

BPaL approved for multidrug-resistant tuberculosis

The shorter, all-oral regimen approved by the US FDA could be an important step towards a universal regimen for tuberculosis. Talha Burki reports.



On Aug 14, 2019, the US Food and Drug Administration (FDA) approved a new, all-oral regimen to treat drug-resistant tuberculosis. The combination of bedaquiline, pretomanid, and linezolid (BPaL) was tested in the Nix-TB trial, which involved patients with extensively drug-resistant tuberculosis (XDR-TB) alongside patients who cannot tolerate or do not respond to therapy for multidrug-resistant tuberculosis (MDR-TB). 6 months after completing treatment, 95 of the first 107 patients who received a 6-month course of BPaL had negative sputum culture and were symptom-free. On the basis of the interim results, the FDA has approved the regimen for use in the studied population. "It is really great news, we now have a short-course combination that will encourage the whole community to think about drug-resistant tuberculosis as a surmountable problem", said Mel Spigelman of the TB Alliance, which conducted the Nix-TB trial.

2017, the most recent year for which records are available, saw 160 684 new diagnoses of MDR-TB and rifampicin-resistant tuberculosis (RR-TB), including 10 800 cases of XDR-TB. The best estimate for the actual burden of disease is much higher, at around 558 000 new cases of MDR-TB and RR-TB. The number of XDR-TB cases is thought to be roughly 40 000. Global treatment success rates for MDR-TB and RR-TB, and XDR-TB, based on numbers from 2015, stood at 55% and 34%, respectively.

"The challenge with XDR-TB and MDR-TB that does not respond to therapy is that patients stay infectious for a long time, and they consequently infect many more people", explains Stephen Gillespie (University of St Andrews, Scotland).

"It is very important for tuberculosis control that we can make new regimens that render resistant patients culture-negative quickly. That way we can start to reduce the number of new cases that are being generated and reverse the trend of increasing MDR-TB."

Last year, WHO amended its guidelines for MDR-TB, grouping the drugs into three classes in order of priority and stipulating that fully oral regimens ought to be preferred. But such regimens have hitherto been unavailable for XDR-TB; nor has there been anything akin to the 9-month MDR-TB regimen that was recommended by WHO in 2016. Current treatments for XDR-TB involve five to eight drugs to be taken for around 2 years. "A shorter regimen should lead to better adherence and better outcomes, and would allow patients to get back to their normal lives more quickly", says Jay Achar (Médecins Sans Frontières; MSF).

The constituents of the BPaL regimen are recent additions to the roster of tuberculosis drugs. In 2012, bedaquiline became the first FDA-approved drug for tuberculosis in 40 years. Linezolid is older, but had not been approved for use in tuberculosis, whereas pretomanid is an entirely new chemical entity. Almost half of the 109 patients in the Nix-TB trial have been followed up for 2 years. The trial was run in South Africa and included patients with HIV co-infection and teenagers. "The data are looking good; we are optimistic that the success rate we saw at 6 months after the end of treatment will turn out to be very close to the longer term cure rate", said Spigelman.

Nonetheless, the regimen is not without its disadvantages. Linezolid is associated with considerable toxicity.

Although none of the patients in the Nix-TB trial dropped out because of adverse events, only a minority were able to remain on the full dose of linezolid for the entire 6 months. Most patients had peripheral neuropathy. Reductions in blood counts were also common. "Programmes are going to have to choose between the 20–24 month regimen currently recommended by WHO, and the Nix-TB regimen, which is considerably shorter but we would expect to be reasonably toxic", said Achar. He cautioned against over-interpreting the Nix-TB trial, given that it was a single-arm study involving a relatively small number of patients, the results of which have yet to be published in a peer-reviewed journal.

The ongoing ZeNix study, also run by the TB Alliance, is investigating whether it might be possible to reduce the dose and duration of linezolid in the BPaL regimen, while maintaining its efficacy. "By the end of next year, we should know if we can potentially give a lower dose of linezolid and/or stop it after 2 months", said Spigelman. He added that in the Nix-TB trial, peripheral neuropathy mostly appeared after the 2-month mark. Gillespie is medical monitor on another TB Alliance trial examining a 4-month regimen of bedaquiline, pretomanid,



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moxifloxacin, and pyrazinamide in drug-sensitive tuberculosis and a 6-month regimen for MDR-TB.

Meanwhile, MSF's TB PRACTECAL trial is investigating how various combinations involving 6-month regimens based on bedaquiline, pretomanid, and linezolid perform in MDR-TB. Gillespie is confident about the prospects for success. "For these regimens the likelihood of resistance is very small", he told *The Lancet Infectious Diseases*. "If we could improve the side-effect profile and maintain the efficacy seen in the Nix-TB trial, then a BPAL regimen could turn out to be a very appealing option for all MDR-TB patients", adds Spigelman.

The cost of the BPAL regimen has yet to be established. Johnson & Johnson sells bedaquiline to the Global Drug Facility for US\$400 per course. Spigelman expects linezolid, which is a generic product, to be priced at around \$300 per course, but since the dose and duration will depend on how well

the drug is tolerated, the cost will vary from patient to patient. The producer of pretomanid is Mylan, who have yet to announce its price. "We do not think the cost of the regimen is going to be the limiting factor", stressed Spigelman. "Mylan is committed to affordability."

Much will depend on the results from the ongoing trials. "XDR-TB regimens cost so much mostly because the volumes are so low", explains Spigelman. "So using the same regimen for more patients could bring down production costs quite dramatically." An effective, short-course treatment would also incentivise programmes to make a concerted effort to track down undiagnosed cases, which in turn could help further push down the cost of the drugs. The 139 114 patients with MDR-TB who were enrolled on treatment in 2017 represented around a quarter of the total estimated burden.

If an effective, non-toxic regimen could be identified that treated all forms of tuberculosis, Spigelman

thinks that, depending on the drugs, the cost could hover at around \$100 per course of treatment. Chances are that this will not be the Nix-TB regimen; linezolid is likely to be more effort than it is worth for patients with drug-sensitive tuberculosis. "If we find a way to replace linezolid, we might have options for a universal regimen", said Gillespie. Restricting the duration of treatment to 4–6 months ought to be achievable, but there are still questions over how to give bedaquiline and pretomanid to children and the interaction between bedaquiline and some antiretroviral drugs. Gillespie is optimistic that the challenges can be overcome. "A few years ago a pan-tuberculosis regimen seemed a long way away; now it seems just round the corner", he said. "Such a regimen could simplify care, increase cure rates, and reduce mortality contributing to the End TB targets."

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Infectious disease surveillance update

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For more on **syphilis in Canada** see <http://outbreaknewstoday.com/syphilis-outbreak-declared-in-the-northwest-territories-1st-congenital-syphilis-case-since-2009/>

Listeriosis in Spain

Three deaths have been reported in the biggest ever outbreak of listeriosis in Spain, which was first reported on Aug 16. As of Sept 6, 204 cases of listeria infection have been reported in Andalusia, with most cases reported in Seville (n=162). The outbreak has been linked to a pork product made by a company based in Seville. The factory has been closed and the pork products recalled from shops. Five women have also had miscarriages due to their illness.

Chikungunya in Brazil

Between January and July, 2019, 97 000 probable cases of chikungunya virus infection have been reported across Brazil, mainly in the northeast and southeast, in Rio de Janeiro, Rio Grande North, and Para states. 40 deaths have been reported with 34 in Rio de Janeiro state. 72 000 cases

were reported in the same period in 2018.

Leishmaniasis in Kenya

Between Aug 19 and 25, 65 additional cases of leishmaniasis have been reported by Kenyan health officials. 2314 cases have been reported in this outbreak since the beginning of the year up to Aug 25, including 28 deaths (giving a case fatality rate of 1.2%). Cases have been reported in Garissa, Mandera, Marsabit, and Wajir counties.

Cholera in Yemen

Between January and July, 2019, 536 000 suspected cases of cholera have been reported in almost all districts of Yemen, including 773 deaths. A quarter of patients are aged younger than 5 years. The government, with support from international organisations, has done a second round of oral cholera vaccination, reaching

more than 400 000 people, including 65 000 children. Since April, 2017, more than 2 million cases of cholera and acute watery diarrhoea have been reported in Yemen in the largest ever outbreak.

Syphilis in Canada

Health authorities in the Northwest Territories, Canada, have declared an outbreak of syphilis, following an increase in cases, as well as the first congenital case reported in almost a decade. Five cases were reported across the region in 2017, and 11 in 2018. As of Aug 24, 28 cases of syphilis have been reported in the province this year, mostly from Yellowknife (n=20). In response, health authorities have set up improved access to rapid testing for sexually transmitted infection, enhanced testing for all pregnant women, and use of targeted health messaging.

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