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Linezolid Induced Peripheral Neuropathy in Multidrug Resistant Tuberculosis- A Prospective Observational Study

Research Article

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Abstract

Background: Linezolid is used for treatment of MDR TB and one of the common adverse effects is peripheral neuropathy. Dose modification or interruption at the onset of peripheral neuropathy can prevent the development of irreversible deficits. We aim to study the clinical features, grade the severity of linezolid induced peripheral neuropathy and effects of dose modification so as to avoid long term deficits.

Methods: MDR TB patients on linezolid treatment who developed peripheral neuropathy were studied. National Cancer Institute Neurosensory Scale was used to grade patients into mild, moderate and severe neuropathy. Mild were continued on linezolid 600 mg, moderate were reduced to 300mg and linezolid was withdrawn for severe neuropathy. Follow up was done regularly and dose modified accordingly. End result was analyzed at 18 months of TB treatment completion.

Results: 84 patients were included in the study. On presentation, 31(36.9%) patients had mild neuropathy, 33 (39.28%) moderate and 20 (23.8%) severe peripheral neuropathies. At the end of 18 months of treatment, linezolid was stopped early in 34 (40.5%) patients and dose reduction to 300mg was done in 50 (59.5%) patients. Final assessment revealed 11(13.09%) patients free from symptoms of peripheral neuropathy, 37 (44.04%) patients had mild, 22 (26.19%) had moderate and 14 (16.6%) had severe peripheral neuropathy.

Conclusion: This study highlights the importance of grading linezolid induced peripheral neuropathy and the need to provide standard guidelines for dose modification to prevent irreversible severe deficits.

Keywords: Linezolid; Peripheral Neuropathy; Multidrug Resistant TB

Introduction

India accounts for highest number of tuberculosis (TB) cases in the world. In 2022, 2.8 million TB cases were reported in India representing 27% of the global burden [1]. Multidrug resistant (MDR) TB cases have increased by 32% in 2022 compared to 2021 [2]. In 2018, linezolid (LNZ) was included to group A drug and recommended it to be used for patients with MDR-TB [3]. It is given in the dose of 600mg/day for initial 6 months followed by 300mg/day for 18 months in adults above 18 years with MDR TB. However, adverse events are common with courses longer than one month, affecting over 80% of patients in some studies [4]. Peripheral neuropathy is a common adverse effect with risks of deficits which

are often irreversible [5]. Recently, CDC has provided guidelines for dosing modification or interruption of Linezolid based on the adverse reactions [6]. In our study, patients on linezolid for MDR TB who complained of pain/ paresthesias for more than 7 days were considered of having peripheral neuropathy. We need to objectively grade the severity of neuropathy and guide on reducing dose or withdrawing the drug accordingly to avoid long term deficits.

We aim to study the clinical manifestations of linezolid induced peripheral neuropathy in patients with Multidrug resistant Tuberculosis and tofollow up and assess the effects of standard drug tapering or withdrawal on long term deficitsat18 months of tuberculosis treatment completion.

Methods

A prospective observational study was done in the Department of Neurology of a tertiary care centrein western Maharashtra. Patients with MDR TB were enrolled for one year (July 2021 to June 2022) and each patient was followed up for 18 months. The duration including analysis period was 3 years and was completed in December 2023. MDR TB was diagnosed on the basis of sputum examination, FNAC in case of lymphadenopathy, CSF study, clinical and radiological features.

Inclusion Criteria: Patients above 18 years diagnosed with Multidrug resistant Tuberculosis and started on treatment with Bed aquiline based all oral regimenthat contains Linezolid in dosage of 10mg/kg/day or maximum dose of 600mg/day developing peripheral neuropathy were included in the study.

Exclusion Criteria: Patients with pre-existing peripheral neuropathy secondary todiabetes mellitus, chronic liver disease, chronic kidney disease, positive serology for HIV, Hepatitis B and C, pregnancy or lactation were excluded

Data collection

MDR TB patients on linezolid treatment presenting to outpatient of Neurology Department with neuropathic symptoms, fulfilling the inclusion criteria were enrolled in the study. All information were collected in a standardized evaluation form. On presentation demographic characteristics including age, sex, weight, height, body mass index (BMI) was recorded. Detailed clinical neurological evaluation was done along with nerve conduction studies (NCS). Common nutritional causes of peripheral neuropathy were ruled out by testing for serum vitamin B12, folic acid and mean corpuscular volume (MCV) levels.

Based on the National Cancer Institute Neurosensory Scale, peripheral neurotoxicity is divided into 4 grades:

Grade 1: Mild paresthesias, loss of deep tendon reflexes

Grade 2: Moderate paresthesias, mild to moderate objective sensory loss

Grade 3: Paresthesias interfering with function, severe objective sensory loss

Grade 4: Permanent sensory loss that impairs function.

Using these grades, patients were divided into mild neuropathy (Grade 1), moderate neuropathy (Grade 2) and severe neuropathy (Grade 3 and 4).

As per our institute's center of care guidelines, those with mild neuropathy were continued on same dose linezolid of 600mg/ day and after completion of 6 months of treatment, dosage was reduced to 300mg. Immediate dose reduction to 300mg/day was done for moderate neuropathy and linezolid was withdrawn for severe neuropathy. All patients were treated with oral neuropathic agents (gabapentin, duloxetine) with oral pyridoxine, benfotiamine and mecobalamin supplementation though vitamin B12 levels were normal. Follow up was doneregularly as and when required and dose of linezolid was modified at each visit after grading the neuropathy. End result was analysed at 18 months of TB treatment completion.

Informed consent was taken for each case and approval of Institutional Ethics committee was taken.

Table 1: Clinicalcharacteristics and nerve conduction studies based on grading of peripheral neuropathy on presentation

GRADE	MILD	MODERATE	SEVERE
CLINICAL SYMPTOMS			
TINGLING (76)	28	29	19
NEUROPATHIC PAIN (69)	21	29	19
NUMBNESS (62)	22	24	16
UPPER LIMB (21)	5	8	8
SENSORY ATAXIA (12)	0	6	6
WEAKNESS (14)	4	3	7
NEUROLOGICAL EXAMINATION			
FINE TOUCH IMPAIRED (84)	31	33	20
VIBRATION IMPAIRED (69)	22	30	17
PROPRIOCEPTION IMPAIRED (37)	6	14	17
PINPRICK IMPAIRED (13)	4	6	3
TEMPERATURE IMPAIRED (32)	9	14	9
ABSENT ANKLE JERK (16)	2	9	5
NERVE CONDUCTION STUDIES			
ABNORMAL (62)	21	26	15
NORMAL (22)	10	7	5
BMI<18.5KG/M^2 (32)	8	12	12

Table 2: Demographics of patients with linezolid induced peripheral neuropathy, severity of neuropathy at onset and at 18 months (after dose modification)

CHARACTERISTIC	VALUE
Age (mean), years	31.2
Sex: Male Female	56 (66.6%) 28 (33.3%)
BMI (mean) kg/m^2	20.67
Duration of onset of peripheral neuropathy from linezolid exposure (mean), months	3.4
TYPE OF MDR TUBERCULOSIS A. Pulmonary tuberculosis B.CNS tuberculosis C.Others (lymphadenopathy, abdominal TB, Disseminated TB etc.)	 53 (63.1%) 11 (13.1%) 20 (23.8%)

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Table 3: Comparison of the grading before and after the treatment. Severity at Presentation * Severity at 18 month follow up (Cross tabulation)

			Severity at 18 month follow up				Total
			Cured	Mild	Moderate	Severe	
Severity at Presentation	Mild	Count	11	14	5	1	31
		% within Severity at Presentation	35.5%	45.2%	16.1%	3.2%	100.0%
		% within Severity at 18 month follow up	100.0%	37.8%	22.7%	7.1%	36.9%
		% of Total	13.1%	16.7%	6.0%	1.2%	36.9%
	Moderate	Count	0	19	10	4	33
		% within Severity at Presentation	0.0%	57.6%	30.3%	12.1%	100.0%
		% within Severity at 18 month follow up	0.0%	51.4%	45.5%	28.6%	39.3%
		% of Total	0.0%	22.6%	11.9%	4.8%	39.3%
	Severe	Count	0	4	7	9	20
		% within Severity at Presentation	0.0%	20.0%	35.0%	45.0%	100.0%
		% within Severity at 18 month follow up	0.0%	10.8%	31.8%	64.3%	23.8%
		% of Total	0.0%	4.8%	8.3%	10.7%	23.8%
Total		Count	11	37	22	14	84
		% within Severity at Presentation	13.1%	44.0%	26.2%	16.7%	100.0%
		% within Severity at 18 month follow up	100.0%	100.0%	100.0%	100.0%	100.0%
		% of Total	13.1%	44.0%	26.2%	16.7%	100.0%

Results

Statistical analysis of the data was performed using SPSS 23.0. Categorical data was represented in the form of frequency and percentage. Descriptive statistics was expressed using mean and standard deviation. Chi square test was used as test of significance and a p value of <0.05 was considered as statistically significant.

We studied 84 MDR TB patients with linezolid induced peripheral neuropathy. There was a high preponderance of females 56 (66.6%) as compared to males 28 (33.3%). The mean age of patients was 31.2 years. Peripheral neuropathy developed after a mean duration of 3.4 months of linezolid treatment. Mean body mass index (BMI) was 20.67 kg/m^2. 32 (38%) patients had low BMI of which moderate and severe neuropathy was present in 12 patients each. There was statistically significant association between development of severe peripheral neuropathy and low BMI (p value= 0.015). Neuropathic symptoms were reported within 2 months in 19 (22.6%), between 2 to 4 months in 46 (54.7%) and beyond 4 months in 19 (22.6%) patients after starting linezolid. Out of the 19 patients who developed symptoms within 2 months of exposure, 2 patientsdeveloped symptoms as early as 21 days. 9 (10.7%) patients had asymmetrical onset of deficits, remaining 75 (89.3%) patients had a symmetrical presentation. Most common clinical symptom was lower limb tingling paresthesias present in 76 (90.5%) patients followed by neuropathic pain and numbness present in 69 (82.14%) and 62 (73.8%) patients respectively. Other symptoms included upper limb complaints, weakness and sensory ataxia present is 21 (25%), 14 (16.6%) and 12 (14.3%) patients respectively. Sensory examination revealed impaired fine touch as the predominant finding seen in all 84 (100%) patients followed by impaired vibration in 69 (82.1%) patients. Other findings were impaired joint position sense, temperature and pin prick seen in 37 (44%), 32 (38%) and 13 (15.5%) patients respectively. Reflex examination revealed absent ankle jerks in 14(16.6%) patients. Nerve conduction studies was abnormal in 62(73.8%) patients. Axonal neuropathy was found in 58 patients and 4 patients had mixed demyelinating with axonal neuropathy while remaining 22 (26.2%) cases had normal NCS findings.

On presentation, 31(36.9%) patients had mild neuropathy, 33 (39.28%) moderate and 20 (23.8%) severe peripheral neuropathies. After monthly followups, the dosage of linezolid was modified according to the severity of neuropathy. Patients were finally assessed at 18 months of TB treatment completion.

The cross-tabulation analysis presents the relationship between the severity of patients' conditions at presentation and their severity at an 18-month follow-up. The results highlight how initial severity impacts long-term outcomes, with significant variations observed across different severity levels.

For patients who presented with mild neuropathy, 35.5% were cured at the 18-month follow-up, 45.2% had mild severity, 16.1% had moderate severity, and 3.2% had severe neuropathy. These patients constituted 36.9% of the total sample, demonstrating that the majority either remained mild or improved.

In the moderate group at presentation, none were cured after 18 months. However, 57.6% remained mild, 30.3% had moderate severity, and 12.1% progressed to severe neuropathy. This group made up 39.3% of the total sample, showing a significant proportion experiencing persistent or worsened conditions.

For those initially presenting with severe neuropathy, 20.0%improved to mild, 35.0% had moderate severity, and 45.0% remained severe. These patients accounted for 23.8% of the total sample, indicating a substantial challenge in achieving improvement within this group. Out of 4 patients with mixed demyelinating and axonal neuropathy, 2 belonged to mild group and remained with

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mild symptoms at 18 months, 1 worsened from moderate to severe group and 1 improved from severe to mild group.

At the end of 18 months of treatment, linezolid was stopped early in 34 (40.5%) patients and dose reduction to 300mg was done in 50 (59.5%) patients. Final assessment revealed 11(13.09%) patients free from symptoms of peripheral neuropathy, 37 (44.04%) patients had mild, 22 (26.19%) had moderate and 14 (16.6%) had severe peripheral neuropathy. Of the 14 (16.6%) patients who had persistent severe deficits at 18 months, 9 were from severe group, 3 from moderate and only 2 from mild group.

Discussion

The exact mechanism of linezolid induced peripheral neuropathy is not fully understood. It may involve mitochondrial dysfunction and autophagy inhibition leading to axonal damage, impaired mitochondrial protein synthesis, loss of neurons and myelin sheath. Some individuals may be more susceptible to developing linezolid neuropathy due to genetic factors [7]. Linezolid induces large fibre neuropathy evidenced by reduction in sensory nerve action potentials on NCS. However, 26.2% patients had normal NCS findings. Detailed analysis of symptoms revealed prevalence of neuropathic pain in 82.14% of patients indicating that small diameter sensory nerves may degenerate early in the course causing small fibre neuropathy[8].

According to literature, the prescribed daily dose of linezolid ranges from 300mg to 1200mg. Adverse effects have found to be linearly correlated with dosage. A daily dose of 1200mg is reported to be associated with peripheral neuropathy in more than 80% patients [9]. Lower dose of 300mg causes less toxicity, but its prolonged exposure has risk of acquired drug resistance [10,11]. To optimize the efficacy and safety, a daily dose of 600 mg for 12–18 months is recommended by WHO for MDR TB.

In our study National Cancer Institute Neurosensory Scale is used to grade the severity of peripheral neuropathy. It is an extrapolation from cancer treatment related peripheral neuropathy as linezolid is also a toxin and causes peripheral nerve involvement due to mitochondrial cell injury [11]. This scale helped us in classifying patients into mild, moderate and severe peripheral neuropathy and thereby deciding on linezolid dosage modification. Our patients initially received 600mg of linezolid. After dose modification at regular follow up, 49received 300mg linezolid till 18 months of treatment completion.

Regular follow up with monitoring is important for timely identification of cases worsening towards severe neuropathy where immediate linezolid withdrawal is crucial. Inspite of frequent monitoring and immediate linezolid withdrawal, 14 (16.6%) patients in our study had severe residual deficits at 18 months follow up. This highlights that linezolid induced peripheral neuropathy can be irreversible. There are various studies reporting irreversibility of linezolid induced peripheral neuropathy [11-14].

In terms of duration of linezolid exposure, he observed that peripheral neuropathy was diagnosed after a mean duration of 3.4 months of linezolid exposure. This is similar to study done in China where peripheral neuropathy occurred 2 to 4 months after treatment initiation [15]. However, in our study19 patients developed neuropathy within 2 months of exposure.

On studying the demographic characteristics, we found that 32 (38%) patients had low BMI. Though we found an association of development of peripheral neuropathy with low BMI, other parameters to evaluate malnutrition as the predisposing factor have to assessed.

Jaspard M et al.[14] diagnosed peripheral neuropathy based on nerve conduction study in 72% cases. In our study, evidence of neuropathy on NCS was found in 73.8% caseswhereas 26.2% had normal NCS. This could be due to small fibre involvement, early testing, lack of age appropriate NCS cutoff values. However, all patients had clinical symptoms and signs of peripheral neuropathy on diagnosis indicating that clinical neurological examination can be effectively used to screen for peripheral neuropathy even if NCS/EMG facility is not available.

Health care providers in TB centers should be trained regarding peripheral neuropathy examination. Definite guidelines need to be provided for grading the neuropathy and implementing linezolid dose reduction and withdrawal as done in our study. This will endow decision making to primary caregivers where Neurology services like Neurophysician, NCS facility are not available and will help in avoiding development of severe irreversible neurodeficits.

Limitations

Some limitations of this study are inherent as it is monocentric with small sample size. Confounding factors play a role in development of linezolid induced neuropathy such as anemia, vitamin B12 and other nutritional deficiencies, other drugs in regimen used to treat MDR-TB which could not be completely eliminated in our study. Relation of LNZ induced neuropathy with serum concentrations of LNZ could not be studied. Long term follow up is needed to know the outcome of peripheral neuropathy in these patients beyond 18 months.

Conclusion

In this study including linezolid induced peripheral neuropathy in MDR TB patients, we highlight the importance of grading the neuropathy based on severity at presentation which appropriately guides in linezolid dose reduction and withdrawal. Regular follow up with monitoring is important for timely identification of cases worsening towards severe neuropathy where immediate linezolid withdrawal is crucial in preventing irreversible severe neurodeficits. Clinical neurological examination should be used by medical personals across all TB centers for early diagnosing peripheral neuropathy. Proposal of definite guidelines for grading the severity of neuropathy shall guide them regarding linezolid dose modification. Further detailed studies are required in identifying various risk factors involved in causing linezolid induced peripheral neuropathy so as to decrease the rate of development of neuropathy without affecting the multidrug resistant TB outcomes.

References

1. Bagcchi S (2023) WHO's Global Tuberculosis Report 2022. Lancet Microbe 4: e20.
2. India TB Report 2022

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3. World Health Organization. Rapid communication: key changes to treatment of multidrug and rifampicin resistant tuberculosis (MDR/RR-TB).

4. Lee M, Lee J, Carroll MW, Choi H, Min S, et al. (2012) Linezolid for treatment of chronic extensively drug-resistant tuberculosis. New England Journal of Medicine 367: 1508-1518.

5. Singh B, Cocker D, Ryan H, Sloan DJ (2019) Linezolid for drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev 3: CD012836.

6. Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease. May 4, 2023.

7. Yuan Y, Li J, Chen Y, Cai Q, Xu Y, et al. (2022) Mechanism underlying linezolid-induced peripheral neuropathy in multidrug-resistant tuberculosis. Front Pharmacol 13: 946058.

8. Chao CC, Sun HY, Chang YC, Hsieh ST (2009) Painful neuropathy with skin denervation after prolonged use of linezolid. BMJ Case Rep 79.

9. Conradie F, Diacon AH, Ngubane N, Howell P,Everitt D,et al. (2020) Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 382: 893-902.

10. Koh WJ, Kang YR, Jeon K, et al. (2012) Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. J AntimicrobChemother 67: 1503-1507.

11. Jones MR, Urits I, Wolf J, Corrigan D, Colburn L, et al. (2020) Drug-Induced Peripheral Neuropathy: A Narrative Review. Curr Clin Pharmacol 15: 38-48.

12. Agyeman AA, Ofori-Asenso R (2016) Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin MicrobiolAntimicrob 15: 41.

13. Jaspard M, Butel N, El Helali N, Marigot-Outtandy D, Guillot H, (2020) Linezolid-Associated Neurologic Adverse Events in Patients with Multidrug-Resistant Tuberculosis, France. Emerg Infect Dis 26: 1792-1800.

14. Xu H-B, Jiang R-H, Li L, Xiao H-P (2012) Linezolid in the treatment of MDR-TB: a retrospective clinical study. Int J Tuberc Lung Dis 16: 358-363.

15. Zhang P, Li W, Liu M, Zhan S, Zhang H, et al. (2022) Linezolid-Associated Neuropathy in Patients with MDR/XDR Tuberculosis in Shenzhen, China. Infect Drug Resist 15: 2617-2624.

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