South African Experience of BpaL

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USAID FROM THE AMERICAN PEOPLE

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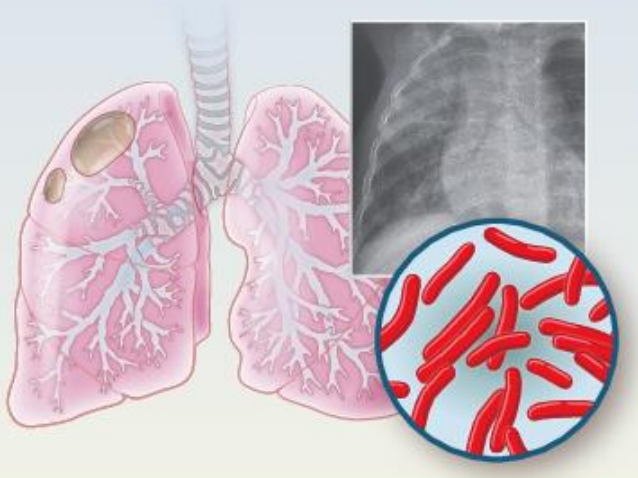
WITS HEALTH CONSORTIUM

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Highly Drug-Resistant Pulmonary TB

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients
with confirmed tuberculosis



Three-drug regimen (26 wk)

Bedaquiline

Pretomanid
(recently approved)

Linezolid

XDR tuberculosis
N=71
(65%)

Nonresponsive or treatment-intolerant MDR tuberculosis
N=38
(34%)

Clinical resolution at 6 mo after therapy

90% of all patients had favorable outcomes
95% CI, 83–95

89%
95% CI, 79–95

92%
95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

F. Conradie et al. 10.1056/NEJMoa1901814

RESEARCH SUMMARY

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

Conradie F et al. DOI: 10.1056/NEJMoa2119430

CLINICAL PROBLEM

Bedaquiline–pretomanid–linezolid has had efficacy against highly drug-resistant tuberculosis, but the incidence of adverse events with the 1200-mg daily dose of linezolid has been high. Whether a different dose and duration of linezolid treatment might reduce adverse events while maintaining efficacy is unclear.

CLINICAL TRIAL

Design: A dose-blind, randomized trial assessed the efficacy and safety of four regimens of linezolid as part of bedaquiline–pretomanid–linezolid treatment for highly drug-resistant tuberculosis.

Intervention: 181 participants (≥14 years of age in South Africa and the country of Georgia and ≥18 years of age in Russia and Moldova) with extensively drug-resistant (XDR) tuberculosis, pre-XDR tuberculosis, or rifampin-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued owing to side effects were assigned to receive bedaquiline and pretomanid for 26 weeks, along with linezolid at one of two doses for either 26 weeks or 9 weeks. The primary end point was treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. A favorable outcome was maintenance of negative culture status throughout follow-up in participants who had not had an unfavorable outcome previously.

RESULTS

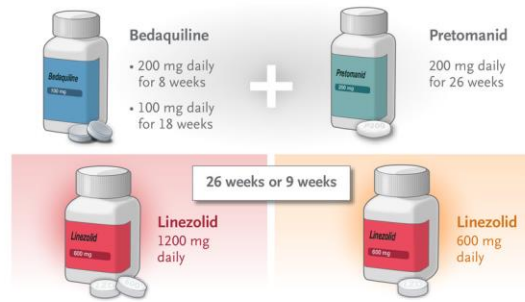
Efficacy: In the four treatment groups, the incidence of treatment failure or disease relapse (the primary end point) ranged from 7 to 16%; the incidence of a favorable outcome ranged from 84 to 93%.

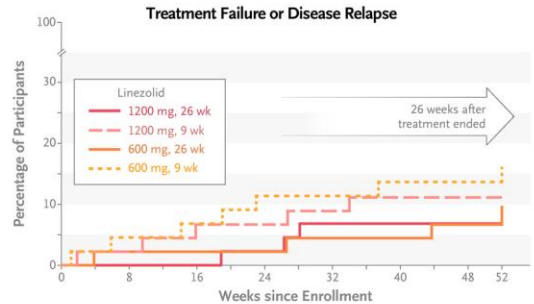
Safety: Fewer linezolid dose modifications, peripheral neuropathy episodes, and myelosuppression events occurred with the lower dose of linezolid than with the higher dose. The higher dose had a poorer safety profile in the 26-week group than in the 9-week group; there was less difference between the two lower-dose groups.

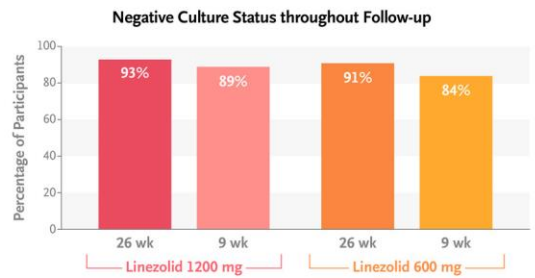
LIMITATIONS AND REMAINING QUESTIONS

- The small sample size limits the precision of estimates of efficacy.
- The trial was not powered for formal comparisons of efficacy among the treatment groups.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

In patients with highly drug-resistant tuberculosis, 600 mg of linezolid for 26 weeks resulted in a more favorable risk–benefit profile than other dose–duration regimens tested.

Epidemiology of RR-TB in South Africa

- 8000 to 10 000 cases every year
- Diagnosis made by GeneXpert Ultra
- Median Age of patients: 35 years
- More men than women
- Most cases are transmitted and not acquired
- 50% of our patients are HIV infected
- 20% of our patients are Pre-XDR

Bedaquiline, Pretomanid and Linezolid Clinical Access program (BPaL CAP)

AIM: To evaluate the effectiveness and safety of the BPaL Regimen for patients with extensively drug-resistant tuberculosis (XDR-TB), fluoroquinolone resistant TB and selected Rifampicin Resistant TB (RR-TB) via pre-approval access

Open Label, single arm intervention study

400 participants to be enrolled

Primary outcomes

Safety and Tolerability:

The proportion of participants who have a Grade 3, 4 or 5 Adverse Event up to 6 months after the end of the treatment.

Effectiveness:

The proportion of participants who have a favorable treatment outcome, defined as cured or treatment completed without recurrence during 12 months after the end of the treatment.

Progress to date

- Started in March 2021; funded by USAID and South African NTP
- Implementation at 5 sites so far.
- 219 screened
- 206 participants enrolled
- 77 participants have complete treatment
- All were culture negative at the end of treatment

Demographics

	Median (IQR)	Min-Max
Age (years)	41 (35-50)	17-82
BMI (m/kg^2)	20.0 (17.5-22.9)	14.1-48.7
	N	**%**
Gender		
Female	50	31.4
Male	109	68.6
Race		
Black	150	94.3
Other	9	5.7
HIV Status		
HIV Negative	53	33.3
HIV Positive	104	65.4
Unknown	2	1.3

Baseline resistance patterns prior to enrolment

	N	%
Known FQ-R RR TB	34	21.4
Known FQ-S RR TB	60	37.7
RR TB-unknown FQ status at enrollment	65	40.9

Time to culture conversion (data lock 28 Nov 2022)

	Number of participants
Started on BPaL regimen	159
Completed at least 60 days of treatment and are not found to be resistant to bedaquiline	124
Achieved sputum culture conversion (N=124)	95 (76.6%)
Median (IQR) time in days to conversion (N=95)	57 days (30-85)
Conversion occurred within the first six months of treatment (N=95)	92 (96.8%)

Safety

	Number of participants
Total enrolled	159
Grade 3-5 AEs	30 incidences among 24 participants
Serious AEs (SAEs)	16 incidences among 14 participants
Deaths	2

Progress to date

- 8 participants have been withdrawn early
  - 4 participants had bedaquiline resistance
  - Two participants died during treatment; one due to linezolid adverse events
  - 2 participants were withdrawn due to adverse events: peripheral neuropathy and optic neuritis.
- Two participants had their treatment extended.

Conclusions

- This is an excellent example of a public private partnership with leadership from the NTP
- This program allows both the access to new regimens for the South African RR TB patients and accumulation of evidence