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Haematological adverse effects associated with linezolid in patients with drug-resistant tuberculosis: an exploratory study

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Abstract

Objectives Identify the incidence of haematological adverse effects associated with linezolid.

Methods Medical records of 27 hospitalised patients in South Africa with drug-resistant tuberculosis (DR-TB) and prescribed linezolid therapy were retrospectively reviewed.

Key findings Approximately a quarter ($n = 7$) of patients experienced haematological adverse effects. These included anaemia (14.8%; $n = 4$), low haemoglobin (7.4%; $n = 2$) and macrocytosis (3.7%; $n = 1$). All patients who exhibited haematological adverse effects were living with HIV.

Conclusion The haematological effects of linezolid manifested in patients who were suffering from co-morbid HIV. Haematological monitoring should be done monthly in order to detect adverse effects timeously and intervene as appropriate.

Introduction

To treat drug-resistant tuberculosis (DR-TB), repurposed drugs (drugs not registered to treat TB, but are effective against the organism) such as linezolid have been introduced.[1] Linezolid is costly, and its use can be limited by severe adverse effects.[2] The South African Guidelines[3] recommend linezolid be used for 2 months during the intensive phase for the shortened regimen and 6–8 months for the standard regimen.

At the study site, linezolid was prescribed for 12 months. This prolonged use may increase the risk of haematological adverse effects, lactic acidosis, peripheral neuropathy, optic neuropathy and hepatotoxicity.[4] The study aimed to determine the incidence of haematological adverse effects associated with the use of long-term linezolid in hospitalised patients with DR-TB.

Methods

A retrospective, quantitative study was conducted between 1 March 2017 and 20 September 2017 at a DR-TB hospital in the Eastern Cape, South Africa. Medical records of patients aged 18–65 years, diagnosed with DR-TB and prescribed linezolid oral therapy were selected (inclusion criteria). Convenience sampling was used, and all patients who met the inclusion criteria were included resulting in 27 patients. Due to the small sample size, this study may be regarded as exploratory.

A self-designed data collection tool was used. Recorded data included patient demographics such as age, gender, diagnosis, HIV status, linezolid dose and frequency, and laboratory results such as white cell count, haemoglobin levels, platelet count, haematocrit and full blood counts. Normal haemoglobin ranges for males were 10.3–16.7 g/dl and 9.0–15.2 g/dl for females.[5] Thrombocytopaenia was defined as low platelet levels with the reference ranges being between 164×10^9/l–396×10^9/l for males and 191×10^9/l–442×10^9/l for females.[5] Macrocytosis referred to the enlargement of red blood cells and was measured by the mean corpuscular volume (MCV), the normal ranges of which were 82–110.4 fl for males and 76.2–106.7 fl for females.[5] All reference ranges were for the South African context in the Cape Peninsula area. The collected data were transferred onto a Microsoft Excel® spreadsheet and analysed using basic descriptive statistics.

Results

Medical records of 27 patients were retrospectively reviewed. All patients had completed 12 months of linezolid therapy. Males constituted the majority ($n = 16$) of the population and the overall age averaged at 36.0 ± 9.0 years (range = 18–55 years). A total of 14 patients were diagnosed with extensively drug-resistant (XDR)-TB, while 13 were diagnosed with multidrug-resistant (MDR)-TB. There were 15 patients living with HIV with three of them receiving zidovudine (AZT) as part of their antiretroviral treatment. All patients were initiated on 600 mg of linezolid.

Seven patients presented with haematological adverse effects and all of these patients were living with HIV. Anaemia was the most commonly experienced haematological adverse effect with six patients being affected, and one patient experienced macrocytosis. All patients who experienced adverse effects were on 600 mg of linezolid.

The adverse effects occurred at an average of 30 days after the initiation of linezolid therapy and were reversed after 7 days of management. Three patients who developed anaemia were successfully managed by dose reduction to 300 mg of linezolid followed by blood transfusion. For all other patients, dose reduction alone was sufficient to increase haemoglobin levels to within normal ranges. Patients were continued on 300 mg of linezolid for the remainder of their treatment. For the patient who experienced macrocytosis, linezolid was reduced to 300 mg daily with no further intervention. The incidence of adverse effects was higher in male patients (5 in 16 males, versus 2 in 11 females; see Figure 1).

For five patients, the recorded data in the patient files were insufficient to establish if haematological adverse effects occurred. Baseline full blood counts and monthly follow-ups were not always available and may have influenced the monitoring of incidence of adverse effects.

Discussion

A quarter of the study population experienced haematological adverse effects related to haemoglobin levels and mean corpuscular volume. A dose reduction to 300 mg daily reduced the frequency of adverse effects. All patients who experienced adverse effects were HIV-positive.

Limitations include the small sample size and focus on a single site. Patients were hospitalised, indicating that they were less clinically fit than outpatients. All patients in this study completed the full 12 months of treatment with linezolid; however, if the sample were larger, it is possible that some patients may have required discontinuation of linezolid due to intolerable adverse effects.

The frequency of observed adverse effects was similar to a study by Srivastava *et al.*,[6] in which myelosuppression was encountered in 30.0% of patients treated with linezolid. Other studies[7,8] reported that thrombocytopenia was the earliest and most frequent haematological toxicity with long-term linezolid therapy.

Reducing the daily dose to 300 mg in response to adverse effects was reported by Park *et al.*[9] as well, where the reversible myelosuppression of linezolid was thought to be dose dependent with reduced risk in patients on 300 mg.

Parinitha *et al.*[10] suggested a correlation between HIV and haematological abnormalities. HIV-related haematological abnormalities could be due to direct effect of the virus, neoplasms associated with HIV, infections secondary to immunodeficiency or to the side effect profile of antiretroviral treatment (ART).[10] Three of the seven patients were on AZT-containing regimens, which could be a compounding factor in the incidence of haematological adverse effects. However, dose reductions of linezolid eliminated adverse effects, implying linezolid may be the primary causative factor.

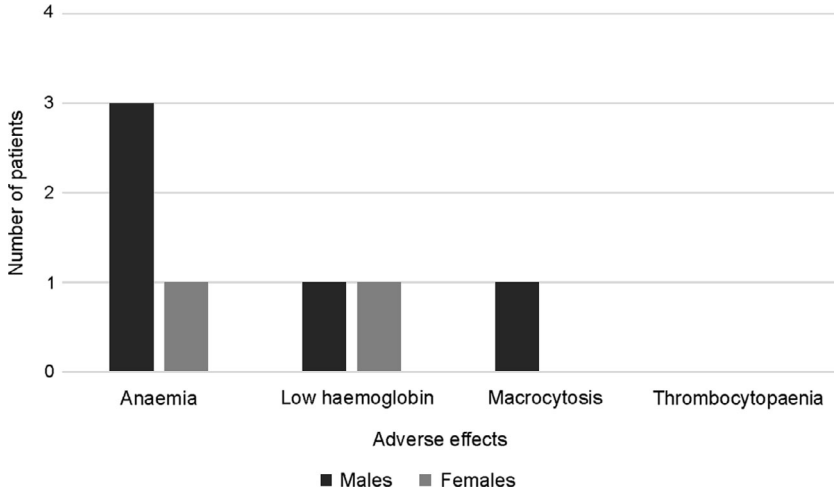

Figure 1 Gender distribution of haematological adverse effects.

Conclusion

Haematological adverse effects manifested after an average of 30 days on treatment. The most common adverse effects were anaemia and macrocytosis and were managed by dose reduction and blood transfusion. Haematological monitoring should be weekly when linezolid is initiated, and thereafter monthly to detect adverse effects timeously, particularly for patients living with HIV who are receiving AZT.

Declarations

Conflict of interest

The Authors declares that they have no conflicts of interest to disclose.

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Authors' contributions

GL and HK conceived the project, wrote the research protocol, collected and analysed the data, wrote the final manuscript. RG and IT – conceived the project, edited and finalized the research protocol, proofread and edited the final manuscript. All Authors state that they had complete access to the study data that support the publication.

Ethical approval

Ethical approval was granted by both the Nelson Mandela University's Research Ethics Committee (Human) (H16-HEA-PHA-008) and the Eastern Cape Department of Health (EC_2017RP54_263). Permission to review the patients' medical records was granted by the Chief Executive Officer of the hospital.

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