Section: Pulmonary Medicine

Case Series

A CASE SERIES IN TO THE INSIGHTS OF LINEZOLID TOXICITY IN MULTI DRUG RESISTANT TUBERCULOSIS PATIENTS

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Abstract

Background: The guidelines for programmatic management of drug resistant tuberculosis (PMDT) released in march 2021 advocates all oral long regime for multidrug resistant Tuberculosis patients1. In this regime, Linezolid (Lzd) is an integral component and is extremely effective in rendering an early sputum conversion and ensuring high cure rates. At the same time, it has certain severe adverse reactions like peripheral neuropathy, optic neuropathy and myelosuppression which leads to discontinuation or replacement of the drug, thus compromising the efficacy of the regime. **Materials and Methods:** We here report case series of three recently encountered cases of Linezolid toxicity presented in the difficult to treat TB clinic(D3TC) which were managed by stopping the drug. **Result:** Two patients developed Linezolid induced transient myelosuppression within 2 months of starting Linezolid and another patient developed severe peripheral neuropathy after about 6 months of taking the drug. In all three cases the state difficult to treat TB Clinic took decisions to exclude the drug from the rest of the treatment schedule. **Conclusion:** Managing MDR/XDR TB with a drug regime containing cheaper options like Linezolid is a crucial decision in view of the cost effectiveness of a programme based management strategy and hence alternative options like low dosing, intermittency or therapeutic drug monitoring should be considered to preserve the drug and exclusion of the drug should be avoided by serial monitoring and timeline based exclusion of side effects.

INTRODUCTION

AOLR (All oral long regime) which is the nationwide practised strategy for treating MDR TB under the PMDT 2021 guidelines in India. Lzd is effective as a second line anti tuberculous medication and has been proven to be effective against Methicillin or Vancomycin resistant Staph aureus (MRSA/VRSA).[1,2] There are several side effects for the drug like painful peripheral neuropathy which could be irreversible, painless optic neuropathy and myelosuppression that might jeopardise the effectiveness of the regime. Being a very effective drug as proven by evidence in terms of early sputum conversion and ensuring a cure, the drug hence cannot be ignored or side-lined.

The aim of the case series presented here is to make the policy makers think of possible solutions to include the drug in the regime, at the same time minimise the side effects related to the same by adopting measures like low dosing, intermittent scheduling and liberal use of therapeutic drug level monitoring (TDM) to alert the treating physician well in time to avoid the side effects related to the drug. None of the measures could be adopted in these three cases due to lack of policy in this regard and non-availability of TDM in most of the centres where treatment is offered.

CASE SERIES

Case 1

A fifty-nine-years-old male was diagnosed as Rifampicin resistant pulmonary TB following a short febrile illness. He gave history of treatment for pulmonary tuberculosis twenty years ago and an episode of extra pulmonary TB ten years ago. Both these episodes were treated with six months of first line anti-TB medications. He was subjected to fibre optic bronchoscopy as a part of evaluation of bilateral upper lobe fibrotic bands and infiltrates. The Broncho alveolar lavage sample (BAL) was sent to the district TB centre which yielded rifampicin resistance by cartridge based nucleic acid amplification test (CBNAAT) in October 2023-which was reported as

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MTB (Mycobacterium tuberculosis) detected high. Hence, he was started on AOLR-MDR TB regime from the same month onwards. Two months later in December 2023 he was admitted with complaints of palpitations and increased tiredness. As he was giving history of palpitation the treating pulmonologist was cautious to rule out a QTc prolongation which may progress to malignant tachyarrhythmia's like torsades des pointes which is a dreaded but rare side effect of the novel anti-tuberculous medication, Bedaquiline (Bdq).

Investigations

His ECG was Normal with Sinus rhythm and QTC 470 msec which was not prolonged. But on further evaluation he was diagnosed to have Pancytopenia with a haemoglobin of 4.2 gm%, Total count of 3400 cells/mm3 and Platelets of 1.3 lakhs/mm3.His Liquid culture drug sensitivity testing for first line and second line anti-TB drugs showed resistance to Rifampicin, INH (Kat G resistant, Inh A sensitive). Other drugs tested were sensitive (Fluoroquinolones and second line injectable) and his serum electrolytes showed - Sodium -131meq/L, Potassium- 4.1 meq/L, Mg -2.6 mg%, Ca -8.1mg%. His RBS was-136 mg%, retro screening was negative, TSH-0.95 IU, S. Bilirubin-1mg%, SGOT-26 IU, SGPT-12 IU, Urea-24 mg%, S. Creatinine -0.6 mg%, Peripheral smear reported as pancytopenia with no atypical cells/ blasts

Management strategy adopted

Anti TB medications were withheld, a cardiology evaluation and echocardiogram ruled out the possibility of anaemia related cardiac failure as it was an acute event and since all the pre-treatment evaluation including ophthalmology work up were normal two months ago with no evidence of leukaemia in the peripheral smear, a bone marrow was deferred. He was given three units of whole blood transfusion and the possibility of Lzd induced pancytopenia was entertained. Patient symptomatically improved and after a week the repeat blood counts showed Hb 8.2 gm%, Total count-5530 cells/mm3 and Platelets 1.90 L/mm3. This case was discussed in the D3TC and was advised to stop Linezolid from the AOLR regime as there was definite evidence of myelosuppression which recovered with discontinuation during the second month of starting treatment. His follow up blood counts after two months of stopping Lzd showed Hb -9.7 gm%, TC-10,000, Platelet count-2.8L/mm3, ESR-85mm/hr which showed that the blood counts were remaining stable after stopping the drug.

Case 2

A fifty-years-old male patient who was diagnosed to have Rifampicin resistant Pulmonary TB in the middle of the month of May 2023, after pre-treatment evaluation was started on AOLR on 31/05/2023 which contained Bedaquiline (Bdq), Clofazimine, Cycloserine, Levofloxacin and Lzd. He completed six months of Bdq and Lzd the second Group A drug in the regime. The dose of Lzd was tapered to 300 mg from initial 600 mg after 6 months. He complained of severe pain and numbness over bilateral lower limbs from this time onwards. He is a known diabetic with good glycaemic control for last eight years and is on optimised doses of oral hypoglycaemic agents. He was already getting pyridoxine and other neurotropic vitamins. He was extensively evaluated by a neurologist and his Nerve conduction study showed sensory motor neuropathy. He was started on Gabapentin and as the dose of Bedaquiline was over he was also put on Tricyclic antidepressants. Patient was severely disabled and had unpleasant paraesthesia and pain over both lower limbs and feet. He was also getting analgesics for pain relief and was not relieved of the symptoms, and he attempted suicide by ingesting large doses of analgesics and hence Linezolid was stopped for the time being. Psychiatric evaluation was done and drug related causes for suicidal tendency was ruled out. Patient became symptomatically better in three weeks' time after stopping Linezolid.

Investigations

Sputum CBNAAT revealed Rifampicin resistance, INH (Kat G) resistance and no other resistance detected. Hb 12.4 gm%, Total count – 12600 cells/mm3, Differential Count-P62L34E6, ESR-90 mm/hr, Platelet count-3.1 Lakh/mm3, RBS – 234 mg%, ECG – QTc -434 msec, TSH- 1.76 mIU/L, Urea -16 mg%, S. Creatinine-0.6 mg%, S. bilirubin -0.3 mg%, SGOT -10 IU/L, SGPT -12 IU/L. Serum electrolytes including calcium and magnesium were normal. Chest X-ray PA view showed Left apical and upper zone non homogenous shadows. Visual acuity was normal. Smear and culture at this point of time were negative.

Management strategy adopted

This case was discussed in the expert panel for state difficult to treat TB clinic(D3TC) and Linezolid was stopped as patient developed severe disabling peripheral neuropathy during the sixth month of starting the regime. The patient was advised to continue the rest 3 drugs, Cycloserine, Clofazimine and Levofloxacin.

Case 3

A seventy-year-old male patient was diagnosed with Rifampicin resistant pulmonary tuberculosis in august 2023 and after pre-treatment evaluation he was started on All oral shorter MDRTB regimen. He was a diabetic, hypertensive and had dyslipidaemia for which he was on long term treatment. He was admitted later with gastrointestinal symptoms two weeks after initiation and managed with symptomatic measures. Two months later he came again with same complaints and in addition developed a left leg foot drop. His liver function tests were deranged, and the nodal committee decided to switch the regimen to All oral longer MDR TB regimen from after a week when the liver function tests were permissible for restarting the new regime. Neurology consultation was sought for foot drop, and it was inferred that foot drop is not drug related. Two months after initiating the AOLR, in December 2023 he complained of increased tiredness and blood investigations revealed

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Pancytopenia (Hb-7 gm%, TC- 3300 cells/mm3, Platelets1L/mm3).

Investigations

He was sputum smear 2+ during diagnosis and his CBNAAT showed medium levels of Mtb detected with rifampicin resistance. However, his liquid culture and drug sensitivity report showed no resistance to other first line and second line anti tuberculosis medications tested. His pre-treatment Hb- 10.6 gm%, Total count –10400, Platelet count – 2.4 lakhs/mm3. RBS – 285 mg%, ECG – QTc -440 msec, TSH- 3.5 mIU/L, Urea -88 mg%, S. Creatinine-1.9 mg%, S. bilirubin -0.7 mg%, SGOT - 58 IU/L, SGPT -32 IU/L. Serum electrolytes including calcium and magnesium were normal. Chest X-ray PA view showed right upper lobe infiltrates. ENT evaluation done initially itself showed Left mild and right moderate Sensorineural deafness

Management Strategy Adopted

Linezolid was stopped and was given multiple blood transfusions as peripheral smear and blood counts showed pancytopenia After two weeks, investigations showed improvement in blood parameters. (Hb 9.1gm%, Total count-7000 cells/mm3, Platelets -1.5 L/mm3, ESR-110 mm/hr) The smear status which was 2+ initially became negative by 2 months and at this point he developed pancytopenia and Linezolid was discontinued as per the advice of the expert panel of D3TC. His rest of the regime comprised of three drugs, levofloxacin, Cycloserine and Clofazimine.However his foot drop was related to diabetes rather than drug induced as the timeline for neurological adverse events as observed in the second case in the series was around 6 months of intake of Linezolid

DISCUSSION

XDR-TB (Extensively drug resistant TB) is a type of MDR-TB which is resistant to isoniazid and rifampicin and additionally resistant to quinolone and one of the remaining Group A - TB drugs (Linezolid or Bedaquiline)3. In 2018, the World Health Organization revised the groups of TB medicines and reclassified Lzd as a group A drug. Lzd has a success rate of more than 80% reported in treating MDR-TB4.

The journey of this molecule in TB care started as a second line agent in the Category V of the DOTs plus regimen for XDR-TB (Extensively drug resistant TB) of the revised national tuberculosis control programme (RNTCP) which was the TB control programme existent in India during after 1992. As per the programmatic management of Drug resistant Tuberculosis (PMDT) - 2012 guidelines, drugs like High dose INH, moxifloxacin also were used under the category V for the treatment of XDR TB patients. WHO initially classified Lzd as a Group 5 drug, as it was considered amongst the drugs with unclear efficacy against MDR-TB. Later in 2019, the revised PMDT guidelines upgraded Linezolid as Group C drug along with other second line drugs, Ethionamide, Prothionamide, Cycloserine and Clofazimine.[5] In 2021, WHO reclassified it as Group A drug as more and more evidence in favour of its efficacy became available.[6]

Second line anti tuberculosis medications with proven efficacy are limited and with more toxic side effects than the first line anti TB medications. Chances of failure rates for XDR TB, Pre XDR & MDR TB were to the tune of 65%,50% & 35% respectively before the introduction of newer anti Tb medicines like Bedaquiline, Delamanid & Pretomanid. Lzd, now being a Group A drug is being proposed as a component of the newer short-course regimens like BPaL and BPaLM following the PRACTECAL-TB, Nix-TB, Ze-Nix TB and BEAT-TB trials.[7-10] Lzd-associated adverse events basically falls into dose-dependent and duration-dependent adverse effects that include anaemia, neutropenia, thrombocytopenia, peripheral neuropathy, and more rarely, optic neuropathy, lactic acidosis, pancreatitis, serotonin syndrome and rhabdomyolysis.[11] Mitochondrial haplogroup U is identified as a risk factor in 15% of Indians who becomes vulnerable to linezolid toxicity

In our case series, we have also seen three elderly males presenting with pancytopenia during the first two months of Lzd therapy and one person presenting with severe painful neuropathy attempting suicide as he had no relief of symptoms until the drug was discontinued. A similar observation regarding the adverse events profile of Linezolid in patients getting treatment for MDR/XDR under the PMDT has been reported recently from North India.[12] Now since the evidence support the benefits of the drug against a disease like MDR and XDR TB which has a high mortality if not properly treated, there is a challenge even amongst the policy makers to decide the dose and duration of this very useful medicine which must be used cautiously and by picking up the possible adverse events as and when it occurs by scheduled therapeutic drug level (TDM)monitoring based on the previous experiences on the possible timeline of the occurrence of the adverse events.

It was observed that patients were able to tolerate linezolid for a longer duration with fewer adverse events and better treatment outcomes when switched to a reduced dose or intermittent dosing schedule.[13,14] It is recommended by certain researchers that patients who have been taking linezolid for more than 28 days should be checked for signs of peripheral and optic neuropathy.[15] It has been proposed that monitoring haemoglobin levels at 4 weeks for a 10% decline from baseline is another indicator of toxicity in patients receiving linezolid for MDR-TB.[16,17]

Currently most MDR/XDR-TB patients can be treated with solely oral drug regimens without the use of injectable drugs and the duration also is expected to be much less as was shown in the Nix TB and Ze-Nix TB trials. The onset of peripheral neuropathy in

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the Nix-TB trial, which used a higher dose of Lzd, occurred mainly in the initial 3 months of treatment and we observed the same in our case series happening at 6 months' time which might be relevant regarding the decisions to be taken for ideal dosing of Lzd to be chosen in suspected cases of evolving peripheral neuropathy. Hence a monthly monitoring is crucial for early detection of the adverse events.[4,6]

CONCLUSION

Current evidence supports the fact that Linezolid containing regimens are crucial in reducing the duration and ensuring the success of MDR and XDR tuberculosis. However, the severe adverse event in some patients often leads to a permanent exclusion of the drug from the current and possibly future short course regimes designed for this. Hence considering its efficacy, the choice of low dose regimes or intermittent Lzd in the regimes should be investigated utilising the therapeutic drug level monitoring of this drug. The policy makers can endorse this by further well-designed cohort control studies which will decide the future fate of this drug in the treatment against this dreaded disease.

REFERENCES

1. Migliori GB, Eker B, Richardson MD, etal; TBNET Study Group. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. Eur Respir J. 2009 Aug;34(2):387-93. doi: 10.1183/09031936.00009509. Epub 2009 Mar 12. PMID: 19282348.
2. Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2012 Apr;16(4):447-54. doi: 10.5588/ijtld.11.0451. PMID: 22325685.
3. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020. Geneva: World Health Organization; 2021. CC BY-NC-SA 3.0 IGO.
4. Lee M, Lee J, Carroll MW etal; Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med. 2012 Oct 18;367(16):1508-18. doi: 10.1056/NEJMoa1201964. PMID: 23075177; PMCID: PMC3814175.
5. Conradie F, Diacon AH, Ngubane N et al; Nix-TB Trial Team. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. N Engl J Med. 2020 Mar 5;382(10):893-902. doi:10.1056/NEJMoa1901814. PMID: 32130813; PMCID: PMC6955640.
6. Diacon AH, De Jager VR, Dawson R etal; Fourteen-Day Bactericidal Activity, Safety, and Pharmacokinetics of Linezolid in Adults with Drug-Sensitive Pulmonary Tuberculosis. Antimicrob Agents Chemother. 2020 Mar 24;64(4): e02012-19. doi: 10.1128/AAC.02012-19. PMID: 31988102; PMCID: PMC7179319.
7. Berry C, du Cros P, Fielding K, Gajewski S etal; TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis. Trials. 2022 Jun 13;23(1):484. doi: 10.1186/s13063-022-06331-8. PMID: 35698158; PMCID: PMC9190445.
8. Solans BP, Imperial MZ, Olugbosi M, Savic RM. Analysis of Dynamic Efficacy Endpoints of the Nix-TB Trial. Clin Infect Dis. 2023 Jun 8;76(11):1903-1910. doi: 10.1093/cid/ciad051. PMID: 36804834; PMCID: PMC10249992.
9. Conradie F, Bagdasaryan TR, Borisov S etal; ZeNix Trial Team. Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med. 2022 Sep 1;387(9):810-823. doi: 10.1056/NEJMoa2119430. PMID: 36053506; PMCID: PMC9490302.
10. Muniyandi M, Ramesh PM, Wells WA, Alavadi U, Sahu S, Padmapriyadarsini C. The Cost-Effectiveness of the BEAT-TB Regimen for Pre-Extensively Drug-Resistant TB. Trop Med Infect Dis. 2023 Aug 11;8(8):411. doi: 10.3390/tropicalmed8080411. PMID: 37624349; PMCID: PMC10459879.
11. Lan Z, Ahmad N, Baghaei P etal; Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2020 Apr;8(4):383-394. doi: 10.1016/S2213-2600(20)30047-3. Epub 2020 Mar 17. PMID: 32192585; PMCID: PMC7384398.
12. Mishra G, Alffenaar JW, Munje R, Khateeb S. Adverse drug reactions due to linezolid in the programmatic management of drug-resistant tuberculosis in India: A retrospective multicenter study. Indian J Tuberc. 2024;71 Suppl 1:S101-S109. doi: 10.1016/j.ijtb.2023.04.006. Epub 2023 Apr 10. PMID: 39067941.
13. Shah, Ritesh & Lamichhane, Samir. (2017). Linezolid induced optic neuropathy, a serious yet reversible adverse effect: a case report. European Journal of Medical Case Reports. 114-121. 10.24911/ejmcr/1/28.
14. Singla R, Caminero JA, Jaiswal A, Singla N, Gupta S, Bali RK, Behera D. Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. Eur Respir J. 2012 Apr;39(4):956-62. doi: 10.1183/09031936.00076811. Epub 2011 Sep 29. PMID: 21965225.
15. Jaspard M, Butel N, El Helali N etal; Linezolid-Associated Neurologic Adverse Events in Patients with Multidrug-Resistant Tuberculosis, France. Emerg Infect Dis. 2020 Aug;26(8):1792-1800. doi: 10.3201/eid2608.191499. PMID: 32687026; PMCID: PMC7392460.
16. Zhang X, Falagas ME, Vardakas KZ, Wang R, Qin R, Wang J, Liu Y. Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. J Thorac Dis. 2015 Apr;7(4):603-15. doi: 10.3978/j.issn.2072-1439.2015.03.10. PMID: 25973226; PMCID: PMC4419320.
17. Sotgiu G, Centis R, D'Ambrosio L etal; Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J. 2012 Dec;40(6):1430-42. doi: 10.1183/09031936.00022912. Epub 2012 Apr 10. PMID: 22496332.

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