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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in clinical investigation

The future of TB treatment: trial shows potential for a new TB drug

Researchers from the TB Alliance have found a potential breakthrough drug regime that could change the way in which both drug-susceptible and, more significantly, multidrug-resistant TB (MDR-TB) are treated. Findings from a Phase II clinical trial suggest that this new combination therapy, called PaMZ, is not only effective at killing more than 99% of TB bacteria within 2 weeks, but may also be capable of reducing treatment timescales considerably. For instance, PaMZ ciykd treat some forms of drug-resistant TB in just 4 months, whereas at present treatment lasts up to 2 years.

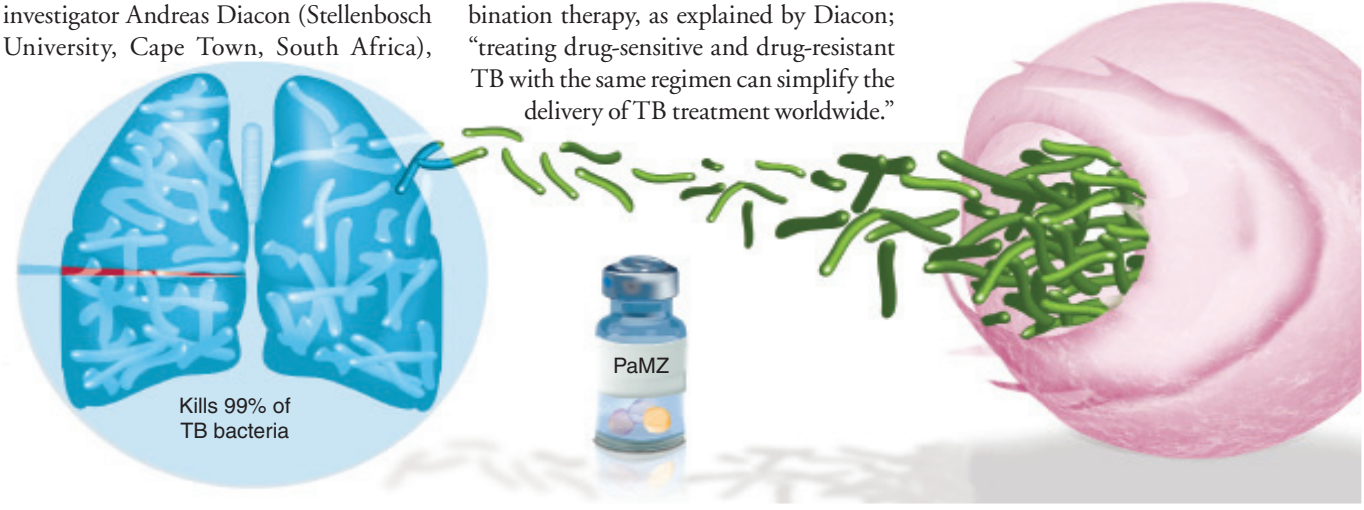
TB infection is becoming a major global burden, with approximately 9 million people developing TB each year and approximately 1.4 million people dying from the disease. It is particularly a problem in HIV/TB co-infection, where TB is the most frequent cause of death in AIDS patients. Currently, TB and HIV treatments cannot be given in conjunction due to drug–drug interactions. This trial therefore presents a huge advance in the treatment of of TB, as well as HIV. Lead author and principal investigator Andreas Diacon (Stellenbosch University, Cape Town, South Africa), enthused that "the results of this study give healthcare providers on the front lines of the TB epidemic hope for better, faster tools needed to stop this disease."

The study, named New Combination 1 (NC-001), consisted of a new blend of drugs; an established antibiotic, moxifloxacin; an existing TB drug, pyrazinamide; and a new TB drug candidate, PA-824. The study took place in South Africa and lasted 2 weeks. The trial also marks a major step forward in the optimization of multidrug regimes to treat TB, potentially changing the way TB treatment is carried out in the future. Mario Raviglione, Director of the Stop TB Partnership at WHO commented that out "because of testing drugs in combination, we have already saved several years in the research process to find new, effective regimens to treat TB."

Furthermore, the results show that both drug-susceptible and drug-resistant TB can be treated similarly. This simplifies the treatment of the different types of TB greatly and also helps to significantly reduce the cost of MDR-TB treatment, further supporting the rationale of drug combination therapy, as explained by Diacon; "treating drug-sensitive and drug-resistant TB with the same regimen can simplify the delivery of TB treatment worldwide."

A second trial using this principle of combinational drug therapy, is underway and enrolling patients in Brazil, Tanzania and South Africa. It will test this drug combination over a longer period of 2 months in order to further progress the clinical development of the drug regime.

This new combinational drug therapy looks promising, with potential to treat both the drug-susceptible and MDR-TB forms in the same way. This is highly advantageous, seeing as some drug-resistant forms are becoming impossible to treat, and these findings bring new hope in the fight against the disease. The new principle of combining different drugs in TB therapy presents a shift in the way TB treatment is carried out, providing not only a cheaper, but a more efficient and ultimately quicker, way to treat the disease, as explained by Mel Spigelman, CEO and TB Alliance President: "these findings confirm the promise of novel TB regimens to be shorter, simpler, safer, and, compared with today's MDR-TB drugs, much less expensive…The next trial to advance this regimen is already



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underway. We now have real momentum toward bringing to market treatments that will ultimately help save millions of lives."

Written by Sophie Wraight

Source: Trial Signals Major Milestone in Hunt for New TB Drugs; www.tballiance.org/newscenter/view-brief.php?id=1046
Diacon AH, Dawson R, von Groote-Bidlingmaier F *et al.* 14 day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* doi:10.1016/S0140–6736(12)61080–0 (2012) (Epub ahead of print).

FDA PrEPares to reduce risk of HIV infection with Truvada®

In mid-July, the US FDA approved Truvada®, an existing antiretroviral drug combining emtricitabine and tenofovir disoproxil fumarate, to reduce the risk of sexually acquired HIV-1 infection in uninfected individuals at high risk of acquiring HIV through sex, making this the first drug to be approved for HIV prevention in a scheme known as pre-exposure prophylaxis (PrEP).

Truvada has previously been approved by the FDA as a treatment for HIV in infected adults and children over 12, when combined with other antiretroviral drugs. According to the PrEP guidelines, Truvada can now also be used effectively when taken daily as part of a prevention strategy, combining it with safer sex practices, risk reduction counselling and HIV testing. Debra Birnkrant, director of FDA's Division of Antiviral Products, was keen to stress that "the drug is not a substitute for safer sex practices."

The approval for Truvada in PrEP is principally due to positive data from two large trials, iPrEx and the Partners PrEP trial. The iPrEx trial, which looked at risk reduction in approximately 2500 high-risk HIV-negative men or transgender women participants. The results showed that Truvada was effective in reducing the risk of HIV infection by 42% compared with placebo.

The Partners PrEP trial had approximately 4800 participants, all of whom were heterosexual couples where only one partner was HIV-infected (serodiscordant couples). Results showed Truvada reduced the risk of becoming infected by 75% compared with placebo. Connie Celum, lead investigator of the Partners PrEP trial, said: "The data clearly demonstrate that Truvada as pre-exposure prophylaxis is effective at reducing the risk of HIV infection acquired through sexual exposure."

A Risk Evaluation and Mitigation Strategy has been put in place by the FDA in order to educate prescribers of PrEP to minimize the risk of uninfected individuals acquiring HIV infection. It is also hoped that education about the use of Truvada for PrEP will help to prevent drug resistant HIV-1 strains developing in the future.

The future of PrEP with Truvada in the prevention of HIV infection in high-risk individuals certainly looks promising, and as Judith Feinberg, acting chair of the Antiviral Drugs Advisory Committee at the FDA, added "Prevention is a key goal in the efforts to stem the HIV epidemic."

Written By Sophie Breeze

Source: US FDA News Release. FDA approves first drug for reducing the risk of sexually acquired HIV infection; www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm

Potential targeted treatment for non-small-cell lung cancer suggested by Phase II trial

A Phase II trial for a targeted treatment for non-small-cell lung cancer suggests benefits over chemotherapy alone.

Targeted treatment for *KRAS*-mutant lung cancer might be closer with the results of a Phase II trial of selumetinib and chemotherapy for this subtype of non-small-cell lung cancer recently presented at the American Society of Clinical Oncology meeting 2012.

The results of this trial, presented by Pasi Jänne (Dana-Farber Cancer Institute, MA, USA), suggest that chemotherapy and selumetinib together are a more effective treatment for patients with mutated *KRAS*. *KRAS* mutations are the cause of a tumor in up to 20% of non-small-cell lung cancer.

According to Jänne: "This clinical trial demonstrates that a combination of chemotherapy and selumetinib is significantly better than chemotherapy alone for this group of patients." He continues that the therapy is: "better in terms of tumor response to therapy and in terms of survival times prior to advance of the disease."

Jänne thinks that this is a significant result because; "It suggests that for the first time we may have an effective treatment for *KRAS*-mutant lung cancer, which is the largest single subtype of the disease."

Patients with mutations in *KRAS* in the trial were randomized to receive either chemotherapy (docetaxel) and selumetinib or just docetaxel. Both rate of response to treatment and progression-free survival improved significantly in patients receiving targeted therapy in comparison with just docetaxel; response to treatment was 37% versus 0% and progression-free survival 5.3 months versus 2.1 months, respectively. Overall survival increased in the targeted therapy group but this was not significant.

There is currently no effective targeted therapy for lung cancer caused by a mutation in *KRAS*. The treatment under investigation does not target the KRAS protein itself, but acts downstream in the signaling pathway, on MEK1/2, to inhibit the pathway.

The most common grade 3–4 toxicity amongst participants was neutropenia, with dyspnea, asthenia and respiratory failure also occuring, as well as other less frequent side-effects.

Treatments resulting from this trial may go beyond lung cancer. Jänne says that;

"These impressive clinical findings not only have implications for the treatment of lung cancer but all cancers that harbor *KRAS* mutations, including pancreatic and colorectal cancer."

Written by Alisa Crisp

Source: Jänne PA, Tsang Shaw A, Rodrigues Pereira J *et al.* Phase II double-blind, randomized study of selumetinib (SEL) plus docetaxel (DOC) versus DOC plus placebo as second-line treatment for advanced KRAS mutant non-small cell lung cancer (NSCLC). *2012 ASCO Annual Meeting*. Chicago, IL, USA, 1–5 June 2012 (Abstract 7503).

Study provides support for linagliptin long-term use

The results of long-running international trials indicate that the oral DPP-4 inhibitor linagliptin is safe and effective, either as a stand-alone treatment or in combination with other selected oral antidiabetic drugs.

The recently published study consisted of a 78-week trial extension that was conducted at 231 sites in 32 different countries and considered 2121 previous participants who took part in four previous 24-week randomized, double-blind, placebo-controlled trials. In the trial extension 1532 of participants who previously received linagliptin continued their therapy, whilst 589 participants who had been in the placebo group in previous trials now also received linagliptin.

"This is the largest data set of long-term clinical evidence for linagliptin to date. Findings from the 78-week open-label extension involving 2121 people with type 2 diabetes demonstrate sustained glycemic control for up to 102 weeks treatment duration. They also provide evidence that supports the efficacy and tolerability profile seen in previously reported 24-week studies. Therefore this extension study shows that linagliptin is an effective and well tolerated therapy for the long-term management of type 2 diabetes," concluded David R Owens, from Cardiff University's Centre for Endocrinology and Diabetes Sciences (Cardiff, UK).

All participants were given linagliptin orally once a day, either on its own or in combination with either metformin or metformin plus a sulphonylurea or pioglitazone. Overall 14.3% of participants experienced drug-related adverse incidents, which led to 3.7% discontinuing medication.

The average baseline glycated hemoglobin and fasting plasma glucose levels were substantially lower in the linagliptin group compared with those who received placebo in the previous 24-week trials.

Written by Laura McGuinness

Source: Gomis R, Owens DR, Taskinen MR *et al.* Long-term safety and efficacy of linagliptin as monotherapy or in combination with other oral glucose-lowering agents in 2121 subjects with type 2 diabetes: up to 2 years exposure in 24-week Phase III trials followed by a 78-week open-label extension. *Intl J. Clin. Prac.* 66 (8) 731–740 (2012).

Intensive insulin therapy could slow diabetes progression

A study by researchers from the UT Southwestern Medical Center (TX, USA) has shown that intensive early treatment of type 2 diabetes could help to preserve β-cell function.

Preserving the body's insulin-producing capacity is important as it can help to slow disease progression. The study showed that intensive insulin treatment, followed by one of two drug regimens, enabled diabetes patients to maintain steady insulin-producing β-cell function for an average of 3.5 years after diagnosis. Both intensive regimes appeared to be equally effective.

Lindsay Harrison, an author of the study published in *Diabetes Care*, from the University of Texas Southwestern Medical Center explained to *Future Science Group*, that "we believe that patients with type 2 diabetes should be treated intensively from the start with either insulin or multiple complimentary oral therapies instead of using one therapy at a time and escalating only when the patient fails which subjects them to often long periods of hyperglycemia and β-cell deterioration."

Intensive treatment has been the standard at UT Southwestern for at least a decade, but elsewhere it can be more normal for physicians to recommend lifestyle changes first. For example, the American College of Physicians suggests losing weight and dieting before drug treatment. The American Diabetes Association also initially recommends lifestyle changes, as well as the use of metformin for those newly diagnosed patients.

"We believe that the stepwise approach exposes patients to long periods of high blood sugar, which leads to complications," said Ildiko Lingvay, lead author of the study, also from the University of Texas Southwestern Medical Center. "Intensive treatments led to excellent control of blood-sugar levels, they were well tolerated, safe and had good compliance," Lingvay explained.

"Diabetes prevalence is rising rapidly; this impacts both the individual patients and society by accounting for 10% of annual US healthcare expenditures. Therefore, early treatment that changes the natural history of the disease by preserving the patient's endogenous insulin secretion, which is linked to fewer disease complications, is important. Our study showed that early and intensive treatment (regardless of therapy choice) can preserve β-cell function, essentially halting the progress of the disease," Harrison told *Future Science Group*.

Written by Laura McGuinness

Sources: Harrison LB, Adams-Huet B, Raskin P, Lingvay I. B-cell function preservation after 3.5 years of intensive diabetes therapy. *Diabetes Care* 35 (7) 1406–1412 (2012); UT Southwestern Medical Center press release; www.utsouthwestern.edu/newsroom/news-releases/year-2012/june/diabetes-lingvay.html