CORRESPONDENCE

Pretomanid in the Treatment of Patients with Tuberculosis in the United States

TO THE EDITOR: According to the Centers for Disease Control and Prevention (CDC), 524 cases of multidrug-resistant (MDR) tuberculosis were reported in the United States (including U.S. territories and freely associated states) for the period from 2014 through 2018. These included 443 cases of tuberculosis that was resistant to isoniazid and rifampin only, 72 cases in which there was additional resistance to either a quinolone or an injectable medication (pre–extensively drug-resistant [XDR] tuberculosis), and 9 cases in which there was additional resistance to both a quinolone and an injectable antituberculosis medication (XDR tuberculosis).[1] Of 518 patients with MDR tuberculosis who were alive at the time of diagnosis, 8% died before completing treatment and 38% did not complete treatment within 18 to 24 months after treatment initiation.

In August 2019, the Food and Drug Administration (FDA) approved pretomanid for use in a 6-month, all-oral regimen of bedaquiline, pretomanid, and linezolid in patients with XDR tuberculosis and nonresponsive pulmonary MDR tuberculosis and in patients who had had adverse events with other regimens.[2] The FDA based the approval on the results of the Nix-TB trial of the combination therapy of bedaquiline, pretomanid, and linezolid in patients with XDR and nonresponsive MDR tuberculosis[3]; 89% of the patients had favorable outcomes. However, all the patients reported at least one adverse event, which included serious neurologic and hematologic toxic effects that were attributed to linezolid, which had been administered at a dose of 1200 mg daily.[3] The CDC analyzed data that was submitted by health departments and clinicians regarding patients with tuberculosis in the United States who began treatment with bedaquiline, pretomanid, and linezolid between August 2019 and September 2020 and had at least 12 months of follow-up data available. The analysis was determined to have met the Department of Health and Human Services requirements for public health surveillance, as defined in regulation 45 CFR 46.102(l)(2).

Of the first 20 patients reported to the CDC as having received bedaquiline, pretomanid, and linezolid, 8 had MDR tuberculosis, 10 had pre-XDR tuberculosis, 1 had XDR tuberculosis, and 1 had drug-susceptible tuberculosis and adverse effects associated with treatment with rifamycins. The mean age of the patients was 42 years (range, 23 to 76); a total of 12 patients (60%) were men, and 17 (85%) were U.S. residents who were non–U.S.-born. Seventeen patients (85%) had pulmonary-only tuberculosis, and 3 (15%) had both pulmonary and extrapulmonary dis-

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Table 1. Bedaquiline, Pretomanid, and Linezolid (BPaL) Regimen for the Treatment of Tuberculosis in 20 Patients in the United States, August 2019 through September 2020.*

Patient No.	Drug Resistance	Antituberculosis Medications Other Than BPaL	Reported Side Effects†	Initial Linezolid Dose	Linezolid Levels Monitored‡	Time from Start of BPaL to Completion§	Time from Start of BPaL to Most Recent Follow-up¶
						months	
1	MDR	INH, RIF, EMB, PZA	None	600 mg daily	No	6	12
2	Pre-XDR	INH, AK, EMB, LFX, PZA	Depression	600 mg daily	No	6	12
3	Pre-XDR	INH, RIF, CS, EMB, MFX, PZA	Diarrhea, pruritus, vestibular dysfunction	600 mg daily, alternating with 1200 mg daily	Yes	6	18
4	Pre-XDR	AK, CS, MFX, PAS, PZA	None	600 mg daily	Yes	6	18
5	MDR	None	None	600 mg daily	Yes	6	16
6	MDR	INH, RIF, AK, CS, EMB, MFX, PZA	Depression, hearing loss, peripheral neuropathy, suicidal ideation or attempt, vestibular dysfunction, vision change or loss	1200 mg daily	Yes	6	23
7	MDR	None	Irregular menses, tinnitus, transient leukopenia	600 mg 3 times per week	Yes	9	15
8	MDR	INH, RIF, CS, EMB, PZA	Peripheral neuropathy	600 mg twice daily	Yes	6	12
9	Pre-XDR	INH, AK, CFZ, CS, EMB, ETA, LFX, PZA	Arthralgia, depression, fatigue, nausea, vestibular dysfunction	600 mg daily	Yes	6	15
10	MDR	None	None	600 mg daily	Yes	6	19
11	MDR	INH, RIF, CFZ, CS, EMB, LFX, PZA	None	900 mg daily	Yes	7	13
12	MDR	INH, RIF, EMB, PZA	None	600 mg daily	Yes	7	16
13	Pre-XDR	CFZ, CS, MFX, PZA	Vision change or loss	600 mg daily	Yes	6	21
14	Pre-XDR	CFZ, CS, LFX, MFX	Arthralgia, depression, peripheral neuropathy, vision change or loss	600 mg daily	Yes	7	22
15	Pre-XDR	CFZ, CS, ETA	None	600 mg daily	Yes	7	25
16	Pre-XDR	CFZ, CS, ETA	Peripheral neuropathy	600 mg daily	Yes	7	25
17	Pre-XDR	INH, RIF, AK, CFZ, CS, EMB, ETA, MFX, PAS, PZA	Peripheral neuropathy	600 mg daily	Yes	7	25
18	Pre-XDR	INH, RIF, AK, CS, EMB, MFX, PAS, PZA	Depression, hearing loss, peripheral neuropathy	600 mg daily	Yes	>17‖	18
19	XDR	INH, RIF, CFZ, CS, EMB, MFX, PZA	Nausea	600 mg daily	Yes	8	30
20	DS**	INH, RIF, EMB, PZA	None	600 mg daily	Yes	6	15

* Multidrug-resistant (MDR) tuberculosis is defined as *M. tuberculosis* that is resistant to at least isoniazid (INH) and rifampin (RIF). Pre–extensively drug-resistant (XDR) tuberculosis is defined as *M. tuberculosis* that is resistant to INH, RIF, and at least one fluoroquinolone or at least one injectable tuberculosis medication. XDR tuberculosis is defined as *M. tuberculosis* that is resistant to INH, RIF, at least one fluoroquinolone, and at least one injectable tuberculosis medication (e.g., amikacin [AK], capreomycin, or kanamycin). After this analysis, in January 2022, the Centers for Disease Control and Prevention updated its definitions of drug-resistant tuberculosis (https://www.cdc.gov/tb/publications/letters/2022/surv-def-xdr.html). CFZ denotes clofazimine, CS cycloserine, DS drug-susceptible tuberculosis, EMB ethambutol, ETA ethionamide, LFX levofloxacin, MFX moxifloxacin, PAS para-aminosalicylic acid, and PZA pyrazinamide.

† The timing of side effects was not reported and could not be correlated to a specific tuberculosis medication or regimen.

‡ Therapeutic drug monitoring was used to attain therapeutic linezolid drug levels while minimizing toxic effects.

§ The patient completed the prescribed course of therapy, as noted in the medical record by the clinician who provided care.

¶ The mode of follow-up encounter (in person or by telephone) was at the discretion of the treating center or physician.

‖ The patient had not completed therapy as of February 2022, owing to the clinician's concerns about the risk of relapse in the patient, who had an extensive history of treatment for tuberculosis. The patient's *M. tuberculosis* sputum cultures had converted from positive to negative, and the patient showed signs of clinical improvement and response to treatment.

** The patient had DS tuberculosis, but treatment with RIF resulted in unacceptable side effects.

ease. All 20 patients had a positive culture for *Mycobacterium tuberculosis*, 12 (60%) had disease that was positive on a sputum smear for acid-fast bacilli, and 7 (35%) had cavitary disease. Of the patients who received the bedaquiline, pretomanid, and linezolid combination, 3 received only the three-drug regimen, 12 had previously received treatment for drug-susceptible tuberculosis, and 8 had received other medications for MDR tuberculosis before receiving bedaquiline, pretomanid, and linezolid (Table 1).

With regard to side effects, 12 patients (60%) reported at least one side effect during treatment (with the combination regimen or another medication). Side effects included peripheral neuropathy (in 6 patients), depression (in 5), vestibular dysfunction (in 3), nausea (in 2), hearing loss (in 2), and vision changes (in 3). The timing of side effects could not be correlated to a specific antituberculosis drug. At the time treatment began, therapy with linezolid was initiated in 18 patients (90%) at less than the dose of 1200 mg daily approved by the FDA (most received 600 mg daily), and in 18 patients (90%), measurement of linezolid levels was used to attain therapeutic levels while minimizing toxic effects.[4] At follow-up 12 months after treatment with bedaquiline, pretomanid, and linezolid was initiated, 19 patients (95%) had completed treatment for tuberculosis, and there had been no treatment failures, recurrences, or deaths.

Patients with MDR tuberculosis in the United States who were treated with a regimen of bedaquiline, pretomanid, and linezolid had good outcomes within 1 year despite starting treatment at a lower-than-approved dose of linezolid; most patients underwent therapeutic drug monitoring. The CDC recently issued guidance in support of the use of bedaquiline, pretomanid, and linezolid under close monitoring.[1] These data suggest that a lower linezolid dose was associated with effective treatment completion among patients in the United States who received a regimen of bedaquiline, pretomanid, and linezolid for the treatment of MDR tuberculosis.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Centers for Disease Control and Prevention. Provisional CDC guidance for the use of pretomanid as part of a regimen [bedaquiline, pretomanid, and linezolid (BPaL)] to treat drug-resistant tuberculosis disease. 2022 (https://www.cdc.gov/tb/topic/drtb/bpal).
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Long-Term MC4R Agonist Treatment in POMC-Deficient Patients

TO THE EDITOR: Mutations in the gene encoding proopiomelanocortin (*POMC*) result in impaired function of the leptin–melanocortin pathway owing to restricted production of α-melanocyte–stimulating hormone (MSH) and β-MSH. Affected patients have hyperphagia and severe early-onset obesity because of the lack of activation of the melanocortin-4 receptor (MC4R). Bariatric surgery is not a long-term therapeutic option for patients with biallelic *POMC* mutations.[1]

We previously reported in the *Journal* that the MC4R agonist setmelanotide could substitute for the missing MSH signal in an investigator-initiated, proof-of-concept study involving two adult patients with POMC deficiency.[2] After 6.1 years (Patient 1) and 5.3 years (Patient 2), the patients were transitioned to an open-label extension