The uphill battle to find new TB treatments

On Jan 17, 2017, Médecins Sans Frontières (MSF) enrolled the first patient in the TB PRACTECAL trial. The phase 2b/3 trial is scheduled to recruit 630 patients with rifampicin-resistant, multi-drug-resistant (MDR), and extensively drug-resistant (XDR) tuberculosis in Belarus, South Africa, and Uzbekistan. The first stage will test three 6-month regimens based on the new drugs bedaquiline and pretomanid alongside linezolid, a re-purposed antibiotic used to treat bacteria-resistant infections. Depending on outcomes after 8 weeks, the second stage will test one or two of these regimens against the standard-of-care. “If the trial is successful, it would mean that patients with drug-resistant disease would have a much shorter, oral regimen that could be given immediately to someone with rifampicin-resistance”, MSF’s Bern-Thomas Nyang’wa (London, UK) told The Lancet Respiratory Medicine. Patients would require fewer drugs and laboratory tests, and health-care workers would not need to be on hand to deliver injections.

Last year, WHO conditionally recommended a 9-month regimen for MDR tuberculosis, a new combination using seven old drugs which showed treatment success rates in excess of 85% under trial conditions. It costs about $1000, compared with $2000–5000 for the standard 18–24 month regimens. The STREAM trial, results from which are expected in 2020, will confirm its safety and efficacy. The ongoing NC005 trial is even more promising. Run by the TB Alliance (New York, USA), it is testing a regimen of bedaquiline, pretomanid, pyrazinamide, and moxifloxacin against MDR tuberculosis. At 2 months, almost all of the patients showed sputum free of tuberculosis bacteria, according to interim results released last year. “There is big hope for that regimen, and we are awaiting with great interest the results at the end of treatment and follow-up”, explained WHO’s Mario Raviglione. But obtaining funding for the next stage of development is proving slightly tricky. Another TB Alliance trial, Nix-TB, is testing a regimen of bedaquiline, pretomanid, and linezolid against XDR tuberculosis. The interim results released last year were encouraging. All the treated patients had converted sputum at 4 months, and treatment was stopped at 6 months. The global cure rate for XDR tuberculosis is currently 28%.

If all goes according to plan—no small proviso in the world of tuberculosis—the two TB Alliance regimes could be available within the next few years according to the Alliance’s Mel Spigelman. “A less toxic, more effective treatment for MDR tuberculosis would immediately have a significant impact on case-finding”, added Nyang’wa. In 2015, 132 000 of the estimated 480 000 patients with MDR tuberculosis had been diagnosed (a further 100 000 patients are thought to be rifampicin resistant only). But the continued use of linezolid is problematic. It is associated with Serious adverse events. During the Nix-TB trial, almost all the patients experienced some kind of neuropathy. When linezolid is used to treat MRSA, it has side-effects, optic neuritis, and other unpleasant effects”, said Nyang’wa. The PRACTECAL trial is using a dose of 600 mg for 4 months, followed by 200 mg for 2 months. “We are hoping that this level will potentially be less toxic than the reported results at 1200 mg”, said Nyang’wa.

Sutezolid is an oxazolidinone antibiotic in the same class as linezolid. In early studies, it showed fewer side-effects than linezolid. On Jan 25, 2017, the Medicines Patent Pool (MPP) announced that it had signed a licensing agreement for sutezolid with Johns Hopkins University, holders of the intellectual property. Were the agent to be brought to full development, it opens up the possibility of an entirely new regimen: bedaquiline, pretomanid, and sutezolid. “If that regimen was much less toxic than the current one involving linezolid, you could foresee that it might become a truly revolutionary treatment that could be widely used”, suggested Raviglione. “But this is still speculative—we will have to see what happens when all the different studies are concluded.”

The sutezolid agreement is the MPP’s first licensing arrangement for tuberculosis. “We will now be looking for drug developers to take out a subsequent licence with us to take the drug further, with the eventual idea of bringing it to market”, said Greg Perry, Executive Director of the MPP (Geneva, Switzerland). “We are using the idea of patent sharing and licensing to encourage the development of a drug”, said Perry. In 2015, global spending on drug-related research and development for tuberculosis was $231·9 million, far short of the $810 million envisaged by the Global Plan to Stop TB 2011–2015. There are currently just four drugs in phase 1 trials—for a reasonable chance of success, Raviglione believes it is probably necessary to have around 20 compounds at this stage of development.

The MPP, MSF, and the TB Alliance are among the organisations involved in the 3P Project, an attempt to stimulate drug development through push and pull mechanisms and the pooling of patents. “If the existing model is not working, and it clearly is not for tuberculosis, then you have to look at a different model”, points out Perry. The market has failed to maintain a healthy drug pipeline for tuberculosis. Unless this is resolved, any resistance to the new medications and regimens would have extremely serious consequences.

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