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Novel treatment for drug-resistant tuberculosis shows promise, but concerns for patient safety remain

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In a viewpoint published this week in *The Lancet*, the Community Research Advisors Group (CRAG) argue that research into bedaquiline – a new drug, fast tracked for multidrug-resistant tuberculosis (MDR-TB) – should proceed cautiously in people with drug-sensitive tuberculosis. CRAG, an international, community-based advisory board for the US Centers for Disease Control and Prevention's Tuberculosis Trials Consortium, writing in *The Lancet* independently, urge researchers to balance the goal of shortening treatment for drug-sensitive TB with patient safety.

Bedaquiline is the first novel drug to be approved for treatment of tuberculosis in forty years. The FDA fast-tracked the approval of the drug after phase 2 studies showed bedaquiline's promising activity against MDR-TB (the drug reduced the average time to a negative TB culture from 18 to 12 weeks, and increased the proportion of participants with a negative culture at 6 months from 58% to 79%). Current treatments for drug-resistant tuberculosis show improved outcomes when continued for 18 to 24 months, and even then cure rates range from 11% to 79% depending on the extent of resistance. This presents a huge burden both on health care facilities and on patients to stick to a strict, toxic, and lengthy regimen, often in settings where available resources and cost make long drug treatments difficult to implement.

However, along with the potential benefits of bedaquiline, the authors point out that the drug presents several safety concerns that should be addressed before testing the drug in people with drug-sensitive TB, who already have a very effective treatment option and as such face different risk-benefit considerations than people with drug-resistant TB. In one phase 2 trial, a significantly higher number of participants receiving bedaquiline died than those receiving placebo. The majority of these deaths had no common cause and occurred months after the trial ended, but due to the long half-life of the drug, adverse effects from the drug cannot be ruled out. Close follow-up monitoring is needed due to an increased rate of liver and cardiac toxicity observed in patients receiving bedaquiline, say the authors.

The authors also call on the drug's developer, Janssen, to make information regarding the drug's safety available to public research groups, and to immediately begin trials on the effects of the drug in populations that use alcohol and drugs, and that have Hepatitis B and C. These groups could both benefit greatly from future shortened tuberculosis treatment regimens, but are also at a greater risk of some of the drug's reported side effects.

According to CRAG co-chair Dorothy Namutamba, "Although up to this point it has only been studied as an addition to existing regimens for drug-resistant tuberculosis, bedaquiline shows a lot of promise for improving treatment in the future. However, the drug also shows potentially serious adverse effects ranging from liver toxicity, disruption of the heart's electrical rhythm, and even death. As trials of this novel drug are considered in patients with drug-sensitive tuberculosis, researchers need to carefully balance the potential benefit of the new drug while making sure to always place the safety of the trial participants at the forefront of any considerations."

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