Linezolid use for drug-resistant tuberculosis in Georgia: a retrospective cohort study

Russell Kempker, Emory University
Marcos Schechter, Emory University
L Mikiashvilli, Natl Ctr TB & Lung Dis
M Kipiani, Natl Ctr TB & Lung Dis
Z Avaliani, Natl Ctr TB & Lung Dis
N Kiria, Natl Ctr TB & Lung Dis

Journal Title: INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE

Volume: Volume 24, Number 4

Publisher: INT UNION AGAINST TUBERCULOSIS LUNG DISEASE (I U A T L D) | 2020-04-01, Pages 436-443

Type of Work: Article

Publisher DOI: 10.5588/ijtld.19.0444

Permanent URL: https://pid.emory.edu/ark:/25593/vv044

Final published version: http://dx.doi.org/10.5588/ijtld.19.0444

Accessed November 4, 2022 10:21 PM EDT
Linezolid use for drug-resistant tuberculosis in Georgia: a retrospective cohort study

L. Mikiashvili¹, M. Kipiani¹, M. C. Schechter², Z. Avaliani¹, N. Kiria¹, R. R. Kempker²
¹National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia
²Division of Infectious Diseases, Emory University School of Medicine, Atlanta, GA, USA

SUMMARY

SETTING: Data on the long-term use of linezolid (LZD) in the treatment of drug-resistant pulmonary tuberculosis (DR-PTB) are limited.

OBJECTIVE: To assess safety, tolerability and efficacy of LZD-containing regimens for the treatment of DR-PTB in the country of Georgia.

DESIGN: A retrospective study was conducted among DR-PTB patients receiving LZD 600 mg/day as part of newly implemented regimens (bedaquiline or delamanid, repurposed and second-line drugs) from July 2014 to October 2015 in programmatic conditions and following WHO recommendations.

RESULTS: One hundred mostly male (82%) patients with a median age of 33 years received LZD. Most patients (77%) had previously been treated for TB; 57% had extensively drug-resistant TB. The median duration of LZD use was 503 days (interquartile range 355–616). LZD-associated adverse events occurred in 12 patients, leading to discontinuation in 4 (2 each due to peripheral neuropathy and cytopenias), and dose reduction to 300 mg/day in 6 cases (4 due to peripheral neuropathy and 2 for cytopenias). Almost all patients (95%) achieved culture conversion and 79% had a successful treatment outcomes.

CONCLUSION: Treatment regimens including lengthy LZD use showed fairly good safety and tolerability and were associated with high rates of culture conversion and favorable outcomes.

RÉSUMÉ

Il n’existe que des données limitées sur l’utilisation à long terme du linézolide (LZD) dans le traitement de la tuberculose pulmonaire pharmacorésistante (DR-PTB).

Evaluer la sécurité, la tolérance et l’efficacité de protocoles contenant du LZD pour le traitement de la DR-PTB dans le pays de Géorgie.

Une étude rétrospective a été réalisée parmi des patients DR-PTB recevant du LZD (600 mg/jour) dans le cadre d’un nouveau protocole (bédaquiline ou délamanide, médicaments recyclés et de deuxième ligne) de juillet 2014 à octobre 2015 dans des conditions de programme et en suivant les recommandations de l’OMS.
Cent patients, en majorité des hommes (82%), d’âge médian 33 ans ont reçu du LZD. La plupart (77%) avaient déjà été traités pour TB; 57% avaient une TB ultrarésistante. La durée médiane de l’utilisation du LZD a été de 503 jours (écart interquartile 355–616). Des effets secondaires associés au LZD sont survenus chez 12 patients dont 4 ont amené à un arrêt du traitement, 2 pour une neuropathie périphérique et 2 pour des cytopénies. Une réduction de la dose à 300 mg/jour a concerné 6 cas : 4 pour une neuropathie périphérique et 2 pour une cytopénie. Presque tous les patients (95%) ont obtenu une conversion de culture et 79% ont eu un bon résultat du traitement. Les protocoles de traitement incluant une utilisation du LZD de longue durée ont montré une assez bonne sécurité et tolérance et ont été associés à des taux élevés de conversion de culture et à de bons résultats.

RESUMEN

Los datos sobre la utilizatión a largo plazo del linezolid (LZD) en el tratamiento de la tuberculosis pulmonar farmacorresistente (DR-PTB) son escasos.

Evaluar la seguridad, la tolerabilidad y la eficacia de los esquemas que contienen LZD, en el tratamiento de la DR-PTB en el país de Georgia.

Se llevó a cabo un estudio retrospectivo de pacientes con DR-PTB que recibieron 600 mg diarios de LZD como parte de esquemas de introducción reciente (bedaquilina o delamanid, fármacos a los que se ha dado un nuevo uso y fármacos de segunda línea) de julio del 2014 a octubre del 2015, en condiciones programáticas y en conformidad con las recomendaciones de la Organización Mundial de la Salud.

Recibieron LZD 100 pacientes, en su mayoría de sexo masculino (82%), cuya mediana de la edad fue 33 años. La mayor parte de los pacientes (77%) tenía antecedente de tratamiento antituberculoso; 57% presentaba TB ultrarresistente. La mediana de la duratión de la administración de LZD fue 503 días (intervalo intercuartílico: 355–616). En 12 pacientes ocurrieron reacciones adversas asociadas con LZD, que necesitaron la interrupción del fármaco en 4 casos, 2 por neuropatía periférica y 2 por citopenia. Se redujo la dosis a 300 mg/día en 6 casos, 4 por neuropatía periférica y 2 por citopenia. Casi todos los pacientes (95%) lograron la conversión del cultivo y 79% tuvo un desenlace terapéutico favorable.

Treatment regimens including lengthy LZD use showed fairly good safety and tolerability and were associated with high rates of culture conversion and favorable outcomes.

Keywords
oxazolidinones; quinolone resistance; efficacy; safety; tolerability
limited available treatment options led the WHO to recommend the use of LZD in the
treatment of complicated drug-resistant tuberculosis (DR-TB) in 2006. It was initially
included as a Group 5 drug, but with increasing evidence of efficacy, it was changed to a
Group C core second-line drug (SLD) in 2016, and in 2018 it was advanced to Group A
along with fluoroquinolones and bedaquiline (BDQ) based on results from an individual
patient data (IPD) meta-analysis. However, caution was advised on its use for >6 months.
A recent Cochrane review was unable to perform a meta-analysis between the two existing
randomized clinical trials (RCTs) due to noncomparable data, which highlighted the
need for further studies on optimal dosage and adverse events (AEs) associated with long-
term LZD use.

With government and international donor support, Georgia implemented LZD into
programmatic use along with other new and repurposed drugs in July 2014. At that time,
Georgia was among the 27 high DR-TB burden countries worldwide, with 12% of new and
39% of previously treated cases presenting drug-resistance. Successful treatment outcome
with standard SLDs was 43% among patients with multidrug-resistant/rifampicin-resistant
TB (MDR/RR-TB), and 21% in extensively drug-resistant TB (XDR-TB) cases in the 2013
cohort. The main goals of our retrospective study were to determine the characteristics of
LZD long-term use, describe the tolerability and AEs associated with its use in routine
programmatic settings at the standard dosage of 600 mg/day, and evaluate the relationship
between LZD-containing regimens and sputum culture conversion (SCC) time, as well as
final treatment outcomes. We expect our results to help Georgia and other similar countries
effectively manage LZD for long-term use within a National TB Program (NTP) setting.

METHODS

Study design and population

A retrospective study was conducted among consecutive adult (age ≥16 years) DR-PTB
patients who received LZD-containing regimens between July 2014 and October 2015
within the Georgian NTP, including the penitential system. All patients were followed up to
31 October 2017 to ensure a minimum of 24 months of follow-up. The target groups for
starting new regimens included culture-positive patients with XDR-TB/pre-XDR-TB and
DR-TB patients experiencing either treatment failure or drug intolerance in keeping with
WHO recommendations. Exclusion criteria for LZD included baseline hemoglobin < 9.0
g/dl, platelets < 100×10⁹/L, total white blood cell (WBC) count < 4.0×10⁹/L, absolute
neutrophil count (ANC) < 1.5×10⁹/L, baseline moderate-to-severe peripheral/optic
neuropathy, concomitant medications with myelosuppression effect, MAO (monoamine
oxidase) inhibitors, and serotonergic antidepressants. Patients were routinely screened for
hepatitis B and C virus, diabetes mellitus (DM), and human immunodeficiency virus (HIV)
infection.

Individualized regimens were constructed based on phenotypic first- and second-line drug
susceptibility testing (DST), as previously described. LZD was administered orally at a
dosage of 600 mg/day; in cases of intolerance, LZD was either discontinued or the dose
reduced to 300 mg/day. Regimens varied but included some combination of the following:
BDQ or delamanid (DLM) for 24 weeks, clofazimine (CFZ), β-lactams (imipenem-cilastatin
+amoxicillin-clavulanate), and other SLDs to which the strain retained susceptibility to ensure at least four active medications. DST for pyrazinamide, LZD, and other newly implemented drugs was not available. All patients received pyridoxine prophylaxis ≥ 50 mg/day, with higher dosing determined by cycloserine (CS) (50 mg pyridoxine for every 250 mg of CS). Continued hospitalization from the initiation of DR-TB treatment to sputum smear (SS) conversion and clinical improvement was recommended. Active drug safety monitoring and management (aDSM) for novel regimens was provided according to WHO recommendations. The routine procedures included hematological, biochemistry and urinary laboratory testing and electrocardiography at baseline, weekly during the first month, twice in the second month and monthly throughout treatment; ophthalmological (visual acuity, Ishihara color test, slit lamp examination) and peripheral neuropathy (PNP) assessments at baseline and then monthly while in hospital; electromyography (EMG) as indicated. After hospital discharge, all treatment and clinical management were continued at the NTP outpatient clinics. As all treatment was administered under directly observed treatment (DOT), patients remained under the supervision of medical personnel trained in pharmacovigilance and aDSM during their whole course. In case of symptoms consistent with peripheral/optic neuropathy, specialists were consulted. All patients received social and psychological support under NTP. Decisions about treatment regimen changes were discussed and approved by the NTP Central DR-TB Committee.

Definitions

An AE was defined as clinically significant when it prompted medication discontinuation or dose reduction or required closer monitoring. AEs known to occur with LZD, including cytopenias and neuropathy, were attributed to LZD, given the known association. Anemia was defined as a hemoglobin level < 9.0 g/dL, thrombocytopenia as platelets ≤ 100×10⁹/L, leukopenia as WBC < 4.0×10⁹/L, and neutropenia as ANC < 1.5×10⁹/L. PNP was diagnosed by patient-reported symptoms, including numbness, tingling/burning sensation, or pain and subsequently, confirmed by EMG and/or neurological examination (diminished or absent deep tendon reflexes). For the grading of AEs, we used the Adult Toxicity Table of the Division of Microbiology and Infectious Diseases (National Institutes of Health, Bethesda, MD, USA). SCC time was defined as the time in days between the baseline positive culture and the first of two negative sputum cultures. Cure and treatment completion were classified as successful outcomes; death, loss to follow-up, and failure were classified as unsuccessful outcomes.

Data management

Data were extracted using a standardized case report form from the following sources: medical charts, monitoring forms, national TB database, NTP Central DR-TB Committee records, NTP pharmacovigilance database, and laboratory records. All collected data were entered into an online REDCap database (Vanderbilt University, Nashville, TN, USA) and analyzed using R software v3.4.1 (R Computing, Vienna, Austria). For univariate comparisons, differences in nominal variables were tested using either a Fisher’s exact or χ² test, and for continuous variables, either a Mann-Whitney or 2-sample t-test was used as appropriate. A two-sided P < 0.05 was considered significant. Kaplan-Meier analysis was used to describe the time to SCC after initiation of LZD.
Ethics statement

The study was approved by the Institutional Review Boards (IRBs) of the National Center for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia, and Emory University (Atlanta, GA, USA). As this was a retrospective study, a waiver for informed consent was granted.

RESULTS

The first 100 consecutive DR-PTB patients receiving LZD in Georgia were included. The median age was 33 years (interquartile range [IQR] 28–45); most were male (82%) and the median BMI was 19.8 kg/m² (IQR 17.7–21.6). XDR-TB or pre-XDR fluoroquinolone-resistant TB was detected in 85%. Rates of prior TB (71%) and previous treatment with SLDs (62%) were high. All patients were culture-positive for M. tuberculosis at baseline, and 80% had a positive SS (31% with SS ≥3+). Baseline chest radiography revealed 94% of patients had cavitary disease and 65% had bilateral lung involvement. Five patients had concomitant pulmonary and extrapulmonary TB: two had central nervous system disease, two bone disease, and one cervical lymphadenitis. The prevalence of a positive anti-hepatitis C (HCV) antibody was 19%; hepatitis B surface antigen 5% and 4% of patients had HIV (CD4 range 40–186 cells/mm³). All HIV-infected patients were on antiretroviral therapy (ART) at the time of LZD initiation. DM was present in 8% of the cohort. Full baseline characteristics are reported in Table 1.

Treatment characteristics and adverse events

All patients were started on a LZD dose of 600 mg/ day, except one patient with DM and PNP grade I, who initiated LZD at a dose of 300 mg/day. In regards to companion drugs, most patients received BDQ (95%), CFZ (92%), and β-lactams (68%); 18 patients received DLM, including 13 after BDQ use. For the complete list and durations of companion drugs see Figure 1. The median duration of LZD use was 503 days (IQR 355–616) (Table 2).

Overall, 12 patients developed LZD-attributed AEs, including 8 cases of PNP and 4 cases of cytopenia. No patients had cytopenia and PNP concomitantly. All cases of PNP involved lower extremities. The range of symptoms included numbness, decreased sensation, tingling, and/or burning. Among nine patients complaining of symptoms compatible with PNP all were confirmed by a neurologist clinical assessment, and seven were additionally confirmed by EMG. In six patients, EMG results revealed axonal polyneuropathy with sensory/sensorimotor impairments and in the additional patient, a mild demyelinating process. LZD was discontinued in two patients with grade II PNP and was reduced to 300 mg/day in four cases of PNP (grades I-II). In the remaining two patients with minor changes on EMG and a limited choice of drugs due to XDR-TB, LZD 600 mg/day was continued under close monitoring of the neurologist and no further deterioration occurred. The median time to LZD discontinuation/dose reduction due to PNP was 162 days (IQR 86–286). Based on neurologist assessment, symptoms of neuropathy gradually resolved after LZD discontinuation/dose reduction in all patients who survived (n = 6). PNP was associated with a pyridoxine dose of 50 mg/day vs. 100–200 mg/ day (P < 0.01). Associations with other risk factors were not statistically significant (Supplementary Table S1).
One patient developed color vision disorder while on ethambutol (EMB). Following EMB discontinuation, the patient received LZD and did not develop any signs of optic neuritis.

Figure 2 shows the median difference between cell counts at the start and end of LZD treatment. Median baseline hemoglobin was below the normal range for males (12.5 g/dL, IQR 11.0–13.8) and females (11.2 g/dL, IQR 10.4–12.4). There was an increase in median hemoglobin by the end of LZD treatment ($P<0.01$ for males and females). However, the median hemoglobin level for males remained below the normal range (14.1 g/dL, IQR 12.7–15.0); the median hemoglobin level in females returned to the normal range (12.8 g/dL, IQR 12.0–13.2). Although WBC count and platelets decreased during LZD use, their median values remained within the normal range ($P<0.01$), except for 13 cases with leukocytosis (WBC ≥10.0×10⁹/L).

Four patients developed cytopenias: LZD was prematurely discontinued in two, including one patient with anemia (hemoglobin 8.0 g/dL) and another with anemia and thrombocytopenia (hemoglobin 8.6 g/dL, platelets 55×10⁹/L). LZD dose was reduced to 300 mg/day in two patients due to thrombocytopenia (100×10⁹/L and 81×10⁹/L). The median time to LZD discontinuation or dose reduction due to cytopenias was 111 days (IQR 90–248). All cases of anemia and thrombocytopenia resolved, except one patient, whose platelets increased after discontinuing LZD but did not return to normal levels in the subsequent 5 months (55 to 76×10⁹/L). There were no significant associations with cytopenias (Supplementary Table S1).

Regarding AEs not attributed to LZD, hepatotoxicity was the most common (19%), requiring treatment discontinuation in 5% of cases. Three patients developed nephrotoxicity. QTcF prolongation (>450 ms) was observed in five patients (highest value, 530 ms).

**Clinical outcomes**

SCC was achieved in 95% of patients in a median of 92 days (IQR 58–158). Among 79 patients who were culture-positive at the start of LZD use, SCC was achieved in 74 patients (94%) in a median of 57 days (IQR 30–91) (Table 3 and Figure 3). A successful treatment outcome was achieved in 79% of patients. The remaining 21% with an unsuccessful outcome included 9% with death (median time to death, 262 days; IQR 150–355), 1% treatment failure, and 11% lost to follow-up. The median length of TB treatment prior to loss to follow-up was 380 days (IQR 309–464). All 11 cases lost to follow-up had XDR-TB and in nine patients, SCC had already been achieved when exiting treatment. Adjuvant surgical resection was successfully performed in 16 patients.

**DISCUSSION**

We found that LZD use was fairly well tolerated and associated with a high rate of successful clinical outcomes among a cohort of DR-PTB patients. The high rates of SCC (95%) and favorable outcomes (79 of 89 patients who completed treatment) are especially impressive given the nature of this cohort, which included patients with high rates of cavitary disease (94%), fluoroquinolone-resistant/XDR-TB (85%), and previous SLD treatment (62%); all factors indicating more severe disease and associated with worse
Our results support the recently updated WHO guidelines on DR-TB, as the most frequent companion drugs used by our study patients included those from Class A and B categories (Figure 1 and Supplementary Table S2). We also provide much-needed data on the safety and tolerability of LZD and are one of the few studies to report on patients receiving LZD for >1 year.

LZD use has quickly accelerated in recent years and will likely continue to do so given its promotion to a Class A drug in the new WHO DR-TB guidelines. However, clinical data remain limited, as there have been only two RCTs (71 patients total) evaluating LZD use among patients with TB, and <1000 of ~12,000 patients from the recent IPD meta-analysis which informed WHO guidelines received LZD. Our data thus provide important additional experience on the use of LZD in a programmatic setting, and while we could not determine the drug-specific impact of LZD we can conclude that when used with BDQ, CFZ, CS, fluoroquinolones, and β-lactams (our most commonly used companion drugs) outcomes were excellent. These data support regimens recommended by WHO and those being tested in RCTs, and also suggests that a dose of 600 mg/day may be sufficient when used in similar regimens.

The biggest concern regarding the use of LZD has been the development of drug-related AEs, including neuropathy (potentially irreversible) and cytopenias (reversible). Using data from the IPD meta-analysis, the WHO DR-TB guidelines indicated that LZD has the highest rate of AEs (those requiring drug discontinuation or classified as Grade 3–5) among all drugs used for MDR-TB treatment, at 17.2%.

Another systematic review reported that 26% of patients receiving LZD ≤ 600 mg/day had a major AE and that 35% (95% confidence interval 22–47) of all patients receiving LZD had a drug-related interruption of treatment, although the pharmacokinetic study showed that therapeutic drug monitoring significantly mitigate AEs.

Utilizing an aDSM program, we observed an AE rate of 12%, with 4% of patients permanently discontinuing LZD, which is lower than other reports, but similar to endTB interim analysis findings, which reported that 11% of patients receiving LZD had drug-attributed AEs.

Although our study and the endTB results have lower overall LZD-attributed AE rates, these continue to be high, at >10%, and emphasize the need for caution and aDSM. In our cohort, none of the LZD-attributed AEs were serious; aDSM may have allowed for early detection and intervention before the development of severe AEs. Our association of lower pyridoxine dose and development of neuropathy is also worth noting and may deserve further study. Studies to date examined the role of pyridoxine in preventing LZD-associated toxicity have mainly focused on cytopenias and have not found an effect.

Pharmacogenomic studies revealed significantly reduced LZD toxicity in patients with mitochondrial DNA haplogroup H, which is the most common maternal lineage in the Caucasus (about 40% of the population belong to the H haplogroup). Patients belonging to this haplogroup manifest 40.7% fewer clinical reactions to LZD. This also may be one of the reasons for comparatively low AEs in our cohort, which comprised 96% of Caucasians.
The main limitations included the retrospective nature of the study with the possibility of missing some AEs, although in this case, they would be insignificant, not leading to changes in treatment, and the lack of a control group, which precluded an analysis of a LZD-specific effect on outcomes and AEs. Cases of asymptomatic neuropathy may have been missed, although this was likely minimized by aDSM, including baseline and follow-up neurology assessments on all patients.

Despite some limitations and possible biases due to retrospective and non-randomized nature of the study, the results of our 100 patient observational cohort support the growing evidence of the high efficacy of LZD in the treatment of DR-TB and demonstrate fairly good tolerability and safety of long-term use of LZD in combination with other new and repurposed drugs. Further study on predictors of toxicity including pharmacokinetic and pharmacogenomic studies could help us better define high-risk patients and ensure we optimize the use of this promising drug.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgements**

The study was funded in part by the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (K23AI103044 and R21AI122001 to RRK), the NIH Fogarty International Center (D43TW007124), the Georgia Clinical and Translational Science Institute (UL1TR000454) and the Emory Global Health Institute. The authors also thank Médecins Sans Frontières, Paris, France for supporting the Georgian NTP during the study period.

**References**


Figure 1.
Linezolid companion drugs. BDQ = bedaquiline; CFZ = clofazimine; CS = cycloserine; FQ = fluoroquinolone; CPM = capreomycin; PAS = para-aminosalicylic acid; PZA = pyrazinamide; DLM = delaminid; PTH = prothionamide; KM = kanamycin; CLM = clarithromycin; EMB = ethambutol.
Figure 2.
Cell counts before and after LZD therapy. LZD = linezolid; IQR = interquartile range.
Figure 3.
Time to culture conversion after starting linezolid.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median [IQR]</td>
<td>33 [28–45]</td>
</tr>
<tr>
<td>Male</td>
<td>82</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>54</td>
</tr>
<tr>
<td>Current alcohol use</td>
<td>11</td>
</tr>
<tr>
<td>History of injection drug use *</td>
<td>19</td>
</tr>
<tr>
<td>History of incarceration</td>
<td>37</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8</td>
</tr>
<tr>
<td>Hepatitis C antibody-positive</td>
<td>20</td>
</tr>
<tr>
<td>HIV infection</td>
<td>4</td>
</tr>
<tr>
<td>Baseline CD4, cells/mm³ (range)</td>
<td>40–186</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>19</td>
</tr>
<tr>
<td>Reason for starting LZD</td>
<td></td>
</tr>
<tr>
<td>XDR-TB</td>
<td>57</td>
</tr>
<tr>
<td>Pre-XDR-TB †</td>
<td>37</td>
</tr>
<tr>
<td>Fluoroquinolone-resistant</td>
<td>28</td>
</tr>
<tr>
<td>MDR-TB treatment-non-responsive ‡</td>
<td>4</td>
</tr>
<tr>
<td>MDR-TB treatment-intolerant §</td>
<td>2</td>
</tr>
<tr>
<td>TB history and presentation</td>
<td></td>
</tr>
<tr>
<td>Prior TB</td>
<td>71</td>
</tr>
<tr>
<td>Prior treatment with first-line drugs</td>
<td>9</td>
</tr>
<tr>
<td>Prior treatment with SLDs</td>
<td>62</td>
</tr>
<tr>
<td>SLD treatment failure, n (%)</td>
<td>42 (59)</td>
</tr>
<tr>
<td>Pulmonary + extrapulmonary site ‡</td>
<td>5</td>
</tr>
<tr>
<td>Body mass index, kg/m², median [IQR]</td>
<td>19.8 [17.7–21.6]</td>
</tr>
<tr>
<td>Sputum smear-positive</td>
<td>81</td>
</tr>
<tr>
<td>High-grade baseline smear (3+, 4+)</td>
<td>31</td>
</tr>
<tr>
<td>Culture-positive</td>
<td>100</td>
</tr>
<tr>
<td>Culture-positive at LZD start</td>
<td>79</td>
</tr>
<tr>
<td>Duration of index hospital admission, days, median [IQR] (n = 97)</td>
<td>178 [90–368]</td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>65</td>
</tr>
<tr>
<td>Cavity</td>
<td>94</td>
</tr>
<tr>
<td>Bilateral cavities</td>
<td>35</td>
</tr>
</tbody>
</table>

* Information missing for four patients.
† Ofloxacin-resistant (n = 28); injectable-resistant (n = 9).
‡ Defined as positive sputum culture ≥6 months of treatment.
Defined as intolerance to SLDs leading to discontinuation of ≥2 medications.

Bone (n = 2), central nervous system (n = 2), lymph node (n = 1).

Three patients started treatment on an outpatient basis.

TB = tuberculosis; LZD = linezolid; IQR = interquartile range; HIV = human immunodeficiency virus; XDR-TB = extensively drug-resistant; MDR-TB = multidrug-resistant; SLD = second-line drug.
Table 2

Treatment characteristics and adverse events among patients with DR-TB treated with a LZD-containing regimen

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from DR-TB treatment initiation to starting LZD, days, median [IQR]</td>
<td>29 [0–179]</td>
</tr>
<tr>
<td>LZD starting dose of 600 mg/day</td>
<td>99</td>
</tr>
<tr>
<td>Dose reduction to 300 mg/day</td>
<td>7</td>
</tr>
<tr>
<td>Total duration of LZD treatment, days, median [IQR]</td>
<td>503 [355–616]</td>
</tr>
<tr>
<td>Duration of LZD 600 mg treatment, days, median [IQR] (n = 99)</td>
<td>486 [338–612]</td>
</tr>
<tr>
<td>Time to LZD dose reduction, days, median [IQR] (n = 7)</td>
<td>219 [134–351]</td>
</tr>
<tr>
<td>Duration of LZD 300 mg treatment, days, median [IQR] (n = 8)</td>
<td>265 [161–364]</td>
</tr>
</tbody>
</table>

LZD-attributed adverse events

| Any adverse event                                                             | 12               |
| PNP                                                                           | 8                |
| LZD stopped due to PNP                                                        | 2                |
| LZD dose reduced due to PNP                                                   | 4                |
| LZD continued without dose reduction                                          | 2                |
| Time to LZD discontinuation or dose reduction among patients with PNP, days, median [IQR] | 162 [86–286]    |
| Cytopenias                                                                    | 4                |
| LZD stopped due to cytopenias                                                 | 2                |
| LZD dose reduced due to cytopenias                                            | 2                |
| Time to LZD discontinuation or dose reduction among patients with cytopenias days median [IQR] | 111 [90–248]    |

*Duration of LZD treatment was as follows: in the cured (n = 79; median 598 days, IQR 399–627); in patients who stopped LZD due to adverse events (n = 4; median 138 days, IQR 60–315); in those lost to follow up/died (n = 21; median 274 days, IQR 197–392).

DR-TB = drug-resistant tuberculosis; LZD = linezolid; IQR = interquartile range; PNP = peripheral neuropathy.
Table 3
Clinical treatment outcomes among patients with drug-resistant tuberculosis treated with a LZD-containing regimen

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum culture conversion</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>95</td>
</tr>
<tr>
<td>Time from treatment initiation to conversion, days, median [IQR]</td>
<td>92 [58–158]</td>
</tr>
<tr>
<td>On LZD, n (%) (n = 79)‡</td>
<td>74 (94)</td>
</tr>
<tr>
<td>Time from LZD initiation to conversion, days, median [IQR]</td>
<td>57 [30–91]</td>
</tr>
<tr>
<td>Acquired drug resistance</td>
<td></td>
</tr>
<tr>
<td>Prior to starting LZD†</td>
<td>5</td>
</tr>
<tr>
<td>On LZD‡</td>
<td>1</td>
</tr>
<tr>
<td>Surgical resection§</td>
<td>16</td>
</tr>
<tr>
<td>Final outcomes</td>
<td></td>
</tr>
<tr>
<td>Cured or completed treatment</td>
<td>79</td>
</tr>
<tr>
<td>Lost to follow-up‡</td>
<td>11</td>
</tr>
<tr>
<td>Failure</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>9</td>
</tr>
</tbody>
</table>

* Among patients with positive sputum culture for tuberculosis prior to starting LZD.
† Capreomycin (n = 3; 63 susceptible at baseline), ethambutol (n = 1; 7 susceptible at baseline), ofloxacin (n = 2; 17 susceptible at baseline), 1 patient with acquired drug resistance to ethambutol and ofloxacin.
‡ Capreomycin (n = 1; 60 susceptible at the time LZD started).
§ Lobectomy (n = 8), segmentectomy (n = 6), pulmonectomy (n = 2)
¶ The median length of treatment prior to loss to follow-up = 380 days; last sputum culture-positive (n = 2).

LZD = linezolid; IQR = interquartile range.