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Bedaquiline and Repurposed Drugs for Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: How Much Better Are They?

To the Editor:

Treatment outcomes of conventional multidrug-resistant tuberculosis (MDR-TB) treatments are overall unsatisfactory, particularly for fluoroquinolone-resistant MDR-TB (1). In addition, long-term follow-up studies have shown that patients who have experienced previous treatment failure contribute importantly to ongoing transmission in the community (2). The introduction of two new drugs, bedaquiline and delamanid, has been reported to improve treatment outcomes for MDR/extensively drug-resistant (XDR)-TB (3, 4). In addition, there is growing evidence that repurposed drugs such as linezolid, clofazimine, and carbapenems with amoxicillin/clavulanate also have a role to play in MDR/XDR-TB treatment (5, 6). However, few reports have assessed new regimens rather than the addition of a single new or repurposed drug to a regimen (3, 4, 6).

In Armenia, Médecins Sans Frontières (MSF) has supported the National Tuberculosis Program for the treatment of MDR-TB patients since 2005. In 2013, bedaquiline was introduced into clinical practice through a compassionate use (CU) mechanism. At the same time, the repurposed drugs linezolid and imipenem/cilastatin became available for the first time. Clofazimine was already available. The objective of this study was to assess the clinical impact of regimens containing bedaquiline, linezolid, and/or imipenem/cilastatin.

Methods

We performed a retrospective cohort analysis of patients who started MDR-TB treatment in Armenia. Consecutive patients with confirmed fluoroquinolone-resistant MDR-TB were included in the analysis. We compared the treatment outcomes of patients who received World Health Organization (WHO)-recommended MDR-TB regimens with bedaquiline through CU and linezolid with or without imipenem/cilastatin from April 2013 to April 2015 (CU cohort) with those of patients who received WHO-recommended MDR-TB regimens without bedaquiline, linezolid, or imipenem/cilastatin from September 2005 to April 2015 (non-CU cohort).

Treatment regimens were individually tailored to include sufficient effective drugs according to WHO recommendations. Treatment before CU for patients with fluoroquinolone-resistant TB included kanamycin or capreomycin, a fluoroquinolone even if resistant, prothionamide, *para*-aminosalicylic acid, cycloserine, and two of the following: clofazimine, clarithromycin, and amoxicillin-clavulanate. Treatment regimens for the CU cohort included the addition of bedaquiline for only 24 weeks according to the CU protocol, and linezolid and imipenem/cilastatin (given with amoxicillin clavulanate) as needed, supplied by MSF. Delamanid was not available. All patients received a support package, directly observed treatment, and were followed up monthly with bacteriological and laboratory tests. Drug sensibility testing was performed in the Borstel Supranational Reference Laboratory until 2010 and then by the quality-assured Armenia National Reference Laboratory. Outcomes were assigned according to WHO guidelines (7). Treatment success was defined as cured or treatment completed.

We estimated the average treatment effect (receiving bedaquiline and repurposed drugs) by inverse-probability-weighted regression adjustment. The treatment model included sex, age, previous treatment for MDR-TB, previous and current use of clofazimine, and resistance profile at treatment initiation, and the outcome model included adherence. Sensitivity analyses excluding patients who were lost to follow-up were performed. Analyses were performed using Stata 15 (Stata Corp.).

The study was approved by the relevant health authorities in Armenia and met the exemption criteria set by the MSF ethics review board for *a posteriori* analyses of routinely collected clinical data.

Results

A total of 140 patients with pulmonary TB were included in the study (91 in the non-CU cohort and 49 in the CU cohort). The two cohorts presented similar characteristics at treatment initiation (Table 1), although in the CU cohort more patients had previously been treated for MDR-TB ($P < 0.001$), had previously received treatment with clofazimine ($P < 0.001$), and had XDR-TB ($P = 0.058$). All patients in the CU cohort received bedaquiline and linezolid, 76.0% received imipenem/cilastatin plus amoxicillin/clavulanate, and 83.7% received clofazimine as part of the treatment regimen. In the CU cohort, clofazimine use was more frequent ($P < 0.001$) and the total number of drugs received at initiation was higher ($P < 0001$).

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Table 1. Patient Characteristics at Start of Treatment and Treatment Outcomes for Noncompassionate-Use and Compassionate-Use Cohorts

	Non-CU Cohort (*n* = 91)	CU Cohort (*n* = 49)	*P* Value
Characteristics			
Male	72 (79.1)	43 (87.8)	0.203
Age, yr, median (IQR)	45 (32–53)	41 (30–52)	0.465
BMI, kg/m^2, median (IQR)	20.5 (17.6–23.7)	20.2 (17.8–23.4)	0.930
Previously treated for MDR-TB	47 (51.6)	49 (100)	<0.001
HIV positive	6/63 (9.5)	1/49 (2.0)	0.110
XDR-TB	28 (30.8)	23 (46.9)	0.058
Number of drugs resistant to, median (IQR)	6 (5–7)	7 (5–8)	0.300
Previous use of Cfz	1 (1.1)	13 (26.5)	<0.001
Cavity in X-ray	85 (93.4)	45 (91.8)	0.731
Extensive disease	87 (95.6)	46 (93.9)	0.655
History of imprisonment	21 (23.1)	11 (22.5)	0.933
Diabetes	9 (9.9)	5 (10.2)	0.953
Treatment regimen			
Number of drugs received at treatment start*, median (IQR)	6 (6–7)	7 (7–7)	<0.001
Cfz in current regimen	21 (23.1)	41 (83.7)	<0.001
Treatment outcomes			
Cured	11 (12.1)	23 (46.9)	
Treatment completed	9 (9.9)	7 (14.3)	
Death	14 (15.4)	5 (10.2)	
Failure	30 (33.0)	5 (10.2)	
Lost to follow-up	27 (29.7)	9 (18.4)	
Treatment success†	20 (22.0)	30 (61.2)	<0.001
Treatment success excluding lost to follow-up	20/64 (31.2)	30/40 (75.0)	<0.001

Definition of abbreviations: BMI = body mass index; Cfz = clofazimine; CU = compassionate use; IQR = interquartile range; MDR-TB = multidrug-resistant tuberculosis; non-CU = noncompassionate use; XDR-TB = extensively drug-resistant tuberculosis.
Data are *n* (%) unless otherwise indicated.
*Including effective and noneffective prescribed drugs.
†Sum of cured and treatment completed.

Faster culture conversion was observed in the CU cohort (Figure 1A; $P < 0.001$). Among patients with a positive culture at baseline, 6-month culture conversion reached 73.0% (27/37) in the CU cohort and only 35.6% (31/87) in the non-CU cohort ($P < 0.001$). The median time to culture conversion was 2.7 months (interquartile range, 1.9–4.9) in the CU cohort and 5.7 months (interquartile range, 2.7–11.4) in the non-CU cohort.

Treatment success was higher in the CU cohort (30/49, 61.2%) than in the non-CU cohort (20/91, 22.0%) (Table 1; $P < 0.001$). The CU cohort also showed a lower proportion of unfavorable outcomes (death or treatment failure) (Figure 1B; $P < 0.001$). The inverse-probability-weighted regression adjustment analysis showed that patients in the CU cohort had an estimated statistically significant increase in treatment success of 30.2% (95% confidence interval, 15.8–44.5%). Exclusion of patients who were lost to follow-up did not change the results (data not shown).

Discussion

This study shows that regimens containing bedaquiline and repurposed drugs improved treatment success by 30% compared with previously available conventional regimens for fluoroquinolone-resistant MDR-TB in Armenia, with a higher probability of conversion and faster time to culture conversion. The difference in treatment success between the two cohorts is striking and is principally due to a lower proportion of treatment failure, indicating better treatment efficacy in the CU cohort. Although the outcomes of the CU cohort were improved, they were still inferior to those reported in high-resource settings; many factors, including treatment support and social conditions, may account for this difference (8, 9). Patients were given all available effective drugs to construct the regimens, and the lower total number of effective drugs reported in the non-CU cohort likely reflects the lack of access to some drugs at this time.

This study has several limitations: the retrospective design, the observational nature of the data, and the historical comparator. Some of the differences in the baseline characteristics may have also impacted the results. However, the robustness of the statistical method used supports the validity of our findings. Safety aspects will be described in a separate study.

In conclusion, new and repurposed drugs can make fluoroquinolone-resistant MDR-TB, and potentially XDR-TB, a disease that is curable in the majority of cases. Despite this evidence, only an estimated 15.7% of patients with MDR-TB who are likely to benefit from either bedaquiline or delamanid have received them (10), and no data are available for repurposed drugs. An important scale-up of access to bedaquiline and repurposed drugs should be a public health priority, and more evidence is needed regarding cost-effective models of care. ■

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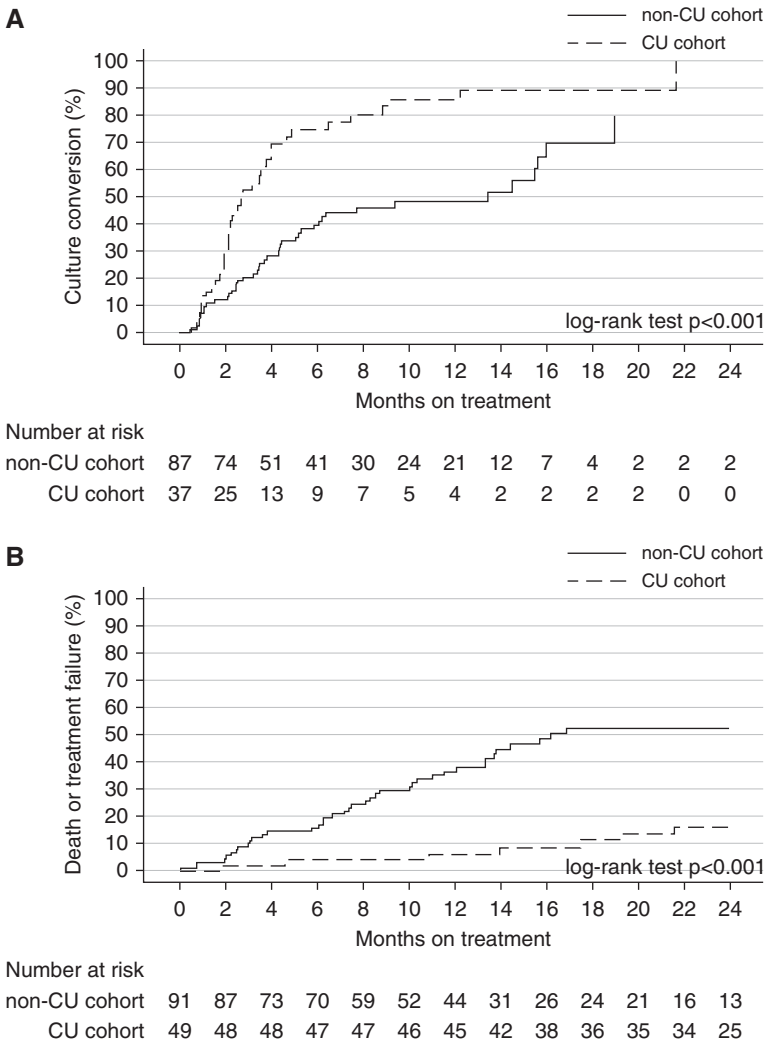

Figure 1. Kaplan-Meier estimates of (*A*) culture conversion among patients with positive sputum culture at treatment start and (*B*) unfavorable outcome (death or treatment failure) for noncompassionate use (non-CU) and compassionate use (CU) cohorts.

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SOX17 Mutations in Japanese Patients with Pulmonary Arterial Hypertension

To the Editor:

Recently, Gräf and colleagues (1) reported that rare causal heterozygous variants in *SOX17* (SRY-related high-mobility group box family member 17) were significantly overrepresented in a pulmonary arterial hypertension (PAH) cohort, with *SOX17* mutations identified in nine patients with PAH among 1,038 PAH index cases.

In this study, whole-exome sequencing in 12 Japanese patients with PAH and 12 asymptomatic family members in six families, as well as in 128 Japanese idiopathic or heritable PAH index cases, identified four patients with PAH and 1 asymptomatic family member with *SOX17* mutations. The characteristics of these 4 patients with PAH are listed in Table 1.

Case 1, a woman, was diagnosed with idiopathic PAH at 33 years of age (Figure 1A). Her clinical condition was severe, and she died 2 years after the diagnosis, despite combination therapy, including intravenous epoprostenol infusion. Final heart catheterization revealed a mean pulmonary arterial pressure (PAP) of 53 mm Hg and pulmonary vascular resistance (PVR) of 17.0 Wood units. After case 1's death, lung specimens were obtained at autopsy, and staining of these sections demonstrated plexiform and concentric neointimal lesions, suggesting Grade IV on the Heath–Edwards classification (Figure 1B). Before her death, case 1 agreed to undergo genetic analysis. Whole-exome sequencing was negative for mutations in all known genes pathogenic for PAH (*BMPR2* [bone morphogenetic protein receptor type 2], *ACVRL1* [activin A receptor–like 1], *ENG* [endoglin], *CAV-1* [caveolin-1], *TBX4* [T-box 4], *KCNK3* [potassium two-pore-domain channel subfamily K member 3], *EIF2AK4* [eukaryotic initiation translation factor 2 α kinase 4], and *SMAD*s), as well as for mutations of *ATP13A3* (ATPase 13A3), *AQP1* (aquaporin 1), and *GDF2* (growth differentiation factor 2), which are novel pathogenic genes for PAH recently reported by Gräf and colleagues (1). However, case 1 had a heterozygous missense mutation in *SOX17* (NM_022454.3): c.397C>G, p.Pro133Ala. Her parents were apparently healthy and did not participate in the genetic analysis. Importantly, Gräf and colleagues (1) reported the same positional mutation (c.397C>T, p.Pro133Ser) in *SOX17* in their patient with PAH, although the replaced amino acid was different. These findings suggest that this base position (c.397C) of *SOX17* may be a pan-ethnic "hot spot" causing PAH.

Cases 2 and 3 came from a family in which the proband mother (case 2) and her son (case 3) developed heritable PAH, whereas other family members did not (Figure 1C). Two older sisters of the PAH proband mother died in early childhood because of unspecified causes. The proband mother was diagnosed with PAH at 51 years of age. Mean PAP and PVR before treatment were 43 mm Hg and 7.7 Wood units, respectively. Case 2 had a small atrial septal defect that did not contribute to the development of PAH because of the trivial amount of shunt (Qp/Qs = 1.1). After initial combination medical therapy, PAP and PVR decreased to 30 mm Hg and 5.5 Wood units, respectively. Case 3 was diagnosed with PAH at 25 years of age. Case 3 had a patent foramen ovale. After initial combination therapy, including subcutaneous treprostinil infusion, case 3's mean PAP decreased from 63 mm Hg at diagnosis to 36 mm Hg, and PVR decreased from 12.1 to 4.8 Wood units. Case 2, her son with PAH (case 3), her husband, and her second daughter participated in genetic analysis. Whole-exome sequencing was negative for mutations in all known genes pathogenic for PAH (*BMPR2*, *ACVRL1*, *ENG*, *CAV-1*, *TBX4*, *KCNK3*, *EIF2AK4*, and *SMAD*s) and other novel pathogenic genes (*ATP13A3*, *AQP1*, and *GDF2*), although cases 2 and 3 had the same heterozygous missense mutation in *SOX17* (c.209G>A, p.Arg70Gln); this mutation was not present in the other two unaffected family members.

Case 4, a 24-year-old woman, was diagnosed with idiopathic PAH at 2 years of age (Figure 1D). Despite combination therapy, including intravenous epoprostenol infusion, case 4 had a severe and refractory clinical condition. Case 4 also had a patent foramen ovale and had survived for >20 years since diagnosis. Case 4 and her healthy parents participated in genetic analysis by whole-exome sequencing, which revealed that case 4 and her mother had mutations in *SOX17* and *TBX4*; both had a heterozygous missense

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