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Linezolid Tolerability in Drug Resistant TB Patients and Its Future use in all Oral Shorter Regimens

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ABSTRACT

Linezolid (Lzd) belongs to group of Oxazolidinones a repurposed drug to treat Drug resistant TB (DR TB). WHO in 2019 placed Lzd in Group A Drugs along with Levofloxacin/Moxifloxacin and Bedaquiline as most effective drugs to treat RR/MDR TB. The RR/MDR TB regimen should be constructed with a combination of at least 4 likely effective drugs. The toxicity profile of Lzd may feature from 22% to 80% and among most common toxicities are myelosuppression and neuropathy and such frequent toxicities lead from temporary interruption to permanent discontinuation of Lzd during RR/MDR TB treatment. The median time to development of toxicity is around 5-6 months of treatment but toxicity may occur even during early weeks of treatment. The Linezolid (Lzd) usual dose of 600 mg OD is also used for <28 days to treat various gram-positive infections. Linezolid toxicity is frequent but relatively easy to detect and manage and is reversible other than complete nerve damage if not detected early and drug interrupted timely. Linezolid (600 mg daily) is also part of WHO recommended BPaLM and BPaL regimens which are safe, shorter, low cost and highly effective as future RR/MDR TB treatment. To ensure safety of patients all TB programs must ensure appropriate adverse drug safety, monitoring and management (DSM) mechanism as essential component of Drug resistance TB treatment.

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Introduction and Background

WHO in 2019, recommended all oral regimens to treat RR/MDR TB based on regrouping of medicines. As per evidence Group A agents Moxifloxacin (Mfx)/Levofloxacin (lfx), Bedaquiline (Bdq) and Linezolid (Lzd) are considered highly effective agents to treat drug resistant TB [1]. Therefore, WHO strongly recommends to add all three group A drugs in the all oral regimen unless there is contraindication to any of group a drugs. According to evidence as per WHO 2019 guidelines, Bdq is safest with 2.4% risk of toxicity, while Lzd is most toxic with 17% attributed risk factor, but reversible anemia and peripheral neuropathy (except peripheral neuropathy if damage to nerve is permanent which may be irreversible). The Linezolid (Lzd) usual dose of 600 mg OD is also used for <28 days to treat gram-positive infections including complicated bacteremia. Moreover, the elimination half-life of Linezolid is 5-7 hours and an AUC/MIC ratio of 100 in the presence of a companion drug at relevant exposure is required [2].

Linezolid (Lzd) belongs to group of Oxazolidinones, it inhibits bacterial protein synthesis by targeting the peptidyl transferase activity of the 23S rRNA in the 50S ribosomal subunit [3]. Mammalian mitochondrial ribosomal components are closely related to their bacterial counterparts, and decreased mitochondrial function correlates with toxicity of lzd, leading to drug discontinuation [4].

The introduction of Pretomanid (Pa) by TB Alliance and its approval by US FDA in 2019 was a landmark to unveiling innovative, even shorter, and effective treatment regimens (BPaLM & BPaL) to treat DR TB. These 6-month shorter all-oral regimens are a combination of Bedaquiline (Bdq)-Pretomanid (Pa)-Linezolid (Lzd) and Moxifloxacin (Mfx) BPaLM to treat RR/MDRTB without additional resistance to the fluoroquinolone (FQ), and Bedaquiline (Bdq)-Pretomanid (Pa), and Linezolid (Lzd) BPaL to treat RR/MDR TB with additional resistance to FQ (Pre-XDRT-B) [5]. Likewise, WHO in 2022 guideline also recommended Linezolid variant in addition to Ethionamide (Eto) variant for shorter oral regimen to treat RR/MDR TB without additional resistance to fluoroquinolone (FQ).

It is obvious that Linezolid being repurposed drug and among most efficacious drugs to treat DRTB (Drug resistant TB) is essential part of all DR TB regimens. There are some concerns about its tolerability with Lzd based regimens due to significantly high number of adverse effects occurrence and interruption of Linezolid. Therefore, the findings below based on literature review and evidence will help to further understand using Lzd in DR TB regimens its dosages and duration of use in WHO recommended DR TB treatment.

Methods
We searched original articles published from 2010 up till now where Linezolid (Lzd) was used as part of core regimen with other companion drugs on board per WHO recommendations to treat RR/MDR, Pre XDR and XDRTB. The search criteria to find relevant studies was; Linezolid use in DR TB treatment, Dose of Linezolid, impact on treatment, Linezolid interruption, Linezolid toxicities. We also searched the WHO recent guidelines and recent recommendations to use in the context and support future decision making for Drug resistant TB treatment using Linezolid as part of regimen.

Findings from Literature Review
A study prospectively followed up 63 South African XDR-TB patients (58.7% HIV-infected) with Bdq based regimen including Lzd [6]. The median body weight of patients was 51.8kg. The frequency and severity of linezolid-associated adverse events and the impact on treatment outcomes were compared between linezolid interrupters and non-interrupters. The findings suggest that 52%, 71%, 36% reported grade 1, grade 2 and grade 3 adverse events respectively, but no patient had life threatening adverse event. Lzd interruption due to adverse events occurred in 22 (34.9%) patients during treatment while the remaining 41 (65.1%) completed one year of uninterrupted linezolid therapy. Anemia occurred in 31% and Peripheral neuropathy reported in 31% of patients while body pain in 27% of patients, two of these patients had blood transfusion. Anemia, peripheral Neuropathy and Optic Neuritis developed at a median of 5 weeks, 18 weeks and 23 weeks after Lzd treatment initiation with a median of 26% drop in baseline Hb% by 12 weeks of treatment. The study findings also suggest that patients who received linezolid for greater than three months are more likely to survive. This study from TB/HIV endemic country also revealed that linezolid interruption does not negatively impact treatment outcomes.

Furthermore, a study reported that anemia, peripheral neuropathy and optical neuritis occurred in 16%, 19%, and 2% of the patients [7]. However, in this study 75% of the patients included received erythropoietin in a dose of 2000 IU twice a week and this may be the reason of lower anemia reported.

The treatment data from Myanmar (2018) for 45 patients who have been treated with Bdq based regimen in 2018 including Lzd for Pre XDR, XDR TB and failures of RR/MDR TB. As it can be observed in table 1 that in 13 % patients Lzd was stopped and in 24% dose reduced to 300 mg and time to stop Lzd was 160 days and dose reduction 177days.

Table 1: Duration of Lzd use and time to reduce dose or stopped (Source: Data from ASTBH, Yangon 2018)

Table 1	Number	%	remark
Jan-June cohort 2018	45		
# and % who were stopped Lzd	6	13%	3 due to haemato, 2 due to PN, 1 due to both
# and % who were reduced dose to 300 mg	11	24%	5 due to haemato, 3due to PN, 3 due to both
Time to stop Lzd (average)	160 days		
Time to reduced dose (average)	177 days		

To see more evidence on effectiveness and tolerability of Lzd one of the study shows about available evidence of Lzd to treat MDR/ XDR patients its adverse events, duration of exposure and discontinuation rate (Table 2) [8]. The table below explains that adverse vents rate range from 40% to 94% and Lzd discontinuation rate due to various adverse events range from 6% to 68%. This study also expresses that longer the Lzd exposure higher the adverse events.

Table 2: Lzd associated adverse events discontinuation rate and duration of exposure in days [8]
(Source: Giovanni & Emmanuelle, 2015)

First author [ref.]	Adverse events	Discontinuation rate	Anaemia	Neuropathy	GI events	Duration of exposure days
Observational studies						
Sotgiu [31]	63/107 (58.9)	54/79 (68.4)	32/84 (38.1)	40/85 (47.1)	14/84 (16.7)	300#
Zhang [35]	6/15 (40.0)		4/15 (26.6)	1/15 (6.7)	3/15 (20.0)	60#
Xu [36]	17/18 (94.4)		12/18 (66.7)	11/18 (61.1)	15/18 (83.3)	180¶
Experimental studies						
Lee [32]	33/38 (87)	3/38 (7.9)+	7/38 (18.4)	21/38 (55.3)		At least 180
Tang [34]	27/33 (81.8)	2/33 (6.1)+	17/33 (51.5)	8/33 (24.2)	16/33 (48.5)	360¶

presented as n/N (%), unless otherwise stated. GI: gastrointestinal. #: median; ¶: mean; +: permanent.

Another study demonstrated that the serum concentrations of linezolid obtained following each 300 mg administration b.i.d. are well above the minimum inhibitory concentration ((MIC), i.e.0.125–0.5 mgL-1againstM. tuberculosis) and that the serum concentration–time curve over 24 h/MIC ratios were sufficiently high to predict efficacy in seven out of the eight patients studied [9]. This study provides evidence that a 300 mg b.i.d. dosage may be used to prolong treatment with linezolid, with sustained efficacy and limitation of adverse events.

A daily dose of 600 mg seems appropriate to balance between efficacy and toxicity. However, literature is inconclusive about the preferred administration of a daily dose of 600 mg being a drug with a very narrow therapeutic window [2].

The ZeNix TB Trial results published in 2022, established that as compared to 1200-mg linezolid dose, 600-mg lead to smaller number for linezolid dose adjustments, no optic neuropathy, and less episodes of peripheral neuropathy and myelosuppression. Hematologic toxic effects were uncommon in the two 600-mg linezolid groups. While peripheral neuropathy that ensued or deteriorated during treatment occurred more often in the group that received linezolid at a dose of 600 mg for 26 weeks, both the 9-week group and the 26-week group had the same incidence (13%) of linezolid dose adjustments. In addition, favorable outcome reported in ZeNix trial were 89% in the group that received 1200 mg of linezolid for 9 weeks, 91% in the group that received 600 mg of linezolid for 26 weeks, 84% in the group that received 600 mg of linezolid for 9 weeks [10]. It is important to highlight that Lzd for any duration in combination improved with other effective drugs supports better treatment response and outcome in RR/MDR TB patients.

Discussion and Conclusion

Linezolid is among most effective second line drugs along with other likely effective companion drugs to treat DR TB with most frequent toxicity profile. From the above information, the drug characteristics, and its side effect profile (though common but manageable) points towards well monitored outpatient-based use in combination with the new companion drugs for RR/MDR TB treatment. Linezolid treatment may benefit from a more personalized approach, that is, measuring actual MIC values and therapeutic drug monitoring and strict DOT to identify and manage related toxicities.

Still inconclusive that 300 mg daily, 300 mg BID or 600 mg alternative day is the best way to avoid toxicities while maintaining the efficacy, while its half-life is 5-7 hours. A dosage of 600 mg per day seems the best recommendation, as it minimizes the occurrence of adverse events while not compromising efficacy. Moreover, this recommendation is also in line with WHO 2019 recommendations to use 600 mg OD and dose to be reduced to 300 mg daily in patients with side effects.

This has also been observed that longer the treatment duration of Lzd better the favorable outcome but with increased toxicity risk. In addition, WHO also mentioned that use of Lzd for at least 6 months has shown to increase effectiveness and its use for whole duration of treatment was shown to optimize its effect. However, toxicity associated with Lzd may limit its use. However, Lzd dose reduction to 300 mg because of toxicity during RR/MDR TB treatment may still retain efficacy given that regimen contains sufficient likely effective core and companion drugs on board.

The information from the studies and data referenced above determine that Lzd optimum safe duration of use could be around 5-6 months during DRTB treatment. Similarly, even during this period or at any point of time Lzd may be stopped or dosages reduced in significant number of patients due to toxicity. This poses a question to those regions where patents' on MDR TB treatment with Lzd based regimen cannot be routinely monitored and demands for appropriate monitoring mechanism to avoid undue adverse effects. However, still Lzd based regimens are much safer and easy to monitor as compared to previously used Injectable based MDR TB treatment.

The high proportion of patients experiencing adverse events and requiring drug interruption or dosage reduction suggests a strong a DSM mechanism in place that is able to detect and manage side effects early and timely. Its frequency of side effect profile also demonstrates that close and carefully monitoring for any occurrence of serious adverse events along with well-equipped facilities/PMDT sites are essential to manage any serious toxicities (including the possible need for blood transfusion). Nevertheless, it is also known that the Lzd associated side effects are reversible (until there is permanent nerve damage) and side effect profile becomes normal after stopping or dose reduction of Lzd. with relatively easy to detect adverse effects as compare to Injectables used to treat DR TB.

Keeping in view the above and recent evidence from Nix, ZeNix TB trials, TB PRACTECAL study which lead WHO to make recommendation in 2022 for BPaLM and BPaL for eligible patients under programmatic conditions is a great way forward to treat RR/MDR and Pre XDRTB [10-11]. These shorter and highly effective regimens will allow RR/MDR TB patients to complete treatment in 6 months with reduced chances of toxicity. WHO in its 2022 DR TB guidelines recommend flexible approach for Lzd use after 9 weeks of treatment where in case of toxicity either Lzd dose can be reduced to 300 mg or temporarily withhold. Likewise, in BPaLM/BPaL during 1st 9 weeks of treatment, due to Lzd toxicity whole regimen can be interrupted up to 14 days and re-introduced with 600 mg daily if it is safe to do so. The newer forms of Oxazolidinones which are Sutezolid (Szd) and Delpazolid (Dzd) are in clinical development for treatment of Mycobacterium TB (MTB) and seems to be promising agents with equal potency and lower toxicity profile [12].

Suggested way Forward

1. National TB reference laboratories in high to low TB burden countries should have capacity to perform Phenotypic DST (pDST) to Bdq, Lzd, Cfz drugs at baseline and whenever patient fails treatment. Xpert MTB/XDR should be adopted as rapid DST to Fluoroquinolone at baseline for all RR TB patients for appropriate treatment.
2. As per DR TB guidelines BPaLM (for FQ susceptible) and BPaL (for FQ resistant) 14 years or older age should be the priority choice for treating Drug resistant TB [5]. If patients are not eligible for BPaLM, the 2nd priority should be oral shorter (9-11months) MDR TB regimen. Manage patients as per WHO and National TB Control Program guidelines.
3. BPaLM/BPaL can be used in mild to moderate level of baseline anemia and peripheral neuropathy, while if toxicity develops during treatment then to be managed per a DSM protocols.
4. Systems development programmatically which is a DSM (adverse drug safety, monitoring) at all MDR TB Treatment centers by NTP that is able to capture Lzd related toxicity early and then manage accordingly in timely manner to avoid happening of serious adverse events
5. Linezolid related adverse events predictive score (LAPS), should be used by physicians to assess pre-therapeutic risk of patients for developing adverse events [13]. Likewise, BPNS scoring and appropriate assessment of neuropathy is imperative.
6. Where resources allow use Therapeutic drug monitoring (TDM) for optimum management of patients on linezolid based regimens.

7. Assess and treat effectively co-morbid conditions i.e. Diabetes, HIV, Hepatitis, pre-existing anemia including patients with low BMI which may exacerbate the Lzd toxicity.
8. Adopt appropriate patients counselling, psycho-social support, build trust on health care providers, patients centered approach for optimum treatment outcome [14-15].

References

1. World Health Organization (2019) WHO consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization. https://apps.who.int/iris/handle/10665/311389
2. Mathieu S Bolhuis, Onno W Akkerman, Marieke G G Sturkenboom, Samiksha Ghimire, Shashikant Srivastava, et al. (2018) Linezolid-based Regimens for Multidrug-resistant Tuberculosis (TB): A Systematic Review to Establish or Revise the Current Recommended Dose for TB Treatment. Clin Infect Dis 28: S327-S335.
3. Leach KL, Brickner SJ, Noe MC, Miller PF (2011) Linezolid, the first oxazolidinone antibacterial agent. Ann N Y Acad Sci 1222: 49-54.
4. Song T, Lee M, Jeon HS, Park Y, Dodd LE, et al. (2015) Linezolid trough concentrations correlate with mitochondrial toxicity-related adverse events in the treatment of chronic extensively drug-resistant tuberculosis. EBioMedicine 2: 1627-1633.
5. WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update.
6. Olatunde Olayanju, Aliasgar Esmail, Jason Limberis, Phindile Gina, Keertan Dheda (2019) Linezolid Interruption In Patients With Fluoroquinolone- Resistant Tuberculosisreceiving A Bedaquiline-Based Treatment Regimen. Int J Infect Dis 85: 74-79.
7. Mathieu S Bolhuis, Simon Tiberi, Giovanni Sotgiu, Saverio De Lorenzo, Jos G W Kosterink (2015) Linezolid tolerability in multidrug-resistant tuberculosis: a retrospective study. European Respiratory Journal 46: 1205-1207.
8. Giovanni Sotgiu, Emanuele Pontali, Giovanni Battista Migliori, (2015) Linezolid to treat MDR-/XDR-tuberculosis: available evidence and future scenarios. European Respiratory Journal 45: 25-29.
9. Jan Willem C Alffenaar, Richard van Altena, Ilse M Harmelink, Patricia Filguera, Esther Molenaar, et al. (2010) Comparison of the pharmacokinetics of two dosage regimens of linezolid in multidrug-resistant and extensively drug-resistant tuberculosis patients. Clin Pharmacokinet 49: 559-565.
10. Francesca Conradie, Tatevik R. Bagdasaryan, Sergey Borisov, Pauline Howell, Lali Mikiashvili, et al. (2022) BPaL regimen for Drug resistant TB. N Engl J Med 387: 810-823.
11. Bern Thomas Nyang'wa, Catherine Berry, Emil Kazounis, Ilaria Motta, Nargiza Parpieva et al. 2022 A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med 387: 2331-2343.
12. Dereje A Negatu, Wassihun Wedajo Aragaw, Julianna Cangialosi, Véronique Dartois, Thomas Dick (2023) Side-by-Side Profiling of Oxazolidinones to Estimate the Therapeutic Window against Mycobacterial Infections. American Society for Microbiology 67: e0165522.
13. R Buzelé, A Lemaignen, X Pourrat, P Rosset, G Gras et al. (2015) Linezolid-related adverse events predictive score (LAPS): Usefulness in clinical practice. nt J Antimicrob Agents 46: 727-728.
14. Giovanni Sotgiu, Rosella Centis, Lia D'Ambrosio, Jan William C Alffenaar, Holly A Anger, et al. (2012) Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. European Respiratory Journal 40: 1430-1442.
15. Shashikant Srivastava, Gesham Magombedze, Thearith Koeuth, Carleton Sherman, Jotam G Pasipanodya, et al. (2017) Linezolid dose that maximizes sterilizing effect while minimizing toxicity and resistance emergence for tuberculosis. Anti microb Agents Chemo ther 61: e00751-17.