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SUPPLEMENT ARTICLE

The Sterilizing Effect of Intermittent Tedizolid for Pulmonary Tuberculosis

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Background. Linezolid exhibits remarkable sterilizing effect in tuberculosis; however, a large proportion of patients develop serious adverse events. The congener tedizolid could have a better side-effect profile, but its sterilizing effect potential is unknown.

Methods. We performed a 42-day tedizolid exposure-effect and dose-fractionation study in the hollow fiber system model of tuberculosis for sterilizing effect, using human-like intrapulmonary pharmacokinetics. Bacterial burden was examined using time to positivity (TTP) and colony-forming units (CFUs). Exposure-effect was examined using the inhibitory sigmoid maximal kill model. The exposure mediating 80% of maximal kill (EC_{80}) was defined as the target exposure, and the lowest dose to achieve EC_{80} was identified in 10 000-patient Monte Carlo experiments. The dose was also examined for probability of attaining concentrations associated with mitochondrial enzyme inhibition.

Results. At maximal effect, tedizolid monotherapy totally eliminated 7.1 $\log_{10}$ CFU/mL *Mycobacterium tuberculosis* over 42 days; however, TTP still demonstrated some growth. Once-weekly tedizolid regimens killed as effectively as daily regimens, with an EC_{80} free drug 0- to 24-hour area under the concentration–time curve-to-minimum inhibitory concentration (MIC) ratio of 200. An oral tedizolid of 200 mg/day achieved the EC_{80} in 92% of 10 000 patients. The susceptibility breakpoint was an MIC of 0.5 mg/L. The 200 mg/day dose did not achieve concentrations associated with mitochondrial enzyme inhibition.

Conclusions. Tedizolid exhibits dramatic sterilizing effect and should be examined for pulmonary tuberculosis. A tedizolid dose of 200 mg/day or 700 mg twice a week is recommended for testing in patients; the intermittent tedizolid dosing schedule could be much safer than daily linezolid.

Keywords. optimal dose; intermittent dosing; pharmacokinetics/pharmacodynamics; time to positivity; susceptibility breakpoint.

Linezolid has been shown to have dramatic sterilizing effect in patients with tuberculosis (TB), even when it is the only effective drug in the treatment of patients with extensively drug-resistant TB (XDR-TB) [1–3]. Unfortunately, this efficacy comes at the cost of high toxicity rates, encountered in >35% of patients treated with the standard doses [1, 3, 4]. Recently, a new oxazolidinone, tedizolid (formerly DA-7157; prodrug DA-7218), was licensed for use against gram-positive bacterial skin and soft tissue infections [5]. In the hollow fiber system model of intracellular pulmonary *Mycobacterium avium* disease, tedizolid maximal kill (E_{max}) was higher than with linezolid [6, 7]. Similarly, for intracellular *Mycobacterium tuberculosis* (*Mtb*) infection that is typical of disseminated pediatric disease and comprises up to 20% of cavitary bacillary subpopulations in adult-type disease, tedizolid at optimal exposures had >4 $\log_{10}$ colony-forming units (CFU)/mL *Mtb* kill compared to linezolid optimal exposure after 4 weeks in the hollow fiber system model of tuberculosis (HFS-TB) [8]. However, in adult-type tuberculosis, 80% of bacteria are extracellular [9]. Here, we investigated the efficacy of tedizolid against extracellular semidormant bacteria at pH 5.8, whose kill defines sterilizing effect [10–12].

In theory, tedizolid has several advantages over linezolid in the treatment of chronic pneumonias. First, the epithelial lining fluid concentration (ELF)–to-plasma ratio and the alveolar macrophage, 0- to 24-hour area under the concentration–time curve (AUC_{0-24})–to-plasma ratio are 40-fold and 20-fold for tedizolid vs 0.14-fold and 3.3-fold for linezolid, respectively [13, 14]. However, the true extents of penetration into TB cavity lesion of each drug are unknown. On the other hand, while linezolid is only 30% protein bound, tedizolid is 90% protein bound, which could reduce the potency of tedizolid [14]. Moreover, the effect of an acidic pH on tedizolid efficacy is unknown. Here, we utilized the HFS-TB to mimic the human intrapulmonary concentration–time profile of tedizolid to

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identify optimal exposures for *Mtb* sterilizing effect under these conditions [15–18]. We then used these results to identify the dose of tedizolid that could be used for treatment of tuberculosis. This approach has been found to be accurate in identifying clinical doses, exposures, and response later shown in tuberculosis patients [16–19].

METHODS

First, we searched PubMed for all tedizolid minimum inhibitory concentration (MIC) studies published up to 31 December 2017. The following Medical Subject Heading (MeSH) terms and strategy were used: "minimum inhibitory concentration" OR "MIC" OR "susceptibility" AND "*Mycobacterium tuberculosis*" AND "tedizolid" OR "DA-7218" OR "TR-701". Next, we searched for tedizolid tuberculosis pharmacokinetic/pharmacodynamic studies using the MeSH headings "tedizolid" and "tuberculosis." There was no exclusion of articles by language.

Mtb H37Rv (American Type Culture Collection strain number 27294) was purchased from American Type Culture Collection (Manassas, Virginia). Prior to each experiment, *Mtb* from stock was grown as described in a number of previous publications [20–22]. Tedizolid, the active moiety of the prodrug tedizolid phosphate, was synthesized by BOC Sciences (Shirley, New York). Hollow fiber cartridges were purchased from FiberCell Systems Inc (Frederick, Maryland). The BACTEC 960 mycobacterial growth tube indicator system (MGIT) and supplies were purchased from Becton Dickinson (Franklin Lakes, New Jersey).

The tedizolid MIC was identified using the MGIT and macrobroth dilution methods [23]. In sterilizing effect HFS-TB experiments, *Mtb* was transformed from logarithmic growth phase (log-phase growth) to semidormant bacteria state using the methods described elsewhere [18, 24]. Twenty milliliters of the semidormant *Mtb* culture was inoculated into the peripheral compartment of each of the 22 HFS-TB units conditioned with media acidified to pH 5.8 using citric acid [18]. The systems either had daily administration of tedizolid AUC_{0-24} exposures of 6, 12, 24, 31, 78, 95, and 143 mg × hour/L or once a week administration with cumulative weekly exposures of 95, 124, and 424 mg × hour/L. The nontreated control systems received no drug treatment. There were 2 HFS-TB replicates per dose. On day 0 of the study, central compartments were sampled at 0 hour (before administration of the drug) and at 1, 6, 10, 18, 21, and 23.5 hours after drug administration to measure the tedizolid concentration [6]. We sampled the peripheral compartment of each HFS-TB on days 0, 7, 14, 21, 28, 35, and 42 and processed the samples as described in previous publication to enumerate the total *Mtb* burden [18, 20–22]. To determine the tedizolid-resistant subpopulations Middlebrook 7H10 agar was supplemented with 3 times the tedizolid MIC and incubated for up to 6 weeks before CFUs were counted.

To measure tedizolid concentrations in samples obtained from the central compartment of each HFS-TB, we used a well-validated method, described in detail previously [6, 8]. The observed concentrations were then modeled using ADAPT 5 software [25]. Steps used for pharmacokinetic modeling were as described in the past [18, 21, 26]. The relationship between effective concentration (EC) and bacterial burden was modeled using the inhibitory sigmoid E_{max} model in ADAPT 5 and in GraphPad Prism version 7 (La Jolla, California) software. We used 2 readouts of bacterial burden: *Mtb* $\log_{10}$ CFU/mL, and time to positivity (TTP) in days. The pharmacokinetics/pharmacodynamics (PK/PD) parameter, either AUC_{0-24}/MIC ratio, or peak concentration to MIC (C_{max}/MIC), or percentage time concentration persists above MIC ($\%T_{MIC}$), or trough/MIC was examined vs bacterial burden using the inhibitory sigmoid E_{max} model, and the model with the highest r^2 was chosen as linked to outcome. We defined the exposure associated with 80% of maximal kill (EC_{80}) as the target exposure to be achieved for E_{max}.

We performed Monte Carlo experiments (MCEs) of 10 000 adult patients with TB to identify the minimal dose of tedizolid that could achieve or exceed the EC_{80}. For population pharmacokinetic parameter estimates entered in subroutine PRIOR of ADAPT, we used values identified from the study of Flanagan et al [27]. The parameters (between individual variability as % coefficient of variation) were an absorption constant of 1.99 $hour^{-1}$ (194%), clearance of 6.69 L/hour (30%), central volume of 69.0 L (18%), peripheral volume of 13.6 L (18%), and an intercompartmental clearance of 0.96 L/hour (30%). The ELF-to-plasma ratio of 40 and protein binding of 90% were used to calculate a free drug penetration ratio from plasma of 4 [14]. For the tedizolid MIC distribution, we used results of our literature search, which identified the study by Vera-Cabrera et al [28]. We examined the target attainment probability of how well the dose of 50 mg, 100 mg, and 200 mg would achieve the EC_{80} in the lung of patients with TB, at each MIC. Cumulative fraction of response was then summated over the MIC distribution, as discussed elsewhere in this supplement [24].

RESULTS

In the literature search we identified only 1 relevant study, performed in mice by us [29]. The study did not perform dose-ranging experiments for tedizolid, or dose-scheduling experiments, but had examined the drug at a single dose in combination with bedaquiline and pretomanid. There were no publications of tedizolid use in TB patients. In the second literature search for the largest distribution of tedizolid MICs in *Mtb*, we found the study by Vera-Cabrera et al in 2006 of 95 clinical *Mtb* isolates plus H37Rv, in which MICs were identified using microbroth dilution assay concentrations of 0.015–64 mg/L: the MICs for 50% of the isolates (MIC_{50}) and 90% of the isolates (MIC_{90}) were 0.25 mg/L and 0.5 mg/L, respectively [28]. In experiments with our laboratory strain of *Mtb* H37Rv, we identified an MIC of 0.25 mg/L with both MGIT and microbroth dilution assays, on 2 separate occasions for each assay.

Tedizolid pharmacokinetics achieved in the HFS-TB was best described using a 1-compartment pharmacokinetic model, based on Akaike information criteria, Bayesian information criteria, and parsimony. The pharmacokinetic model predicted vs observed concentrations were as shown in Supplementary Figure 1. The clearance was 0.013 ± 0.008 L/hour, and volume was 0.249 ± 0.24 L, which translates to a half-life of 13.2 hours.

Time-kill curves for the different tedizolid total concentrations (AUCs) are shown in Figure 1. Figure 1A shows AUC vs response for each dosing schedule, starting with the CFU/mL readout. For the daily dosing schedule, exposures between an AUC_{0-24} of 31 mg × hour/L and 78 mg × hour/L marked the transition to a steep sterilizing effect curve. For the largest once-weekly dose, which is the cumulative weekly (ie, 168 hours) AUC_{0-168} of 424 mg × hour/L, equivalent to a daily AUC_{0-24} of 60 mg × hour/L, the microbial kill fell below limits of detection for the CFU/mL assay by day 42, which would indicate complete eradication of *Mtb* in the HFS-TB replicates. However, using the more sensitive TTP readout, shown in Figure 1B, there was still growth of *Mtb* in those systems, demonstrating that extinction of the bacterial population had not been achieved with monotherapy in 42 days. Nevertheless, the same pattern of sterilizing effect seen with CFU/mL was seen with TTP. Intermittent dosing was effective; the HFS-TB replicates treated with tedizolid AUC_{0-168} of 424 mg × hour/L administered once a week had the highest TTP of all at the end of the experiment, which means that intermittently administered tedizolid can achieve dramatic sterilizing effect.

Supplementary Table 1 shows that the highest r^2 for PK/PD index vs bacterial burden based on the inhibitory sigmoid E_{max} model fits. The table shows that whether bacterial burden was expressed as $\log_{10}$ CFU/mL or TTP, the PK/PD index linked with efficacy was the AUC_{0-24}/MIC ratio. Thus, unequivocally, tedizolid free AUC_{0-24}/MIC was the PK/PD driver for sterilizing

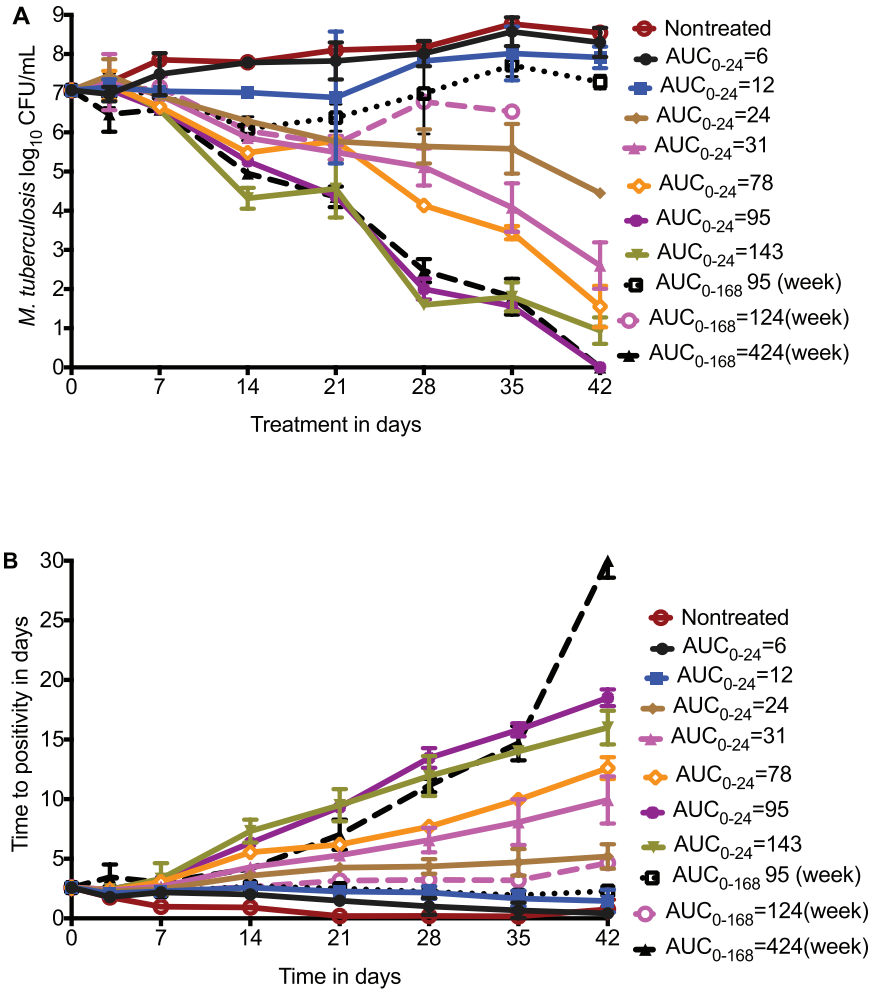

Figure 1. Tedizolid time-kill curves in the hollow fiber system model. Tedizolid doses are shown as area under the concentration–time curve either daily or for the whole week in the once-weekly doses. It can be seen that even with a once-weekly dosing schedule, a steep sterilizing effect slope was achieved. *A*, Shows the results as colony-forming units (CFU)/mL. *B*, Shows results using time to positivity, which, because of greater sensitivity of assay, demonstrates that no systems were totally sterilized by day 42, unlike the CFU/mL results. Abbreviations: AUC, area under the concentration–time curve; CFU, colony-forming units.

effect. The relationship between AUC_{0-24}/MIC and $\log_{10}$ CFU/mL burden is shown in Figure 2A. The EC_{50} varied from an AUC_{0-24}/MIC of 70.22 on day 7 to 125.7 on day 28, consistent with observations with other antituberculosis drugs in the past [20, 30]. The relationship between AUC_{0-24}/MIC and bacterial burden at end of study, on day 42, was described by the equation:

$$\text{Effect}\left[\log_{10}\text{CFU/mL}\right] = 8.53 - 7.76 * \left[\text{AUC/MIC}\right]^{3.38} / \left[88.63 + \text{AUC/MIC}\right]^{3.38};\quad r^2 = 0.97$$

Based on this, the EC_{80}, we calculated a free (f) AUC_{0-24}/MIC of 134. The relationship between TTP and $f AUC_{0-24}$/MIC is shown in Figure 2B. Day 42 results revealed an EC_{50} of 166 (95% confidence interval [CI], 78.08–153.9), and an H of 2.53 (95% CI, .08–5.13), which translates to an EC_{80} of 200 (r^2 = 0.93). This latter $f AUC_{0-24}$/MIC of 200 was adopted as the target exposure for optimal sterilizing effect.

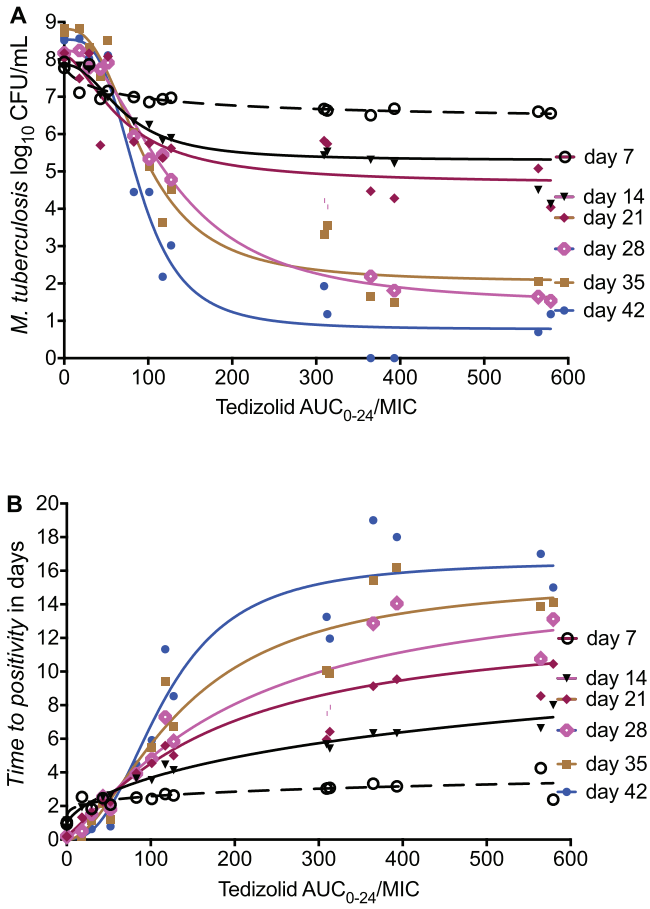

Figure 2. The relationship between tedizolid exposure and bacterial burden. Inhibitory sigmoid maximal kill modeling for each of the weekly sampling days, chosen because the most intermittent dose was once every 7 days. *A*, Results showing colony-forming units/mL inhibition with increasing area under the concentration–time curve (AUC)/minimum inhibitory concentration. *B*, On the other hand, time to positivity (TTP) decreases with increased bacterial burden, so that the "inhibition" is upside down with higher TTP with increasing AUC. This is reflected with a negative Hill slope (H) in the resultant equations. Abbreviations: AUC, area under the concentration–time curve; CFU, colony-forming units; MIC, minimum inhibitory concentration.

We, performed 10 000-patient MCE to identify the dose best able to achieve the $EC_{80} f AUC_{0-24}$/MIC of 200, based on the MIC distribution of Vera-Cabrera et al [28]. With the clinical dose of 200 mg/day, we identified a serum mean ± standard deviation AUC_{0-24} mg/L of 31.0 ± 6.6 in the 10 000 patient simulation, which similar to the steady-state serum AUC_{0-24} mg/L values of 29.2 ± 6.2 and 25.6 ± 8.4 reported for this dose to the US Food and Drug Administration (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205435s000lbl.pdf). This validates that our MCE-identified concentrations that are clinically meaningful [31]. Figure 3A shows that for the doses of 100 mg/day, target attainment probability (TAP) was 100% in patients with *Mtb* isolates that had MIC ≤0.125 mg/L, and then fell below 90% one tube dilution higher. In patients treated with tedizolid 200 mg/day, the TAP was 100% until the highest MIC of 0.5 mg/L, at which point it fell to 84%. The cumulative fraction of response, which is the proportion of patients achieving EC_{80}, calculated by taking an expectation over the MIC distribution, is shown for each dose in Figure 3B. The figure shows that the cumulative fraction of response in patients treated with tedizolid 100 and 200 mg/day was 46.63% and 92.17%, respectively. This means that 200 mg/day tedizolid is the dose to be explored for sterilizing effect in patients. Alternatively, the dose could be given as 700 mg twice a week or 1400 mg once a week and would still achieve the same cumulative fraction of response as the 200 mg/day.

DISCUSSSION

There is need for newer compounds that have sterilizing effect in patients with drug-susceptible TB, MDR-TB, and XDR-TB, with several antibiotics being repurposed for that use [3, 32–36]. Oxazolidinones, in the form of linezolid, have demonstrated great promise in that direction. Here, we provide evidence that the congener tedizolid has good sterilizing effect even as monotherapy in the HFS-TB. In comparison to first-line antituberculosis drugs in the same model system, the sterilizing effect kill rates in the same system were better than isoniazid, pyrazinamide, ethambutol, and standard-dose rifampin as monotherapy [18, 21, 37–39]. In the accompanying article, we have shown that tedizolid also had good efficacy against intracellular *Mtb*, which means that tedizolid may be effective against different bacillary subpopulations encountered in pulmonary cavities and in children with disseminated disease [8]. Thus, at a minimum, tedizolid could be able to replace linezolid in MDR-TB and XDR-TB regimens. However, clinical verification of this sterilizing effect is still required.

Second, we identified the optimal exposure of tedizolid for sterilizing effect, which was an AUC_{0-24}/MIC of 200, or a cumulative weekly AUC_{0-168}/MIC of 1400. This would also be

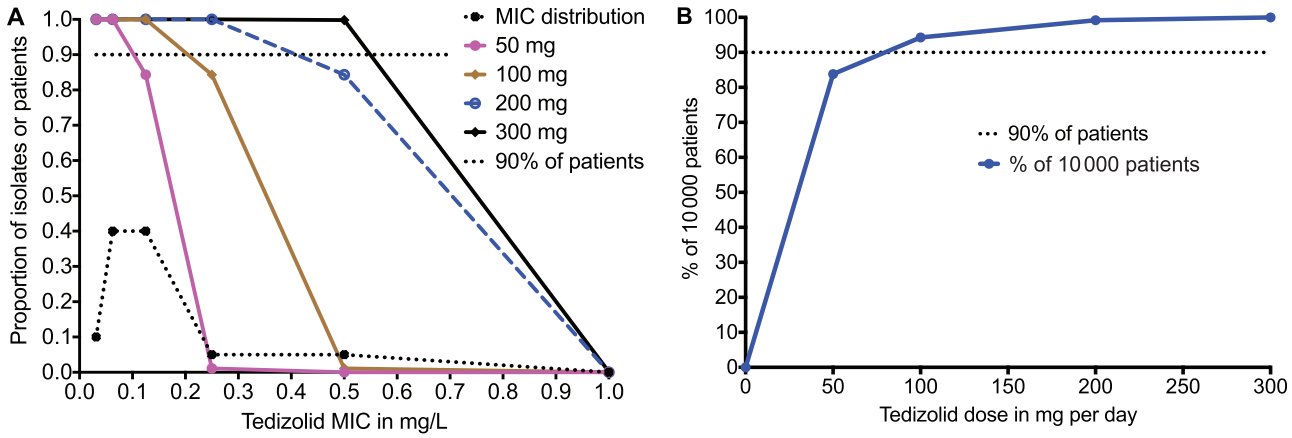

Figure 3. Target attainment of different doses in Monte Carlo simulations. *A*, Target attainment probabilities (TAPs) of the different oral tedizolid doses at each minimum inhibitory concentration (MIC). The MIC distribution ranged from 0.125–0.5 mg/L for 95 isolates [28]. This MIC distribution and the high epithelial lining fluid concentration–to-plasma ratios [14] were advantageous with regard to high TAP. At the dose of 200 mg a day, the TAP falls from 100% at an MIC of 0.25 mg/L to 84% at an MIC of 0.5 mg/L. *B*, After summation at each MIC, the cumulative fraction of response for each dose on a "normogram" reveals that the dose of 200 mg would achieve sterilizing effect exposure target in >92% of patients and a dose of 300 mg per day would achieve the sterilizing effect exposure in 99.9% of 10 000 patients. Abbreviation: MIC, minimum inhibitory concentration.

optimal for intracellular *Mtb* kill, based on the target exposure AUC_{0-24}/MIC of 188 we identified for that subpopulation in separate experiments [8]. Based on MCE, we identified the oral tedizolid dose of 200 mg a day as the candidate for clinical trials. Since this is an AUC/MIC-driven drug, intermittent therapy such as 700 mg twice a week would be as effective as daily doses, allowing for intermittent tedizolid regimens. Indeed, our experiments demonstrated efficacy even with once-weekly dosing. This would allow combination of this drug for intermittent therapy regimens, without compromising efficacy. Intermittent dosing is a great advantage for TB treatment programs.

Third, we have found that toxicity of oxazolidinones such as linezolid is AUC driven with an inhibitory concentration (IC_{50}) for mitochondrial inhibition of 94 mg × hour/L; however, tedizolid AUC_{0-24} of 90 mg × hour/L was not associated with such a mitochondrial enzyme inhibition signature [8, 40]. The tedizolid dose of 200 mg a day or 700 mg twice a week achieves an AUC of 90 mg × hour/L over 3.5 days, lower than tedizolid AUC_{0-24} of 90 mg × hour/L each day that did not generate a mitochondrial toxicity signal [8]. Song et al and Brown et al have proposed that linezolid toxicity is driven by trough concentration [41, 42]. In a recent study, Milosevic et al demonstrated rapid reversal of tedizolid toxic effects upon discontinuous administration and found that an intermittent dosing schedule was what contributed to the drug's lower toxicity [40]. If so, our proposed twice-weekly dosing schedules could be advantageous as regards to safety without compromising efficacy. However, the clinical safety of our proposed tedizolid dosing scheme over the longer durations of therapy that are used to treat tuberculosis still needs to be established.

Finally, our MCEs allow us to establish a proposed tedizolid clinical susceptibility breakpoint, which was an MIC of 0.5 mg/L at the dose of 200 mg/day. This value is virtually the same as that identified using both clinical response, epidemiologic cutoff values, and PK/PD approaches in a variety of mundane gram-positive cocci [43]. We propose the same as that tentative clinical breakpoint in TB. The approach that uses the HFS-TB followed by MCE has had a good track record in identifying MICs above which patients fail combination therapy in tuberculosis [17, 31, 44–46]. Thus, there is a good probability that this will be the final clinical breakpoint.

Our study has its own limitations. The first limitation is use of only 1 laboratory strain of *Mtb* in the HFS-TB experiments. However, in the accompanying article, tedizolid was also tested in HFS-TB of H37Ra, while MICs were also identified in *Mtb* CDC1551, *Mtb* SS18b, and HN878, which were also within the range of MIC distributions of the clinical isolates identified in our literature search [8, 28]. Indeed, the MIC distribution we identified in our literature search means that tedizolid is likely to be effective against >90% of clinical strains. The second limitation is that we did not detect any tedizolid resistance in the current experiment. This could either be that no drug resistance arose, or more likely that our assay of tedizolid 3 times the MIC on Middlebrook agar did not work. However, despite these limitations, our data are adequate for demonstrating that tedizolid has excellent sterilizing effect against *Mtb*.

In conclusion, we identified the optimal exposure target of tedizolid for sterilizing activity against *Mtb*, the susceptibility breakpoint for the optimal dose, and the possibility of intermittent dosing without compromising efficacy. Clinical trials have been designed to combine a tedizolid once-daily 200-mg dose, and a once-weekly dose regimen in combination with other antibiotics with a long half-life in the treatment of MDR-TB, XDR-TB, and drug-susceptible TB.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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