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HAEMATOLOGICAL ADVERSE EFFECTS ASSOCAITED WITH LINEZOLID IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS: AN EXPLORATORY STUDY

Letswee G[1], Kamau H[1], Gaida R[2,3] and I Truter[1,4]

[1]Department of Pharmacy, Nelson Mandela University
[2]Research Associate, Drug Utilisation Research Unit, Nelson Mandela University
[3]Human Sciences Research Council, Post-doctoral fellow
[4]Drug Utilisation Research Unit, Nelson Mandela University

COUNTRY	TB INCIDENCE/100 000
Lesotho	665
South Africa	567
Mozambique	551
Central African Republic	423
Namibia	423

COUNTRY	RIFAMPICIN RESISTANT TB INCIDENCE
Nigeria	24 000
South Africa	14 000
Mozambique	8 800
DR Congo	7 500
Ethiopia	5 500

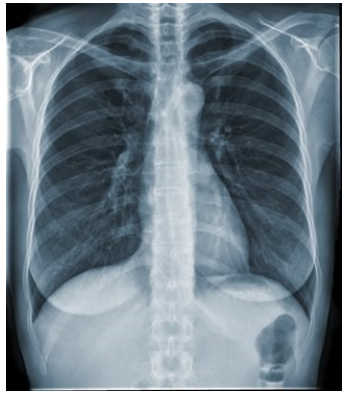
Source: World Health Organization. 2018. Global Tuberculosis Report. Geneva: World Health Organization

BACKGROUND

Drug-resistant tuberculosis (TB) – not responsive to rifampicin OR rifampicin + isoniazid OR rifampicin + isoniazid + injectable/fluoroquinolone OR rifampicin + isoniazid + injectable + fluoroquinolone

Treatment for drug-resistant tuberculosis – no promising outcomes for patients

Bad adverse effects – adherence becomes challenging

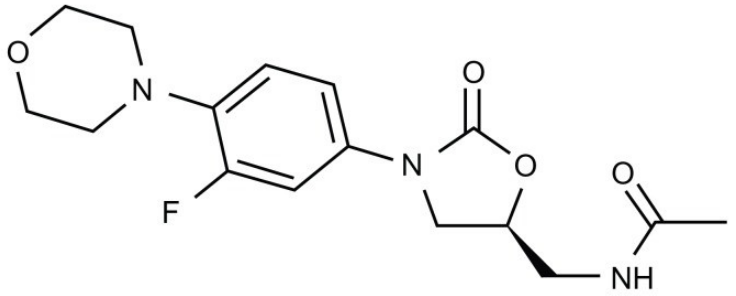


Recent years – CHANGE!
-Shorter regimens[1]
- Injection free regimens
- Bedaquiline
- Repurposed drugs – linezolid and clofazimine[2]

1. Department of Health. 2018. Interim clinical guidance for the implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children Pretoria: Department of Health.
2. Mafukidze et al. 2016. An update of repurposed medications for the treatment of drug-resistant tuberculosis. *Expert Review of Clinical Pharmacology*, 18: 1-10.

BACKGROUND

Linezolid – Oxazolidinone[1]



https://www.researchgate.net

Registered for the treatment of[1]

- Gram-positive infections – vancomycin-resistant enterococci (VREs), *Streptococcus pneumoniae*
- Skin and soft tissue infections

At a recommended dose of 600mg twice daily for a maximum of 28 days

Off label use – DR-TB

Treatment period – up to 12 months

Although effective against M. tuberculosis – long term use can be limited by adverse effects

[1]Rossiter D. ed. *South African Medicines Formulary*, 12th edn. Cape Town: Health and Medical Publishing Group, 2016.

BACKGROUND

Data regarding the safety and tolerability of linezolid for longer periods of time are scarce[1]

Clinical trials were performed with a 28 day treatment period

Although studies have shown that the likelihood of adverse effects is lower with lower doses and vice versa, lower doses may sacrifice sustained culture conversion and increase the risk of resistance developing[2,3]

World Health Organization recommends – 600mg daily, reducing the dose to 300mg daily if adverse effects develop

[1]Vinh, D.C. and Rubinstein, E. 2009. Linezolid: A review of safety and tolerability, Journal of Infection, 59 (S1) S59-S74, September. [Online]. Available: http://www.journalofinfection.com/article/S0163-4453(09)60009-8/pdf

[2]Agyeman, A.A. and 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. Annals of clinical microbiology and antimicrobials, (2016) 15: 41, June 22. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4917997/

[3]Park,I.N.,Hong,S.B.,Oh,Y.M.,Kim,M.N.,Lim,C.M.,Lee,S.D.,Koh,Y.,Kim,W.S.,Shim.D.S. 2006. Efficacy and tolerability of daily half-dose linezolid inpatients with intractable Multidrug-resistant tuberculosis. Journal of Antimicrobial Chemotherapy,58(2006) :701-704.

BACKGROUND

Adverse effects of linezolid

Rash

Dry mouth

Dyspepsia

Metallic taste in the mouth

Headache

Nausea/vomiting/diarrhoea

Abdominal pain and cramps

Pruritis

Fungal infections

Vaginitis

Chills/fever

Tinnitus

Fatigue

Haematological toxicity with prolonged use

Hyperglycaemia

Dizziness

Insomnia

Polyuria

Blurred vision

Hypertension/hypotension

Constipation

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Rossiter D. ed. *South African Medicines Formulary*, 10th edn. Cape Town: Health and Medical Publishing Group.

AIM AND OBJECTIVES

The primary aim of the study was to investigate the incidence of haematological effects of linezolid in patients with drug-resistant tuberculosis

The specific objectives were to:
- identify the specific haematological side effects associated with linezolid usage in DR-TB patients and;
- estimate the incidence of haematological side effects in relation to linezolid doses.

METHODOLOGY

Design: Retrospective, quantitative review of medical records

Site: Drug-resistant tuberculosis hospital in the Eastern Cape, South Africa

Time frame: 1 March to 20 September 2017

Sample: Patients aged 18 to 65 years, diagnosed with any type of drug-resistant tuberculosis and prescribed linezolid as part of their treatment regimen (convenience sampling)

Data collection: Self-designed data collection tool to record demographics, diagnosis, HIV status, linezolid dose and frequency, lab results (white cell count, platelet count, haemoglobin levels, haematocrit and full blood count)

Data analysis: Microsoft Excel®

Ethics: Nelson Mandela University REC-H (H16-HEA-PHA-008) and Easern Cape Department of Health (EC_2017RP54_263)

RESULTS

27 medical records reviewed

Males constituted 59.3% (n=16) of the population and the average age was 36.0±9.0 years (range = 18 to 55 years)

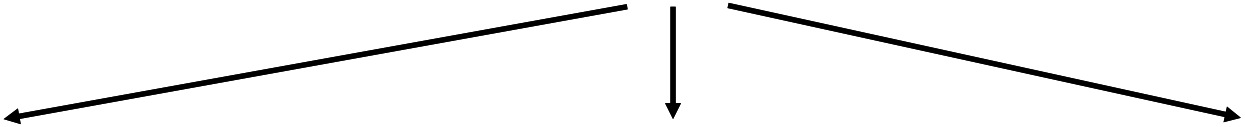
Multidrug-resistant tuberculosis = 13 patients
Extensively drug resistant tuberculosis = 14 patients
HIV-positive = 15 patients (three were receiving zidovudine as part of triple therapy)

All patients were initiated on 600mg of linezolid daily

All patients completed 12 months of linezolid therapy – treatment was tolerated

RESULTS

Seven (25.9%) patients presented with haematologic adverse effects



Anaemia = 6

Macrocytosis = 1

All patients were HIV-positive

Adverse effects started to manifest after approximately 30 days on treatment and were reversed after intervention - All seven patients were receiving 600mg of linezolid daily when adverse effects appeared

Three patients with anaemia were managed by reducing the dose of linezolid to 300mg daily and a blood transfusion

For all other patients dose reduction to 300mg daily was sufficient to return haemoglobin levels to within normal ranges and macrocytosis was reversed – all patients were continued on 300mg of linezolid until the end of the treatment period

DISCUSSION

Srivastava and colleagues[1] found 30% frequency of haematological adverse effects

Other studies[2,3] reported that thrombocytopaenia was commonly observed, but that was not the case in this particular population

A reduction of the daily dose to 300mg to mitigate adverse effects was demonstrated by Park and colleagues[4]

Parinitha and colleagues[5] suggested that there may be a correlation between HIV status and the incidence of haematological adverse effects

[1]Srivastava S et al. 2017. Linezolid dose that maximizes sterilizing effect while minimizing toxicity and resistance emergence for tuberculosis. *Antimicrobial Agents and Chemotherapy*.
[2]Beekmann SE et al. 2008. Toxicity of extended courses of linezolid: results of an infectious diseases society ofAmerica emerging infections network survey. *Diagnostic Microbiology and Infectious Disease*, 62: 407–410.
[3]Brown AN et al. 2015. Preclinical evaluations to identify optimal linezolid regimens for tuberculosis therapy. *MBio*, 6.
[4]Park IN et al. 2006. Efficacy and tolerability of daily half-dose linezolid in patients with intractable multidrug resistant tuberculosis. *Journal of Antimicrobials and Chemotherapy*, 58: 701–704.
[5]Parinitha SS, Kulkarni MH. 2012. Haematological changes in HIV infection with correlation to CD4 cell count. *Australasia Medical Journal*, 5: 157–162.

LIMITATIONS

-Small sample size
-Single site
-Study sample focused on hospitalised patients – less clinically fit than out-patients

CONCLUSION

-In this study anaemia was the most commonly seen haematological adverse effect
-Adverse effects appeared approximately 30 days after initiating linezolid therapy
-Dose reduction in most cases, coupled with blood transfusion in some anaemia cases, were sufficient to reverse adverse effects
-Haematological monitoring should be weekly when linezolid is initiated and thereafter monthly to detect adverse effects

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Short Communication

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

Gotlhe Letswee[a], Hellen Kamau[a], Razia Gaida[b] and Ilse Truter[b]

[a]Department of Pharmacy, Faculty of Health Sciences, and [b]Drug Utilisation Research Unit, Department of Pharmacy, Faculty of Health Sciences, Nelson Mandela University, Port Elizabeth, South Africa

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