rev. *(2009) (Epub ahead of print).*

Anakinra demonstrates a modest benefit for treating RA

The drug anakinra has a moderate beneficial effect for patients suffering from rheumatoid arthritis (RA), according to a recent *Cochrane Systematic Review*. However, the study warns of the possible risks of serious infections and discourages the use of anakinra with other biologic drugs.

The recent review sought to evaluate the clinical efficacy and safety of the drug for treating RA in adults. Data was compiled from five trials of anakinra, involving 2876 patients in total, and the study concluded that the drug is a relatively safe and moderately efficacious biologic therapy for RA.

Nevertheless, the improvements observed were notably less than those demonstrated for other biologics, and the authors recommend caution with the use of anakinra for RA, not least due to the increased rate of serious infections.

Moreover, one study in the review explored the combination of anakinra with etanercept – another biologic used for the treatment of RA – and found a significant increase in the number of serious adverse events. "On the basis of these results, we recommend that doctors avoid combining biologic medications with anakinra when treating patients with rheumatoid arthritis,' said lead researcher Marty Mertens.

Source: Mertens M, Singh JA: Anakinra for rheumatoid arthritis. Cochrane Database Syst. Rev. *1, CD005121 (2009).*

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine. If you have newsworthy information, please contact:

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