Changing the game for multidrug-resistant tuberculosis

Promising new drugs and shorter regimens for the treatment of multidrug-resistant tuberculosis are beginning to emerge. Bharathi Ghanashyam reports ahead of World TB Day.

Sushma from Karnataka, southern India, was diagnosed with multidrug-resistant tuberculosis (MDR-TB) in October, 2014. She is registered for the government directly observed therapy plus regimen and her treatment will last for 2 years. After 17 months of treatment, two of her most recent sputum cultures have been negative. But she does not feel better and continues to complain of fatigue, body ache, and a cough that does not go away.

Contrasting Sushma's situation is that of Ali's in Bangladesh. In 2012, Ali was referred to the Damien Foundation (which implements a large tuberculosis control programme in Bangladesh in partnership with the government) after his 6 months of treatment with standard first-line tuberculosis drugs failed. His sputum culture showed resistance to several of the drugs. Ali was treated for MDR-TB with a 9-month regimen that included the drug gatifloxacin and declared free of tuberculosis in 2013 at the end of 10 months of treatment. He remained culture negative during the 2-year follow-up period and is presently doing well.

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New drugs (panel 1) and shorter regimens such as Ali's could help improve the worrying, global situation for MDR-TB (panel 2). The current treatment regimen is long and hard on patients, and there is already extensive resistance to existing second-line drugs. The Stop TB Partnership's Global Plan to Stop TB 2016–2020 states: "The introduction of a new regimen of shorter duration and containing three or four new drugs with no pre-existing resistance would be a game-changer in the fight against both drug-susceptible and drug-resistant TB."

9-month regimen

Beginning in 1997, efforts have been ongoing in Bangladesh to find an effective cure of shorter duration for MDR-TB. A study done in Bangladesh by Armand Van Deun and colleagues published in 2010 reported good success rates in a cohort of more than 200 patients with MDR-TB treated with a standardised regimen given for only 9 months (4-month intensive and 5-month continuation phase). Gatifloxacin was the main drug used in this regimen. Regarding concerns about the side-effects of this drug, Van Deun from the Institute of Tropical Medicine, Belgium, noted: "We initially used ofloxacin as recommended in the WHO 1996 guidelines but changed to

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BG received a scholarship to take part in the 2015 Journalist in Residence Programme of the Institute of Tropical Medicine, Antwerp, Belgium

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The names of the two patients featured in this report have been changed

Panel 1: New drugs for tuberculosis

Two new drugs—bedaquiline and delamanid—developed specifically for tuberculosis, have shown promise against multidrug-resistant tuberculosis (MDR-TB) in phase 2 trials. WHO issued interim guidance on bedaquiline in 2013 and delamanid in 2014, which allows their use under certain conditions—proper patient inclusion, adherence to WHO recommendations when designing MDR-TB treatment regimens, effective treatment and monitoring, pharmacovigilance and management of adverse events, and informed consent. However, uptake has been slow. By the end of 2014, only 43 out of the 144 countries that reported drug-resistant tuberculosis had used bedaquiline to treat patients. And, according to Médecins Sans Frontières (MSF), Otsuka—the manufacturer of delamanid—has only registered the drug in four countries, none of which have high burdens of drug-resistant tuberculosis, and only 180 people have received it worldwide.

Lucica Ditiu, Executive Director of the Stop TB Partnership, said: "The TB community has traditionally had low budgets and therefore a need to limit investments. Across countries, the common barrier to scaling the new drugs was registration, followed by the fear about side-effects and costs. We have worked on making these two drugs accessible to countries through donation programmes from USAID and Janssen. We have just announced the availability of delamanid via the Global Drug Facility (GDF)."

The GDF was established in 2001 as a part of the Stop TB Partnership to expand access to and availability of high quality tuberculosis drugs. However, in a statement on Feb 24, Grania Brigden, TB Advisor for MSF's Access Campaign, noted, "Otsuka should...register delamanid quickly in all countries where the drug has been tested in clinical trials, as well as in countries with the highest burdens of drug-resistant TB. If people can't access delamanid, this promising new drug will be effectively worthless."

Panel 2: Multidrug-resistant tuberculosis (MDR-TB)—a global overview

- 480 000 cases of MDR-TB are estimated to have occurred in 2014, but only 123 000 were detected and reported
- An estimated 300 000 cases of MDR-TB would have been identified if all of the notified cases had been tested for drug resistance
- An estimated 3·3% of new and 20% of previously treated cases had MDR-TB
- About 9·7% of MDR-TB cases had extremely drug-resistant tuberculosis (XDR-TB)
- In 2014, an estimated 190 000 people died of MDR-TB
- Globally, only 50% of MDR-TB patients were successfully treated

Source: WHO's Global tuberculosis report 2015

gatifloxacin because the bacteriological data showed that it is eight times stronger. It was locally produced at lower costs than ofloxacin. We did not see the serious dysglycemia problems associated with gatifloxacin."

In a follow-up study of 515 patients who were successively enrolled from 2005 to 2011, 84·4% had a bacteriologically favourable outcome. 50% completed treatment within 9 months, while 25% required an additional month of the intensive phase and 15% required 2 months owing to delayed sputum conversion.

Similar results were reported at the 46th Union World Conference on Lung Health, Cape Town, in 2015. An observational study done in nine countries in Francophone Africa in partnership with national tuberculosis programmes, and coordinated by the International Union against Tuberculosis and Lung Disease (The Union) used the drug moxifloxacin instead of gatifloxacin. The study recruited 1029 patients over 27 months and results were presented for 408 patients who began treatment before July, 2014. 22·4% of the recruited patients were HIV positive. Patients were treated over a period of 9 months with a standardised regimen. Of the 408 patients for whom results were presented, 328 (80·4%) were cured.

In all the studies, patients were closely monitored and socioeconomic support was provided. Side-effects such as hearing loss, liver enzyme elevations, kidney toxicity, and gastrointestinal problems were common, but none were severe enough for treatment to be withdrawn. The results collectively point to an effective, less punishing regimen for MDR-TB.

Pros and cons

The 9-month regimen, despite showing success in studies, has been viewed with varying degrees of scepticism and caution. Salmaan Keshavjee, director, Harvard Medical School Center for Global Health Delivery-Dubai, said: "It is not clear how the regimen will work in patients with HIV, or whether it works similarly with all strains of resistant tuberculosis. There are also safety concerns around the use of the main drug, gatifloxacin. Emerging data might change that. However, it makes sense to use the regimen where possible, because the short duration reduces the challenges of care delivery."

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Associated Press

India has high rates of multidrug-resistant tuberculosis

Zarir Udwadia, consultant physician, Hinduja Hospital, Mumbai, states that the 9-month regimen "cannot work in a place like India because of vast differences with Bangladesh, particularly with regard to HIV status and advanced patterns of drug resistance".

WHO has been cautious in its reaction. Although reporting that shorter MDR-TB regimens are less costly than the standard 20-month treatment regimen and likely to be better tolerated by patients, WHO currently recommends that countries adopt it on a case-by-case basis. This adoption has to be with approval from a national ethics committee, and under operational research conditions and monitoring by an independent board set up by, and reporting to, WHO.

The concerns about the regimen are likely to be addressed in a trial (STREAM) that The Union has been undertaking since 2010 in several countries, partly to assess the efficacy in different populations. The results are expected in 2017. In a later phase, it will also assess the new drug bedaquiline by substituting one drug in the 9-month regimen with it.

Ditiu says, "The 9-month MDR-TB regimen is already being used by a number of countries and the treatment success rate seems to be much better. Once the use of this regimen is recommended, countries will rush to use it. It will also be very good for patients and their adherence owing to the shorter time they will be on treatment. Treatment outcomes [will be better], and side-effects and costs will also be less. We hope that WHO will recommend wider use of the regimen very soon."

For people with tuberculosis, the prospects of a shorter regimen is certainly welcome news. Sushma had hoped that she was eligible for the 9-month regimen; she is disappointed that she is not. But there are thousands of other people who might be.

Bharathi Ghanashyam