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24-week regimens for treatment of rifampicin-resistant tuberculosis: four-arm randomised trial

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Introduction

Rifamipcin-resistant tuberculosis (RR-TB) affects around 465,000 people each year globally. Current treatment is of 9-20 months' duration; is toxic and poorly efficacious. TB-PRACTECAL is a multi-arm, 2-stage, randomised controlled, multi-country, non-inferiority trial comparing 24-week regimens to the locally approved standard of care (control). We report TB-PRACTECAL stage 1 and 2 outcomes as well as additional analyses from dropped arms.

Methods

Participants 15 years and above with pulmonary RR-TB from Uzbekistan, South Africa, and Belarus were included regardless of HIV status or CD4 count. Patients were randomized in a 1:1:1:1 ratio in stage 1 and 1:1 in stage 2. Randomization lists were stratified according to trial site. The BPaL regimen was comprised of bedaquiline 400mg daily for 2 weeks then 200mg three times weekly for 22 weeks, pretomanid 200mg daily for 24 weeks, and linezolid 600mg daily for 16 weeks followed by 300mg daily for 8 weeks. BPaLM additionally contained moxifloxacin 400mg daily and BPaLC contained clofazimine 100mg daily. Treatment was administered daily under observation. Transition to stage 2 occurred after enrolment of 240 participants and BPaLM was found to be the most promising arm. Randomisation continued during transition and all participants continued their allocated regimen and were followed up to 108 weeks. A post-hoc analysis was conducted comparing the three investigational arms to control using the primary efficacy outcome: proportion of patients with unfavourable outcome (death, treatment discontinuation, treatment failure, recurrence, lost to follow-up) at 72 weeks. We also assessed the proportion of patients with grade ≥3 or serious adverse events (SAE) by 72 weeks and mean change in QT corrected using Fridericia's formula (QTcF) at week 24.

Ethics

This study was approved by the Ethics Review Board (ERB) of the London School of Hygiene and Tropical Medicine and the local ERBs in Uzbekistan, Belarus and South Africa; and by the MSF ERB.

Results

In March 2021, TB-PRACTECAL was terminated for efficacy at which point, 552 patients were enrolled. In the modified intention-to-treat population (comprising all randomised patients dispensed study medication at least once, excluding patients who did not have microbiologically-proven RR-TB), 252 patients had reached 72 weeks of follow-up, 44.0% of whom were female and 22.6% were HIV positive. In the modified intention-to-treat population, the percentage of unfavourable outcomes were 48.5% (32/66) for control, 23.3% (14/60) for BPaL, 18.8% (12/64) for BPaLC, and 11.3% (7/62) for BPaLM. There were three recurrences in BPaL, one in BPaLC, and none in BPaLM. Percentage of Grade ≥3 or SAE were 19.4% (14/72; 16 events), 31.9% (23/72; 32 events) and 21.7% (15/69; 24 events) in BPaLM, BPaLC and BPaL respectively, compared with 58.9% (43/73; 69 events) in the control. Mean change in QTcF at week 24 was 27.0 milliseconds (ms), 40.2 ms, and 23.3 ms in BPaLM, BPaLC, and BPaL respectively; compared with 44.89 ms in the control.

Conclusion

24-week all-oral regimens of bedaquiline, pretomanid and tapered-dose linezolid, with and without clofazamine or moxifloxacin are safe and efficacious in the treatment of RR-TB. Trial results show that treatment with BPaLM was more effective and had a better safety profile than the Control. BPaLC and BPaL were also highly effective.

Conflicts of interest

None declared.

Dr Ronelle Moodliar is a Physician that incorporates Family Medicine into her unique approach to clinical research.

In 2007, Ronelle joined the drug-resistant tuberculosis department at King Dinuzulu Hospital. She has dedicated the past 12 years to clinical research in this field where she has been the principal investigator for leading trials working with sponsors such as the TB Alliance, MSF, Janssen pharmaceuticals and Vital Strategies.

She currently is part of the executive committee and serves as the head of the clinical trial department at (THINK) Tuberculosis and HIV Investigative Network, where over the last 8 years she has established three successful clinical trial units for TB research.