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Implementation of bpal in the United States: Experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant TB disease

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Abstract

Background: Rifampin-resistant tuberculosis is a leading cause of morbidity worldwide; only one-third of persons initiate treatment and outcomes are often inadequate. Several trials demonstrate 90% efficacy using an all-oral, six-month regimen of bedaquiline, pretomanid, and linezolid (BPaL), but significant toxicity occurred using 1200mg linezolid. After U.S. FDA approval in 2019, some U.S. clinicians rapidly implemented BPaL using an initial linezolid 600mg dose adjusted by serum drug concentrations and clinical monitoring.

Methods: Data from U.S. patients treated with BPaL between 10/14/2019 and 4/30/2022 were compiled and analyzed by the BPaL Implementation Group (BIG), including baseline examination and laboratory, electrocardiographic, and clinical monitoring throughout treatment and follow-up. Linezolid dosing and clinical management was provider-driven, and most had linezolid adjusted by therapeutic drug monitoring (TDM).

Results: Of 70 patients starting BPaL, two changed to rifampin-based therapy, 68 (97.1%) completed BPaL, and two of these 68 (2.9%) patients relapsed after completion. Using an initial 600 mg linezolid dose daily adjusted by TDM and careful clinical and laboratory monitoring for side effects, supportive care, and expert consultation throughout BPaL treatment, three (4.4%) patients with hematologic toxicity and four (5.9%) with neurotoxicity required a change in linezolid dose or frequency. The median BPaL duration was 6 months.

Conclusions: BPaL has transformed treatment for rifampin-resistant or intolerant tuberculosis. In this cohort, effective treatment required less than half the duration recommended in ATS/CDC/ERS/IDSA 2019 guidelines for drug-resistant tuberculosis. Use of individualized linezolid dosing and monitoring likely enhanced safety and treatment completion. The BIG cohort demonstrates that early implementation of new tuberculosis treatments in the U.S. is feasible.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. This article does not overlap substantially with any articles already published or accepted for publication. Preliminary findings from some patients in this report are broadly referenced in a brief Letter to the Editor and in one case report (both attached as Supplementary documents), but the current manuscript provides substantially more detailed clinical information on individual patients and includes a much larger cohort with longer follow-up.

*Study Group team members are listed in the Acknowledgments.

Keywords

Tuberculosis; drug resistance; bedaquiline; pretomanid; linezolid

BACKGROUND

In 2021, an estimated 10.6 million people developed tuberculosis and 1.6 million died from the disease worldwide.[1] Outcomes are relatively poor among the 450,000 persons with at least rifampin-resistant tuberculosis (RR-TB), with only one-third initiating treatment and a global treatment success rate of approximately 60%.[1] In the United States and its affiliated areas, 618 cases of RR-TB alive at diagnosis were reported between 2014 and 2018 (CDC, unpublished data). Only 62% completed treatment within 24 months and 8% died before treatment completion. Of additional concern, persons living with RR-TB face economic, psychological and social costs.[1–3]

Until recently, the U.S. standard of care for patients with RR-TB and rifampin-intolerant tuberculosis included five or more drugs in the intensive phase and four drugs in the continuation phase, totaling 15–24 months duration.[4] Molecular (genotypic) and culture-based (phenotypic) drug susceptibility testing are used to identify effective drugs.[4, 5] Rifampin-sparing regimens require high pill burden, long duration, high toxicity of “second-line” drugs, complex monitoring, prolonged infectiousness, lengthy respiratory isolation and profound psychosocial impacts on patients and their families.[3, 4, 6]

In August 2019, the U.S. Food and Drug Administration (FDA) approved an all-oral, six-month regimen of bedaquiline, pretomanid and linezolid (BPaL) for some patient with drug-resistant pulmonary tuberculosis based on data from the NIX-TB Trial conducted in South Africa.[7–9] Using a linezolid dose of 1200 mg daily, this trial found BPaL to be 90% effective against treatment-intolerant/non-responsive MDR-TB (resistant to both rifampin and isoniazid) and extensively drug-resistant tuberculosis (XDR-TB, MDR plus resistance to both fluoroquinolones and injectable agents using pre-2021 definitions from the World Health Organization, WHO[10]). However, linezolid caused significant hematologic and neurologic toxicity, and more than 80% of patients experienced an adverse event.

In October 2019, some U.S. tuberculosis physicians began prescribing BPaL using 600 mg of linezolid daily along with therapeutic drug monitoring (TDM). The BPaL Implementation Group (BIG) was convened with the goal of compiling and disseminating clinical information about the U.S. experience with BPaL. We report the real-world management and outcomes of U.S. patients treated with BPaL, 2019–2022.

METHODS

BIG cohort development

We collected data on patients who were diagnosed with RR-TB or rifampin-intolerant tuberculosis and treated with BPaL between 8/14/2019 and 4/30/2022, regardless of anatomical site of disease or indication for BPaL. Patients were managed by their treating clinician, with consultation available from the Centers for Disease Control and

Prevention (CDC)'s tuberculosis Centers of Excellence (COE, https://www.cdc.gov/tb/education/tb_coe/) and local experts. Patients were educated and included in the decision to use the novel BPaL regimen.

Bpal treatment and monitoring

Treatment included bedaquiline 400 mg daily for 14 days then 200 mg thrice weekly (TIW), pretomanid 200 mg daily, and linezolid with provider-determined dosing, supervised with directly observed therapy (DOT).[4, 11] Providers used existing guidelines and protocols for treatment and monitoring of patients with drug-resistant TB,[4, 7, 12] but management was not standardized.

Before treatment, patients underwent history, physical examination, laboratory testing (including hemogram, HIV serology, pregnancy test, chest-radiograph (CXR), electrocardiography (ECG), blood biochemistry (with metabolic panel, magnesium, liver panel, thyroid panel), and visual acuity testing. Patients were typically assessed monthly for treatment response and adverse effects. Providers monitored the QT interval (Fridericia formula QTcF), facilitated in some patients by using a KardiaMobile personal ECG (AliveCor, Inc., Mountain View, California). CXRs were usually repeated two months after treatment initiation and at the end of therapy. For pulmonary tuberculosis, sputum samples were examined for acid fast bacilli (AFB) and cultured for *M. tuberculosis*, normally at least monthly. After discontinuation of BPaL, providers aimed to follow patients for relapse and resolution of adverse events for at least two years.

Laboratory assessment

Laboratory identification and drug susceptibility testing for *M. tuberculosis* was performed by CDC's Division of Tuberculosis Elimination Laboratory Branch (Atlanta, Georgia) and Florida's Bureau of Public Health Laboratories (FLBPHL, Jacksonville, Florida). CDC performed molecular detection of drug resistance (MDDR) using DNA sequencing to detect mutations associated with resistance to rifampin (*rpoB*), isoniazid (*katG, fabG1* and *inhA*), pyrazinamide (*pncA*), ethambutol (*embB*), fluoroquinolones (*gyrA* and *gyrB*) and the injectable drugs amikacin (*rrs*), kanamycin (*rrs* and *eis*), and capreomycin (*rrs* and *tlyA*).[13] Phenotypic testing was performed by the indirect agar proportion method as previously described.[14] The FLBPHL performed MDDR using Sanger sequencing to detect mutations associated with linezolid (*rrl* and *rplC*) and bedaquiline (*atpE* or *rv0678*) resistance in addition to those tested by CDC MDDR (*B. Jones, personal communication*). Phenotypic susceptibilities were determined using a customized Sensititre (Trek Diagnostics System, Thermo Fisher Scientific, Cleveland, OH) broth microdilution plate for first- and second-line drugs. Linezolid minimum inhibitory concentration (MIC) ≤1mcg/mL was considered susceptible; MICs were not available for bedaquiline or pretomanid when these patients started BPaL. Therapeutic drug monitoring (TDM) for linezolid using patient blood samples was performed at the University of Florida Infectious Disease Pharmacokinetics Laboratory using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a Thermo Endura tandem mass spectrometer and a Dionex Ultimate 3000 ultrahigh-performance liquid chromatography (UHPLC) system. The recommended sampling times were a pre-dose trough followed by 2- and 6-hour post dose samples; alternatively, 2-,

6-, and 24-hour samples following a single daily dose. If linezolid is given TIW, the recommended trough sampling time is 48 hours following the last dose. Because oral drugs can display delayed absorption for various reasons, 2 post-dose samples improve the probability of estimating Cmax. The trough is most closely linked to toxicity. Two, and preferably three samples also allow for a reasonable estimation of AUC. Clinicians typically adjusted the linezolid dose and/or dosing interval targeting a pre-dose trough concentration <2 mcg/mL and peak concentration of 12–26 mcg/mL between 2 and 6 hours after the dose.

Data collection and definitions

The treating teams abstracted data from medical records and securely transmitted data to the University of Florida. The principal investigator verified and categorized data into consistent categories, including demographics, co-morbidity, TB disease characteristics, treatment and monitoring.

Drug resistance was classified using the pre-2021 WHO definitions in place when this cohort was created (MDR, pre-XDR defined as MDR plus resistance to either fluoroquinolones or injectable agents, and XDR).[10] Baseline anemia was defined as having a documented diagnosis or hemoglobin <13.2 mcg/dl for men or <11.6 mcg/dl for women, thrombocytopenia as platelet count <150,000/uL, and leukopenia as leukocyte count <4,000 cells/uL. Hematologic toxicity was defined by the treating provider as a clinically significant change in hemoglobin, platelets or white blood count from baseline. Baseline neuropathy required a documented diagnosis; neurologic toxicity was defined as any new or worsened neurologic symptoms during treatment. Culture conversion was defined as having two consecutively negative cultures taken 30 days apart, and treatment failure was defined as lack of culture conversion after four months of BPaL or having culture reversion to positive on two consecutive samples thirty days apart.[15] QT interval prolongation was defined as an absolute QTcF >500 ms or an increase from baseline of >60 ms. BPaL treatment interruption was defined as the number of consecutive days of missing both bedaquiline and pretomanid.

The University of Florida Institutional Review Board (IRB) determined this study to be research exempt from additional review (IRB202002323). A Data Use Agreement was enacted between the University of Florida and each contributing site. CDC IRB approval was not required because CDC involvement was limited to assistance with data interpretation and manuscript writing.

RESULTS

Baseline cohort characteristics

Seventy patients in 12 states and U.S. territories were included in this cohort. Median age at diagnosis was 37 years (range 14–83), and median weight prior to BPaL was 58.0 kilograms (range 40.0–132.7). Most were male (n=46, 65.7%), non-U.S.-born (n=63, 90%), non-White (n=54, 77.9%), and not Hispanic (n=59, 84.3%) (Table 1). Co-morbidities prior to BPaL use included anemia (n=17, 24.2%), diabetes (n=28, 20%), neuropathy (n=11, 15.7%), liver disease/alcohol use disorder (n=9, 12.9%), renal disease (n=7, 10%), hypothyroidism (n=5,

7.1%), and HIV-infection (n=4, 5.7%). Five patients (7.1%) reported prior tuberculosis treatment, and two others (2.9%) arrived in the U.S. on inadequate MDR-TB treatment and were changed to BPaL treatment.

TB disease characteristics

Anatomically, 53 (75.6%) patients had pulmonary tuberculosis, 7 (10.0%) had extrapulmonary tuberculosis, and 10 (14.2%) had both (Table 1). Half of those with pulmonary disease had acid-fast bacilli detected on sputum smear (n=34, 54.0%) and 29 (46%) had cavitation on radiography. Rifampin monoresistance was reported for 9 patients (12.9%), MDR for 43 (61.4%), pre-XDR for 10 (14.3%), and XDR for one patient (1.4%). Three MDR-TB (4.2%) patients had negative cultures at diagnosis; one was diagnosed by molecular results and two were close contacts to persons with culture-confirmed MDR-TB. An additional patient inadvertently received rifampin monotherapy for latent tuberculosis infection before initial cultures grew and isoniazid-resistant tuberculosis was diagnosed; this patient was empirically treated with BPaL since subsequent cultures were negative. Seven (10%) patients received BPaL for drug-susceptible tuberculosis because of rifamycin-intolerance (Text box).

Linezolid MIC values were reported for 61 (87%) patients with MICs of 0.12—1.0 mcg/mL (Table 1). Among 55 patients with FLBPHL molecular results, no mutations known to be associated with bedaquiline resistance were detected at baseline, and no patients had linezolid resistance-conferring mutations. One patient had a point mutation (Val144Ala, GTG/GCG) in *rplC*, but the organism was linezolid-susceptible on phenotypic testing (MIC=0.5mcg/ml)

Bpal treatment and linezolid dosing

For 19 patients (27.1%), BPaL was their only tuberculosis treatment regimen (Table 2). Rifamycin-based treatment was the initial regimen for 29 (41.4%). A conventional longer regimen for RR-TB regimen was administered to 33 (47.1%) before BPaL. All but four patients (94.3%) started BPaL with linezolid 600 mg daily; one started 900 mg daily, two started 1200 mg daily, and one started 600 mg TIW due to peripheral neuropathy. No patients received other tuberculosis drugs concurrently with BPaL. Two patients changed from BPaL to rifampin-based therapy based on phenotypic susceptibility results and were excluded from subsequent analyses.

Among the remaining 68 patients, TDM was performed for 66 patients (97.1%) (Table 2). Linezolid dose was changed from 600mg daily for 42 (61.6%) individuals, 36 (52.9%) based on TDM results and 6 (8.8%) by provider decision. In 20 patients (29.4%), linezolid trough on 600 mg daily was >2 mcg/mL, and 20 (29.4%) patients had serum peak concentrations below the target range 12–26 mcg/mL.

Bpal treatment effectiveness

All 68 patients completed their prescribed duration of BPaL, 50 (73.5%) with no treatment interruption (Table 3). No patients were lost or died during treatment, and none failed treatment. Ten (14.7%) had BPaL duration extended to >39 weeks for bone involvement

(7.4%), extensive tuberculosis disease/delayed culture conversion (4.4) or non-adherence (2.9%). Overall, median time from first to last dose of BPaL was 26.9 weeks (range: 112 to 325 days). Among 14 pulmonary tuberculosis patients with who received only BPaL and had serial cultures obtained, the median time to culture conversion was 37 days (range 1–90).

Bpal treatment side effects

Four patients with baseline anemia required a blood transfusion during linezolid treatment; linezolid was changed from 600 mg daily to TIW (Table 3) and one discontinued linezolid at week 23 of BPaL. Three had a linezolid trough concentration >2 mcg/mL, and one did not have TDM. One of these patients with a high linezolid trough also reported blurry vision that resolved with transfusion and change to TIW linezolid. Two other patients experienced a decrease in hemoglobin during BPaL, both had low linezolid trough concentrations and linezolid dose/frequency was not changed.

With regards to neurologic events, two patients discontinued linezolid prematurely for worsening peripheral neuropathy despite trough concentrations <2ug/mL; bedaquiline and pretomanid were completed. One patient developed neurologic symptoms and had a linezolid trough concentration >2umcg/mL; symptoms resolved with a change from linezolid 600mg daily to TIW and the patient completed a full course of BPaL. Transient numbness and tingling of extremities were also reported in five patients with varying trough concentrations but did not require linezolid dose or frequency adjustment (Table 3). Other minor side effects included gastrointestinal symptoms (n=14, 20.6%), rashes (n=8, 11.8%), and anxiety (n=4, 5.9%). In seven (10.3%) patients, serum aspartate aminotransaminase and/or alanine aspartate aminotransaminase levels increased to >3 times the upper limit of normal (ULN, 40mcg/mL) and 2 had a level >5 times ULN (Table 3). None developed a prolonged QTcF interval or lactic acidosis.

Follow up after bpal completion

At the time of writing, 55 of 68 (80.9%) patients who completed BPaL had at least 6 months of follow up without relapse, 36 (52.9%) had at least 12 months and 19 (27.9%) had at least 24 months. Two (2.9%) patients were lost after BPaL completion, and three (4.4%) were lost after 6 months of follow up. Of the remaining 65, all but two (96.9%) are still alive; two experienced a relapse of tuberculosis disease. (Table 3).”

DISCUSSION

We describe a cohort of 70 U.S. patients treated with BPaL for rifampin-resistant or rifampin-intolerant tuberculosis disease under program conditions. Preliminary data on early outcomes in 16 of these patients has been reported previously, but this in-depth review of detailed clinical courses for additional patients with longer follow-up provides more robust information for clinical use of this new regimen.[16, 17] All patients completed bedaquiline and pretomanid, with only three stopping linezolid prematurely. An initial linezolid 600 mg daily dose, use of TDM, careful monitoring for effectiveness and toxicity, and supportive care contributed to this success. The median BPaL duration of 27 weeks was less than

half of the recommended duration for traditional regimens in 2019 U.S. guidelines for drug-resistant tuberculosis.[4, 9]

Concerns about bone marrow suppression, peripheral neuropathy, and optic neuritis may hinder uptake of BPaL and other linezolid-containing regimens. Linezolid has a narrow therapeutic window. It inhibits protein synthesis and growth by disrupting bacterial mitochondria but can similarly poison human mitochondria. Suppression of ATP synthesis in bone marrow precursor cells leads to myelosuppression, one of linezolid's most predictable toxicities.[18] Although the exact mechanism of neurologic injury is less clear, linezolid-induced neurotoxicity is also likely mediated via mitochondrial dysfunction.[19, 20] Both linezolid's efficacy and its toxicity are concentration- and duration-dependent, with higher trough concentrations increasing mitochondrial dysfunction.[21, 22] For patients with linezolid trough concentrations <2 mcg/ml, toxicity may also be influenced by genetic variations in human mitochondria as well as clinical risk factors that increase risk of mitochondrial damage despite the lower linezolid concentrations.[18, 23–25] In this cohort, the four patients requiring blood transfusion had baseline anemia, and the four requiring reporting neuropathy requiring discontinuation of linezolid or extension of the dosing interval had other risk factors including baseline neuropathy, diabetes, thyroid disease, vitamin B12 deficiency, and opioid abuse. Thus, toxicity may be minimized by closely monitoring high-risk patients and using TDM to guide linezolid exposure. This strategy of linezolid dosing and monitoring is consistent with an established high-quality, patient-centered precision medicine approach frequently used in the United States.[5, 26–29]

While an alternative strategy is to decrease the daily linezolid dose from 600 mg to 300 mg when toxicity or a high serum trough level is detected, we preferred the 600 mg TIW approach based on pharmacokinetic data. High trough values reflect slow clearance. Extending the dosing interval directly addresses slow clearance, and this should allow linezolid concentrations at the mitochondria to fall to zero. Using the higher dose of 600 mg TIW also produces higher Cmax than 300 mg daily. This would favor a higher concentration gradient driving drug into the mycobacterial-laden lesions. Head-to-head comparison of these strategies has not been performed to our knowledge.

Using 600 mg of linezolid adjusted by clinical symptoms and TDM, our patients experienced less linezolid-associated hematologic and neurologic toxicity compared to patients receiving 1200 mg daily in both NIX-TB and ZeNIX Trials.[7, 30] With high tolerability, there were few prolonged interruptions and 100% completed BPaL treatment in a much shorter duration compared with the prior MDR-TB standard of care.[4] While the long-term efficacy of this approach remains to be seen, only two relapses have been reported thus far, and follow-up continues. Availability of drug susceptibility testing for patients in this cohort was important, and broader availability of both molecular and phenotypic testing to evaluate for both baseline and acquired resistance to BPaL agents will be critical.[5, 26] To date, half of this cohort (36 patients) remains tuberculosis-free one year after BPaL completion and a quarter (18 patients) successfully completed two years of follow up. The use of a collaborative entity, BIG, enabled broad dissemination of challenges and successes encountered by early BPaL adopters, and offered a platform for rapidly advancing clinical expertise and scale-up of this novel regimen across the U.S.

Recent evidence further supports linezolid dosing of 600 mg daily when combined with bedaquiline and pretomanid.[7, 30, 31] ZeNix, a multinational randomized controlled clinical trial addressed this directly.[30] With a factorial design, the study compared daily linezolid at 1200 mg for 26 weeks or 9 weeks, and 600 mg for 26 weeks or 9 weeks, combined with bedaquiline and pretomanid. The overall risk-benefit ratio favored linezolid at 600 mg for 26 weeks, based on lower toxicity and fewer dose modifications coupled with rare bacteriological failure (1 of 45 participants).[30] In May 2022, WHO endorsed BPaL with or without moxifloxacin (BPaLM) for rifampin-resistant tuberculosis, recommending linezolid 600 mg daily throughout treatment, allowing dose reduction for toxicity or poor tolerability.[32] However, uniform dosing throughout treatment may not be the most effective, safest approach to maximize treatment completion. In our study, based on TDM or toxicity, 30% of patients required linezolid dosing >600mg daily and half changed to TIW. Despite evidence that TDM decreases time to culture conversion and enhances treatment success for drug-susceptible tuberculosis, most providers do not obtain serum drug concentrations for their patients.[26, 33, 34] Challenges include a paucity of laboratories specialized for TDM, lack of funding, and technical challenges obtaining and shipping multiple blood samples to the few laboratories performing these assays.[35, 36] Collective efforts by tuberculosis providers, programs and policy-makers to optimize capacity for TDM for individualized drug dosing has potential to increase safe, relapse-free cure.[4, 5, 26, 36–38]

Despite the advantages of BPaL, it was FDA-approved only for patients with highly drug-resistant pulmonary disease.[8] The BIG cohort expanded BPaL treatment to any patient with rifamycin resistance or intolerance and to patients with extrapulmonary tuberculosis, populations not included in trials.[7, 30, 31] Current U.S. guidelines for RR-TB contain no explicit recommendations for treating extrapulmonary disease or rifampin-intolerant drug-susceptible TB.[4, 32] BPaL's ability to sterilize extrapulmonary tissues has not been determined in clinical trials, and the optimum duration for various forms of extrapulmonary tuberculosis remains uncertain. Despite the paucity of data, WHO recommendations were updated in December 2022 to endorse the use of the BPaLM/BPaL regimen for all forms of extrapulmonary disease except for tuberculosis involving the CNS, and osteoarticular and disseminated (miliary) TB.[39] Results from the BIG cohort are reassuring, and we aim to closely follow these patients and report on long-term outcomes in the future.

Our study has limitations inherent to any retrospective observational study, including missing data, inadequate details of adverse events, and lack of standardized patient evaluation, treatment, monitoring or follow up. Consistency was gained by using only one laboratory to perform TDM, but not all serum samples for linezolid concentrations were obtained with standardized timing. Optimal timing for TDM is 2 weeks after linezolid is initiated, and at the time of any adverse event; Preferably, TDM also is repeated after any change in dose or dosing frequency. Another limitation is that many patients in this cohort had treatment with other first or second line tuberculosis medications prior to BPaL, which could also have affected treatment outcomes. Because this study describes real world practice, these findings are still useful for informing U.S. clinical practice using this new regimen. A strength of our study was including diverse patients with respect to

race, comorbidities, age, and clinical care under routine TB program conditions making our findings more generalizable to the U.S.

Three years since FDA approval, BPaL has transformed treatment for rifampin-resistant or intolerant tuberculosis in the U.S. The findings from this study confirm the current WHO recommendations to use an initial linezolid dose of 600 mg per day rather than 1200mg. Notably, the addition of personalized drug dosing with close monitoring and early management of side effects likely enhanced safety and treatment completion. Support to local providers by BPaL-experienced tuberculosis expert consultants was also likely influential. The BIG cohort demonstrates that with collaborative efforts among providers and public health programs, early implementation of new tuberculosis treatments is feasible, serving as a model for future innovations.

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Text box:

Reasons that seven patients with rifampin-susceptible tuberculosis were treated with BPaL instead of a rifamycin-based regimen.

- Anaphylaxis during rifampin treatment for latent tuberculosis infection
- Significant drop in hemoglobin and elevated transaminases with fatigue, shortness of breath, and tachycardia during rifamycin treatment.
- "Intolerant" of rifamycins, pyrazinamide and fluoroquinolones
- Severe cytopenia with fever during rifamycin treatment
- Severe gout, pancreatitis, transaminitis and acute kidney injury (possibly autoimmune) during rifamycin treatment but tolerated BPaL with steroids.
- Severe neutropenia on both isoniazid and rifamycins
- Known resistance to isoniazid, pyrazinamide, ethambutol but not rifamycins on initial molecular testing, so given concern for additional rifampin resistance, BPaL was started while waiting for final phenotypic drug susceptibility testing; BPaL completed even though rifampin was reported susceptible by MIC.

Abbreviations: BPaL, bedaquiline, pretomanid, and linezolid; MIC, minimum inhibitory concentration

Note: This does not include the two patients who initiated BPaL based on initial molecular results, then were changed to a rifampin-based regimen when rifampin susceptibility was determined by phenotypic results.

Table 1.

Baseline patient characteristics (N=70)

Patient Characteristics	**N (%)**
Median age (range, years)	37 (14–83)
<25 years	12 (17.4)
25–44 years	31 (44.3)
45–64 years	14 (20.0)
≥65 years	13 (18.6)
Male	46 (65.7)
Race	
White	16 (22.9)
Black	9 (12.9)
Asian	45 (64.3)
Hispanic ethnicity	11 (15.7)
Born outside of the United States	63 (90)
Baseline Co-morbidities	
Baseline weight (kg) median (range)	58.03 (40.0–132.7)
HIV-infected	4 (5.7)
Diabetes	14 (20.0)
Renal disease	7 (10.0)
Liver disease or alcohol abuse	9 (12.9)
Anemia	18 (25.7)
Neuropathy	11 (15.7)
Immunosuppression	2 (2.9)
Malignancy	2 (2.9)
Hypothyroid	5 (7.1)
Tuberculosis Disease Characteristics	
Prior tuberculosis treatment	5 (7.1)
Inadequate MDR-TB treatment on U.S. arrival	2 (2.9)
Drug resistance[a]	
Rifamycin susceptible[b]	9 (12.9)
Rifampin mono-resistant	7 (10.0)
Multi-drug resistant	43 (61.4)
Pre-extensively drug resistant	10 (14.3)
Extensively drug resistant	1 (1.4)
Site of tuberculosis	
Pulmonary only	53 (75.7)
Extrapulmonary only	7 (10.0)
Both pulmonary and extrapulmonary	10 (14.3)
Total pulmonary	63 (90.0)
Sites of extrapulmonary tuberculosis	17 (24.3)
Male genitourinary tract	2

Patient Characteristics	N (%)
Male genitourinary tract and pelvic bone	1
Spine	2
Spine and miliary	1
Intrathoracic adenopathy, 3 ribs and iliac crest	1
Chest wall musculature	1
Chest wall and pleural	1
Peritoneal	1
Mediastinal and hilar adenopathy	1
Cervical lymphadenopathy	4
Cervical lymphadenopathy and pleural	1
Adenopathy, unspecified	1
Cavitation on chest radiograph among patients with pulmonary tuberculosis (n=63)	29 (46.0)
Positive sputum AFB smear among patients with pulmonary tuberculosis (n=63)	34 (54.0)
Positive mycobacterial culture, any site	67 (95.7)
Positive sputum culture	50 (71.4)
Linezolid MICs reported (n=61)	
0.12 mcg/ml	2 (3.3)
0.25 mcg/ml	22 (36.1)
0.5 mcg/ml	30 (49.2)
1.0 mcg/ml	7 (11.5)
Molecular detection of drug resistance results reported	61 (87.1)
Results reported by FLBPHL[c]	55 (78.6)
Results reported by CDC	33 (47.1)

Abbreviations: MDR-TB, multi-drug resistant tuberculosis; AFB, acid fast bacilli; MIC, minimum inhibitory concentration; FLBPHL, Florida Bureau of Public Health Laboratories; CDC, Centers for Disease Control and Prevention

[a]Using pre-2021 WHO definitions,[10] MDR-TB=resistance to both isoniazid and rifampin, pre-extensively drug resistant tuberculosis (XDR-TB)=MDR plus resistance to an injectable or a fluoroquinolone, XDR-TB=MDR plus resistance to both an injectable and a fluoroquinolone.

[b]Drug-susceptible tuberculosis included two patients with initial molecular results suggesting rifampin resistance that were determined rifampin-susceptible by phenotypic results.

[c]Among these 55 patients, *atpE* failed to amplify for one patient and *rv0678* failed to amplify for another.

Table 2.

Treatment characteristics (N=70)

Tuberculosis treatment before starting BPaL	**N (%)**
Received no tuberculosis treatment before starting BPaL	19 (27.1)
Received rifampin-based regimen[a]	29 (41.4)
Received other regimen for rifampin-resistant tuberculosis	33 (47.1)
Initial BPaL treatment regimen (N=70)	
Initial linezolid dose 600mg QD	66 (94.3)
Prescribed other tuberculosis drugs at the same time as BPaL	0
BPaL stopped after rifampin resistance excluded by phenotypic drug susceptibility testing	2 (2.9)
Linezolid dosing adjustments before or during BPaL (N=68) [b]	
Serum drug concentrations obtained for TDM, any reason	66 (97.1)
Dose or frequency adjusted, any reason	42 (61.8)
Adjusted based on TDM	36 (52.9))
Adjusted based on provider decision followed by TDM	6 (8.8)
Trough >2 mcg/ml on 600mg QD	20 (29.4)
Dose or frequency adjusted without symptoms	14 (20.6)
Dose or frequency adjusted with symptoms	4 (5.7)
Dose or frequency not adjusted with symptoms	2 (2.9)
Dose >600 mg required to reach therapeutic range (12–26 mcg/ml)	20 (30.9)
Final linezolid dose used during BPaL (N=68)[c]	
600mg QD	27 (39.7)
600mg TIW	21 (30.9)
900mg QD	8 (11.8)
900mg TIW	10 (14.7)
1200mg TIW alternating with 600mg QIW	1 (1.5)
1200mg QD	0
1200mg TIW	1 (1.5)

Abbreviations: BPaL, bedaquiline, pretomanid, and linezolid; QD, given daily; TDM, therapeutic drug monitoring; BID, given twice a day; TIW, given three days per week on Monday, Wednesday, Friday; QIW, given 4 days per week on Tuesday, Thursday, Saturday, and Sunday.

Rifampin-resistant tuberculosis includes resistance to at least rifamycins.

[a]Rifampin-based regimens include any combination of drugs including rifampin that was used to treat presumed drug-susceptible tuberculosis. Note that treatment duration of these regimens was not collected. Patients may have received both a rifamycin-based regimen and another regimen for drug resistance prior to BPaL.

[b]Excludes 2 patients who stopped BPaL after diagnosis of drug-susceptible tuberculosis. Some patients had linezolid started and adjusted prior to starting BPaL.

[c]This is the linezolid dose and frequency on which the patient completed therapy after potential adjustments based on symptoms or TDM results. A denominator of 68 was used rather than 66 (the number with TDM results) because some patients had linezolid adjusted based on symptoms alone.

Table 3.

BPaL Treatment Outcomes (N=68)[a]

	N (%)
Completed prescribed course of BPaL	68 (100)
Completed 26 weeks BPaL	55 (80.9)
Completed <26 weeks of BPaL	3 (4.4)
Rifampin-intolerant drug-susceptible tuberculosis, treatment included 70 days of rifampin-based therapy followed by 112 days of BPaL (total 26 weeks)	1
Rifampin-intolerant drug-susceptible tuberculosis, treatment included 3 months of rifampin-based therapy followed by 165 days of BPaL (total >26 weeks)	1
Completed 24 weeks due to bedaquiline prescription error	1
Completed >26 weeks of BPaL	10 (14.7)
Tuberculosis involving bone	5 (7.4)
Significant burden of disease or culture conversion >60 days from start of BPaL	3 (4.4)
Non-adherence/prolonged treatment interruption	2 (2.9)
Median time from first to last dose of BPaL, days (range)	188.5 (112–325)
Treatment interruption during BPaL[b], consecutive days (range)	18 (26.5)
<7	4
7 to 13	6
14 to 20	2
21 to 27	3
≥28	2
Not reported	1
Median time to culture conversion, days (range, n=14)[c]	37 (1–90)
Hematologic and neurologic events during BPaL (N=68)	
Description	*N (%) and trough mcg/ml*
Linezolid discontinued before full BPaL completion	3 (4.4)
Occurrence of both hematologic and neurologic events requiring linezolid change or discontinuation	1 (1.5)
Age ≥65 years, diabetes, breast cancer (treatment unknown), baseline hemoglobin 10.6g/dL and peripheral neuropathy (fingers, toes). After 13 days of linezolid 600mg QD, reported blurry vision and received transfusion; high serum trough concentration, linezolid changed to 600mg TIW. No further transfusions or symptoms, full BPaL completed.	11.6 mcg/ml
Occurrence of only hematologic events requiring linezolid change or discontinuation	3 (4.4)
Age ≥65 years, diabetes, untreated hypothyroidism, baseline hemoglobin 8.0g/dL required transfusions before and 10 days after starting linezolid 600mg QD. Platelets also “decreasing”. Serum trough concentration high, linezolid changed from 600 mg QD to 600mg TIW; No further transfusions or symptoms, full BPaL completed.	9.96 mcg/ml
Age ≥65 years, baseline gout, developed admitted with transaminitis, pancreatitis, and anemia on rifampin, isoniazid, pyrazinamide, and ethambutol. After improvement, changed to BPaL (linezolid 600mg QD). In 5th week of BPaL, readmitted with recurrent transaminitis, pancreatitis, and anemia requiring transfusion of one unit of red blood cells; steroids given for possible autoimmune etiology. High linezolid trough concentration, changed to 600mg TIW. Around week 23, linezolid discontinued for hemoglobin of 6.9g/dL; bedaquiline and pretomanid completed.	2.9 mcg/ml
Age 45–64 years, alcoholic cirrhosis, oxygen-dependent lung disease, baseline anemia with hemoglobin 8g/dL, required transfusion before starting linezolid 600mg QD and again 1 month after. Changed to linezolid 600mg TIW through completion of BPaL.	Not done
Occurrence of only hematologic events not requiring linezolid change or discontinuation	2 (2.9)
Age ≥65 years, linezolid empirically changed from 600mg daily to 600mg TIW after 12 days due to baseline untreated diabetes and renal disease, linezolid trough at 48 hours low; later in therapy, hemoglobin decreased from baseline of 15.4g/dL to 12.3g/dL and platelets decreased from 173×10^9/L to 97× 10^9/L then stabilized and BPaL completed without further linezolid changes.	0.39 mcg/ml

	N (%)
Age 45–64, diabetes, chronic Hepatitis B, linezolid 900mg daily started 5 months before bedaquiline and pretomanid; hemoglobin was 14.2g/dl 6 months after linezolid initiation, trough was trace. 2 months later provider documented "anemia" linezolid continued at 900mg daily and 26 weeks of BPaL completed.	Trace
Occurrence of only neurologic symptoms requiring linezolid change or discontinuation	3 (4.4)
Age ≥65 years, diabetes, stage 3 chronic kidney disease, baseline peripheral neuropathy; Reported blurry vision after starting linezolid 600mg QD but vision exam and Isahara test unchanged. Resolved on change to 600mg TIW, full BPaL completed.	9.3 mcg/mL
Age ≥65 years, started linezolid 600mg QD diabetes, hypothyroidism, and B12 deficiency, discontinued linezolid at 12 weeks for worsened neuropathy despite 1 week trial of 600mg TIW; completed bedaquiline and pretomanid.	1.13 mcg/mL
Age 45–64, smoking-related chronic lung disease, hypothyroidism and opioid use disorder; developed persistent hand numbness, discontinued linezolid 600mg QD at 24 weeks without trial of 600mg TIW; completed bedaquiline and pretomanid.	0.3 mcg/mL
Neurologic symptoms not requiring change or discontinuation of linezolid	5 (7.4)
Age <25 years, reported new numbness in toes. Linezolid 600mg QD continued, symptoms resolved after BPaL completion.	3.3 mcg/mL
Age 45–64 years, baseline anxiety, reported transient tingling in face and scalp and intermittent numbness/tingling in eyes and fingers Symptoms resolved, linezolid 600mg QD continued until BPaL completion.	2.4 mcg/mL
Age 25–44 years, no symptoms on 600mg QD, but reported numbness and tingling in two toes approximately 10 weeks after linezolid increased to 900mg QD; symptoms persisted throughout treatment then resolved after BPaL completion.	1.5 mcg/mL, 2.03 mcg/mL
Age 25–44 years, HIV-infected, dose increased to from 600mg QD to 1200mg TIW based on TDM with trough at 48h reported here, reported arm numbness and weakness that resolved by end of BPaL treatment.	0.1 mcg/mL
Age 45–64 years, B-12 deficiency, 2 days tingling in fingertips when gardening, never recurred, completed BPaL with linezolid 600mg QD.	1.3 mcg/mL
Elevated liver enzymes over 5 times upper limit of normal	2 (2.9)
Age <25 years, no known liver disease, 3 weeks after BPaL started developed asymptomatic ALT=186 ug/mL and AST=372 mcg/mL. BPaL held one week, was then restarted with ALT=82 mcg/mL AST=45 mcg/mL; completed 26 weeks of BPaL without further laboratory or clinical abnormalities.	1
Age 25–44 years, type I diabetes, 1 month after BPaL started became critically ill with COVID-19 requiring prolonged hospitalization, peak ALT=450 mcg/mL AST=141 mcg/mL. BPaL held 8 weeks then restarted with normal AST and ALT; completed 26 weeks of BPaL	1
Lactic acidosis during BPaL	0
Other symptoms not requiring change in BPaL regimen (N=68)	
Gastrointestinal (nausea, vomiting, diarrhea or abdominal discomfort)	14 (20.6)
Rash or pruritis	8 (11.8)
Elevated liver enzymes more than 3 times ULN	7 (10.3)
Anxiety or panic attack	4 (5.9)
Fatigue	3 (4.4)
Hair loss	2 (2.9)
Black hairy tongue	1 (1.5)
Yellow-brown teeth discoloration	1 (1.5)
Dactylitis and tremor	1 (1.5)
QTc Interval >500ms or increase of >60ms	0 (0)
Duration of follow up after completion of BPaL without recurrent tuberculosis (n=68)[d]	
At least 6 months	55 (80.9)
At least 12 months	36 (52.9)
At least 24 months	19 (27.9)
Lost after treatment without any follow up	2 (2.9)
Lost after the 6-month post-BPaL completion follow up	3 (4.4)
Died after BPaL completion (n=68)[e]	2 (2.9)

	N (%)
Relapse after completion of full BPaL regimen[f] (n=68)	2 (2.9)
Patient with extensive cavitary pulmonary disease resistant to rifampin, ethambutol and fluoroquinolones, no HIV or diabetes, clinically improved with culture conversion at 90 days and completed 26 weeks of BPaL under directly observed therapy (DOT). Culture-confirmed relapse approximately 6 months after BPaL completion. Bedaquiline, linezolid, and pretomanid, MICs both before treatment and after relapse were 0.12, 0.5 mcg/ml, and 0.125 mcg ml, respectively (i.e., no MIC increase for BPaL drugs). Similarly, samples before treatment and after relapse showed no linezolid associated mutations (*rplC* or *rrl*) or bedaquiline *atpE* mutations. Retrospectively, both samples had detectable bedaquiline Pro48Leu *rv0678* mutations which have unknown clinical significance.[40] The patient is being treated with BPaL, moxifloxacin and pyrazinamide and continues to be followed closely.	
Correctional inmate at diagnosis, alcoholic, past cocaine use, no HIV or diabetes; cavitary tuberculosis resistant to isoniazid, rifampin, pyrazinamide and ethambutol, transferred to hospital, treated with second-line regimen for 6 months, acquired new fluoroquinolone resistance and linezolid MIC increased 0.5 mcg/ml to 1.0 mcg/ml before culture conversion occurred at 84 days; discharged home, started BPaL (linezolid 600mg) for 3 weeks then was lost; reincarceration and detoxification with 3 week treatment interruption; completed 14 weeks of BPaL while incarcerated, then 9 weeks in the community for 26 total weeks of BPaL (all by DOT). Seven months later, patient hospitalized with respiratory distress requiring mechanical ventilation, bilateral cavitary pneumonia and bloody stools; Patient did not report recent tuberculosis diagnosis or treatment, sputum smears AFB-negative; patient improved on linezolid, piperacillin/tazobactam and high-dose steroids; admission sputum culture grew *M. tuberculosis* after 8 weeks, by which time respiratory status deteriorated; repeat sputum, urine, stool were AFB-positive; patient had respiratory arrest and died in the hospital before anti-tuberculosis therapy could be initiated. MDDR on relapse isolate indicated two *rv0678* frame shift mutations and bedaquiline CC=1 ucg/ml; linezolid MIC unchanged at 1.0 mcg/ml. Pre-relapse isolate testing for bedaquiline resistance pending at time of writing.	

Abbreviations: BPaL, bedaquiline, pretomanid, and linezolid; QD, given daily; TIW, given three times per week on Monday, Wednesday and Friday; HIV, Human Immunodeficiency Virus; ALT, alanine transaminase; AST, aspartate aminotransferase; ULN, upper limit of normal; MIC, minimum inhibitory concentration; AFB, acid-fast bacilli.

[a] Of the initial 70 patients, two discontinued BPaL when drug-susceptible tuberculosis was confirmed.

[b] BPaL treatment interruption defined as missing doses of bedaquiline and pretomanid. Does not include holding linezolid for a few days before changing dosing frequency.

[c] Culture conversion from date of initial positive tuberculosis culture to date of first consecutively negative culture was calculated among patients with only pulmonary disease who had no tuberculosis treatment prior to BPaL and had a documented sputum culture conversion (defined as two consecutively negative cultures taken 30 days apart).

[d] Denominator n=68 excludes the 2 patients who changed from to rifampin-based tuberculosis therapy. Five patients have not had their 6 month follow up visit yet, 2 patients died after BPaL completion and could have no further follow up, and 1 who has relapsed and remains on therapy.

[e] One patient died after completion with no evidence of tuberculosis relapse and one died after relapse developed but before tuberculosis treatment was restarted.

[f] Relapse is when a subject has completed treatment without being declared a failure and has subsequently been diagnosed and require treatment again and for whom there is evidence that the recurrence is due to the same strain recorded in the baseline specimen.