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Ophthalmic evaluation of drug-resistant tuberculosis patients taking linezolid as oral longer anti-tuberculosis regime

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Abstract
Aim: To document ocular toxicity if any in drug-resistant tuberculosis patients taking linezolid as an oral longer regime.
Study and Design: Hospital-based Observational study.
Methods and Material: The study was carried out in tertiary health care from January 2021- October 2022. A total of 94 participants above 18 years of age who were diagnosed with drug-resistant tuberculosis taking Linezolid and had pre-treatment best-corrected visual acuity (BCVA) of 6/6 and N6 with normal color vision were included in the study. Patients were called on follow-up on the 2nd, 4th, and 6th months of post-Linezolid therapy, and BCVA, color vision, anterior segment examination, and dilated fundus examination were done and documented.
Results: Out of 94 participants 45 were males and 49 females. The mean age of participants was 27.41±9.22.
We observed one patient developed a diminution of vision with fundus changes of optic disc edema in the second month of follow-up and the other patient also came with a diminution of vision with optic neuropathy on the sixth month of follow-up. The third patient developed nonsignificant RPE changes without diminution of vision.
Conclusion: Ocular toxicity in three cases in form of Optic Neuropathy, optic disc edema, and nonsignificant RPE changes amongst 94 participants. In our study after the withdrawal of Linezolid therapy, the visual acuity and fundus changes reverted to normal. The study highlights the importance of regular ophthalmic follow-up in patients who were on long-term linezolid therapy.

Keywords: Drug-resistant tuberculosis, oral longer regime, Linezolid, optic neuropathy

1. Introduction
India is the highest TB burden country in the world and accounts for nearly one-fifth of the global burden of tuberculosis [1]. In today's era, antimicrobial resistance is a major issue for public health and the reason for globally rising cases of drug resistance TB. It has become apparent that the widespread dissemination of drug-resistant TB will continue to challenge global efforts to cure patients and meet the ambitious targets of the End TB Strategy for the last 20 years.
Patients suffering from Multidrug-resistant tuberculosis (MDR-TB) are resistant to rifampicin or isoniazid, which are used in the first-line treatment of tuberculosis. Extensively drug-resistant TB (XDR-TB) is a rare type of MDR-TB that is resistant to isoniazid and rifampicin plus any fluoroquinolones and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin or capreomycin) [2]. WHO has recently published evidence-based updates for treating MDR-TB patients, including shorter and longer oral regimes [3].
Ocular toxicity has been observed in patients taking anti-tubercular drugs, especially with ethambutol, isoniazid, streptomycin, thioacetazone, rifampicin, rifabutin, clofazimine, and linezolid.
Linezolid, a newer drug, is a synthetic antibiotic within the oxazolidine class and the first drug approved for clinical use in DR-TB patients. It acts against gram-positive bacteria and mycobacteria. According to the revised guideline of MDR-TB treatment, Linezolid is introduced in an oral longer regime [4]. Toxicity is a matter of concern when the drug has to be used for long periods because it can interfere with the protein synthesis of mitochondria causing its dysfunction and leading to reversible neuropathy, thrombocytopenia, and hematopoietic suppression.

2. Material and methods

The present study was a hospital-based observational study in drug-resistant tuberculosis patients taking linezolid as an oral longer anti-tuberculosis regime at Tertiary health care. All the patients enrolled in the study were evaluated during a period from January 2021- October 2022. The sample size was taken as 94.

2.1 Inclusion criteria

a) Those who give written consent to participate in the study
b) Age 18 years and above
c) Drug resistance tuberculosis patients diagnosed by culture or isolated CBNAAT resistance case.
d) Patients having pre-treatment Best corrected visual acuity (BCVA) 6/6 for distance and N6 for near vision with normal color vision

2.2 Exclusion criteria

a) Participants with pre-existing ocular morbidity.
b) Age below 18 years
c) Patient diagnosed with intellectual disability.
d) Pre-treatment color vision deficiency.

2.3 Methodology

Human resource and ethical committee approval was obtained before the start of the study. All patients who satisfied the inclusion criteria and gave informed consent were included in the study. The district tuberculosis officer of the tertiary health care center as per inclusion criteria referred patients from the outdoor or the indoor department of the respiratory unit who was diagnosed with drug-resistant tuberculosis and wish to start Linezolid in an oral longer anti-T.B. regime. All patients were examined for visual acuity. Best corrected distance vision was measured on illuminated Snellen's vision chart and near vision was recorded on Snellen's near vision chart. if the patient's BCVA is 6/6 and N6 for distance and near respectively were included in the study. A thorough medical history was noted which includes any associated systemic illness, and pre-existing ocular morbidity took an anti-TB drug before the color vision was evaluated on the Ishihara color vision chart. Anterior segment examination including pupillary reaction was examined on a slit lamp. Dilated fundus examination was done with Heine's indirect ophthalmoscope. Above all findings were documented on the pre-treatment sheet before starting the linezolid. The patient was instructed if any symptoms like sudden diminished vision or blurring of vision directly come to the researcher for a thorough ophthalmic examination, the time of onset of symptoms, origin progression, and duration with other demographic details were noted and entered. On the 2nd, 4th, and 6th months during the linezolid treatment patient's BCVA, color vision, anterior segment examination, and dilated fundus examination were done and documented.

3. Results and Discussion

A total of 94 participants were examined who are diagnosed with drug-resistant tuberculosis and taking linezolid.

The mean age of participants was 27.41 years with a standard deviation of ±9.22 years. Almost half of the male participants (44.4%) belong to the young age group (26-35 years). Whereas the majority (73.5%) of the participants in the female group belong to the young age group. Mehta *et al.* [5] and Giri *et al.* [6] suggested that drug-resistant tuberculosis was more prevalent in the young age group. The median age of these patients was 25 years (25-30).

Out of all two patients who developed diminution of vision post linezolid therapy, one patient came on 1 and half months with a complaint of diminution of vision and was examined thoroughly, his vision was 1-meter finger counting with normal color vision and normal anterior segment and had optic disc edema on dilated fundus examination. Treatment was stopped by his treating respiratory doctor. On withdrawal, the patient's vision after 1 month and the fundus changes after 2 months revert to normal.

The second patient had a diminution of vision at the 6th month of follow-up, his vision was 2-meter finger counting with defective color vision and relative afferent pupillary defect (RAPD), diagnosed with optic neuropathy. On the stoppage of a drug, the patient's vision improved to normal after 2 and a half months.

One patient had nonsignificant RPE changes on the fundus at 6th month of follow-up without any complaint. The patient was thoroughly examined. On regular follow, he has no significant changes till the end of the oral longer regime.

Table 1: Distribution of visual acuity of study participants.

Visual Acuity	2ndMonth Evaluation		4thMonth Evaluation		6thMonth Evaluation	
	RE	LE	RE	LE	RE	LE
Normal	93 (98.9)	93 (98.9)	94	94	93 (98.9)	93 (98.9)
Decreased	01 (1.1)	01 (1.1)	00	00	01 (1.1)	01 (1.1)

Mehta *et al.* [5]. conducted a study to determine the frequency of and risk factors associated with linezolid-associated optic neuropathy and document the experiences related to the treatment/care of DR-TB patients on linezolid-containing regimens. 86 of 136 patients (with/without HIV co-infection) initiated linezolid-containing DR-TB treatment. The median age of these 86 patients was 25 (20–35) years and 47% were males. 20 percent of them had HIV co-infection. Of 86, 24 (27.9%) had at least one episode of ocular complaints (the majority blurred vision) and among them, five (5.8%) had optic neuropathy. Patients received appropriate treatment and improvements were observed. In this study, one out of four patients on linezolid had 28 at least one episode of ocular complaints; therefore, systematic monitoring of patients was needed as linezolid will be increasingly added to treatment regimens of DR-TB patients, programs should allocate adequate resources for early diagnosis, prevention, and management of this disabling adverse event.

Karuppannasamy *et al.* [7] performed a case report in which they studied a patient on linezolid. The patient complained about the diminution of vision and was clinically diagnosed with optic neuropathy. After stopping the linezolid for 2-week the patient‟s vision deteriorated but after the withdrawal of linezolid, vision improvement started.

Bano *et al.* [8] encountered a case of progressive deterioration of vision and numbness in the feet in a 32-year-old male undergoing linezolid therapy for 12 months for multidrug-resistant tuberculosis. Nerve conduction studies were highly suggestive of length-dependent axonal sensory polyneuropathy while the fundoscopic image was highly favorable to optic neuropathy. Improvement was

seen in vision with no improvement or worsening of peripheral neuropathy on follow-up visits after the discontinuation of linezolid.

Table 2: Demographic and clinical characteristics of drug-resistant tuberculosis patients on Linezolid-containing regime

Variable	Case 1	Case 2
Age(year)	18	23
Sex	Female	Male
T.B. site	Pulmonary	Pulmonary
DR-resistant T.B. pattern	MDR	XDR
Visual impairment	1 meter finger counting	2 meter finger counting
Colour vision	Normal	Defective
Ocular toxicity	Optic disc edema	Optic neuropathy

4. Conclusion

A study observed ocular toxicity in three cases in form of Optic Neuropathy, optic disc edema, and nonsignificant RPE changes amongst 94 participants. On withdrawal of Linezolid visual acuity became normal after 1 month and fundus change revert to normal after 2 months. Though the study emphasizes the importance of regular ophthalmic follow-up in patients who were on long-term linezolid therapy it also concludes that linezolid has fewer and reversible side effects.

5. The source of funding

None

6. Conflict of interest

The authors declare no conflict of interest.

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