Tuberculosis drug regimens and their efficacies

openaccessgovernment.org

18 October 2022

Andrew Nunn, Professor of Epidemiology in the Medical Research Council Clinical Trials Unit at UCL, analyses different tuberculosis drug development regimens

In a previous OAG article, published in February 2022, the historical background to the treatment of multi-drug resistant or rifampicin-resistant tuberculosis (MDR-TB, RR-TB) was described together with the results of Stage 1 of STREAM, the first phase 3 trial of a shortened regimen.

In brief, Stage 1 demonstrated that a 9-month regimen was non-inferior to the 20-month regimen that was currently recommended by the World Health Organisation (WHO).(1) Stage 2 of STREAM investigated two new shortened regimens; one a fully oral 9-month regimen in which bedaquiline is substituted for the injectable tuberculosis drug, kanamycin, and a 6-month regimen in which both bedaquiline and a shortened intensive phase with kanamycin are included.

An introduction to bedaquiline in treatment

Bedaquiline is the first new tuberculosis drug for over 40 years. It received accelerated regulatory approval by the US Food and Drug Administration (FDA) in 2012 and is widely used in the treatment of MDR-TB.

However, the evidence for its efficacy has been based almost entirely on uncontrolled observational studies. STREAM Stage 2 is the trial which it is hoped will provide robust evidence as to bedaquiline's effectiveness and thereby obtain full regulatory approval by both the FDA and the European Medicines Agency (EMA).

The results of STREAM Stage 2 will be presented at the World Conference on Lung Health in November 2022.

Two other phases 3 trials of bedaquiline have recently been completed. ZeNix-TB is a follow-up to Nix-TB which reported high levels of success of a six-month regimen of bedaquiline, pretomanid and linezolid in patients with extensively drug-resistant tuberculosis or MDR-TB that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects. Results of Nix-TB were very encouraging, and they led to the approval by the FDA of pretomanid, another new tuberculosis drug.

A limitation of this study was that it was uncontrolled and was conducted in only one country, South Africa. Furthermore, there were some concerns about the high proportion of patients who had peripheral neuropathy or hematological side-effect related to

linezolid.

The successes of ZeNix with linezolid

ZeNix was initiated to investigate, in a factorial design, the safety and effectiveness of a reduced dose and/or shortened duration of linezolid given in addition to six months of bedaquiline and pretomanid. A total of 181 patients from four different countries were enrolled. The success rate, as measured by relapse-free cure six months after stopping treatment, was 93% for participants receiving 1200mg throughout treatment; 89% in participants receiving 1200mg oflinezolid for two months, 91% for those receiving 600mg of linezolid for six months, and 84% in those receiving 600mg of linezolid for two months. (2)

The level of adverse effects, in particular, peripheral neuropathy and anaemia were related to the degree of linezolid exposure. The authors concluded that a 600-mg, 26-week regimen of linezolid appeared to have the most favourable risk–benefit profile among the four regimens studied. They acknowledged however that the size of the trial limited the precision of estimates of treatment effects and the absence of a standard of care control group meant there is no clear comparator against which efficacy could be assessed.(2)

The TB-PRACTECAL trial

A second trial, TB-PRACTECAL, is expected to be published in the near future; it is, a phase 2-3 trial designed to assess variations on the three-drug regimen known as BPaL given in Nix-TB; the current WHO standard of care was included as a control. There were three experimental regimens, BPaL plus moxifloxacin, BPaL plus clofazimine and BPaL alone. Linezolid was given 600mg daily for 16 weeks then 300mg daily for the remaining 8 weeks of the regimen.

Moxifloxacin and clofazimine had both been used as part of the STREAM regimen. The main efficacy outcome, unfavourable status at 72 weeks after randomisation was treatment failure, death, treatment discontinuation, recurrence of TB or loss to follow-up, similar to that used in STREAM.

In March 2021 the TB-PRACTECAL Data and Safety Monitoring Committee recommended that further randomisation should be terminated on account of a highly significant difference in outcome rates between the moxifloxacin-containing regimen and the control. Results were presented at the CROI 2022 conference.(3)

Of 66 patients on the Control regimen, 48.5% had an unfavourable outcome compared to only 11.3% of 62 on the BPaL plus moxifloxacin regimen.(3) The commonest reason for an unfavourable outcome was discontinuation on account of an adverse event. There were no failures of treatment or recurrences reported on either regimen. The authors concluded that 24 week all oral regimens containing a backbone of bedaquiline, pretomanid and tapered dose linezolid are both safe and efficacious in the treatment of rifampicin-resistant tuberculosis.

WHO consolidated guidelines for tuberculosis treatment

In February-March 2022 WHO convened an independent Guideline Development Group (GDG) to assess the results of individual patient data analyses from the three trials mentioned above and observational studies using bedaquiline, pretomanid and linezolid. WHO subsequently published a rapid communication to inform key stakeholders in National TB Programmes in advance of detailed recommendations which will be presented later this year in a 2022 update of the WHO consolidated guidelines.(4)

The rapid recommendation stated that the 6-month BPaLM regimen (comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin) may be used programmatically in MDR/RR-TB patients without previous exposure to these medicines in place of the 9-month regimen currently used or the longer (18 months plus) regimen. These are promising developments in an area of research which has been badly neglected in the past. Further work is however still needed to develop safe and highly effective regimens.

References

1. Nunn A J, Phillips PP, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380(13):1201-1213.
2. Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline- Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med. 2022;387(9):810-823.
3. Nyang'wa B, Kazounis E, Motta I, et al. TB-PRACTECAL results: 24 week all-oral regimens for rifampicin resistant tuberculosis (CROI Abstract 79). 2022:29.
4. World Health Organisation. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. 2022.

Please Note: This is a Commercial Profile