

## Study Protocol

### A Retrospective Chart Review of Patients With M(X)DR-TB Commenced On Linezolid

#### Study Team

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## **Background**

HIV and tuberculosis (TB) is a deadly human syndemic that continues to cause immeasurable suffering to individuals, households and communities most affected by the diseases. The emergence of multi- and extensively drug-resistant TB (M/XDR-TB) are even greater public health concerns, threatening basic TB control. Since 2006, the number of M(X)DR-TB cases in South Africa has increased temporally<sup>[1]</sup> and in 2013 the World Health Organisation (WHO) identified South Africa as having the second highest number of MDR-TB cases worldwide.<sup>[2]</sup> Unfortunately, there are limited chemo-therapeutic options for patients diagnosed with M(X)DR-TB. Current treatment regimens are protracted, toxic and are associated with poor treatment outcomes. The emergence of new drugs and re-purposed drugs therefore offer some hope for survival. Linezolid is an antimicrobial agent that was approved for drug-resistant Gram-positive bacterial infections in 2000. In recent months Linezolid has become available to selected M(X)DR-TB patients at some facilities in South Africa. While a recent clinical trial has shown that linezolid improves sputum culture-conversion rates there were however clinically significant adverse effects associated with the drug, necessitating close monitoring.<sup>[3]</sup> There is therefore a critical need to evaluate the drugs used to treat M(X)DR-TB and to assess efficacy endpoints, safety, tolerability and treatment duration, particularly as new anti-tuberculosis agents become available. Unfortunately, there is limited evidence of the efficacy of Linezolid in overburdened, under-resourced, pragmatic settings. This study will examine the efficacy, safety and tolerability of low dose, limited duration linezolid to better evaluate the benefits versus risks of Linezolid in the treatment of M(X)DR-TB. The King Dinuzulu Hospital (KDH), a specialized M(X)DR-TB facility in Durban, South Africa provides us with an ideal opportunity to conduct this study in the epicenter of the drug-resistant TB epidemic.

## **KDH Patient Standard of Care**

Treatment for drug-resistant TB is individually tailored depending on the patient's drug susceptibility test (DST) results according to KDH's standard operating procedures. Medications that comprise potential second-line drug regimens at KDH include ethionamide, para-amino salicylic acid (PAS), ofloxacin, terizidone, kanamycin, capreomycin, ethambutol, amoxicillin-clavulanic acid, clarithromycin, pyrazinamide and moxifloxacin. Based upon WHO guidelines the South African standardized MDR-TB treatment regimen consists of an injectable agent,

Kanamycin or amikacin, administered for a minimum of 6 months and oral drugs, moxifloxacin, ethionamide, terizidone and pyrazinamide, administered for 18 months following conversion to sputum culture negative. Patients with chronic disease that are persistently sputum positive and fail to respond to second-line therapy may have their regimen amended based upon their DST result. The standard empiric XDR TB regimen for South Africa consists of capreomycin, PAS, terizidone, moxifloxacin, ethionamide, PZA, clofazimine.

Patients at KDH are monitored by staff physicians for potential adverse drug effects with a blood count, serum liver enzymes, blood urea measurements, and serum creatinine determinations at the start of treatment and as needed according to clinical signs and symptoms during follow-up. Patients with elevated serum liver enzymes are not generally prescribed a regimen including ethionamide or PAS. Patients showing evidence of significant drug toxicities are evaluated and the regimen changed to a regimen with agents that avoid these side effects. Patients undergo chest radiography at admission and every 6 months thereafter. Monthly/bimonthly sputum is collected for smear and culture testing.

### **Animal Studies**

Cynamon et. al. used a murine model to evaluate the activities of several novel oxazolidinones against a strain of MTB with known resistance profile (ATCC 35801). They found that PNU-100480 (a linezolid-like drug), Isoniazid and Linezolid drugs reduced the colony count of MTB in the spleen and lung of euthanized mice, with PNU-100480 and Isoniazid showing similar activity and Linezolid being slightly less active than PNU-100480 and Isoniazid.<sup>[4]</sup>

### **Clinical Studies**

A recent systematic review and meta-analysis by Cox and Ford report that of the 11 studies (one case series, eight retrospective case-series and two prospective non-randomised case series) included in their review, representing 148 patients, the pooled proportion for treatment success was 68%. There was no significant differences in treatment success with  $\leq 600$  mg vs  $> 600$  mg daily dose of Linezolid or mean Linezolid duration  $\leq 7$  vs  $> 7$  months. In addition, the pooled estimate for the frequency of adverse events was found to be 61.5%, with 36.2% of patients discontinuing Linezolid due to the occurrence of adverse events. The most common adverse

events were neuropathies and bone marrow suppression. Of the nine studies that reported data on culture conversion, the pooled proportion of patients who had converted sputum cultures from positive to negative (during Linezolid treatment) was found to be 97.9%. [5]

More recently, Lee et al., conducted a phase 2a, randomized, two-group study in South Korea. Failed XDR-TB patients received a background regimen in addition to linezolid therapy that started either immediately or after 2 months. Their study showed that Linezolid was effective in achieving culture-conversion in patients with XDR-TB; 87% of patients had a negative sputum culture within 6 months of initiating Linezolid. Eighty-two percent of patients, with exposure to Linezolid, had clinically significant adverse events (mostly neurological/haematological) with three patients discontinuing treatment. [3]

### **Study and Other Agents**

Linezolid is a member of the oxazolidinone class whose antimicrobial effects are related to inhibition of protein synthesis by binding the 23S ribosomal RNA portion of the bacterial 50S ribosomal subunit.[6] The recommended dose for adults is 600mg twice daily.[7] Linezolid exhibits activity *in vitro* activity against *Mycobacterium tuberculosis*, including resistant strains.[8]

Eligible patients will be those receiving linezolid and other second-line agents depending on their DST results and prior drug exposure. These drugs may include (but are not limited to) ethionamide, para-amino salicylic acid (PAS), pyrazinamide, ofloxacin, levofloxacin, moxifloxacin, terizidone, capreomycin, amikacin, and kanamycin. There are no known interactions between these drugs and Linezolid. The interaction with Linezolid and ARV's are unknown and data on all documented adverse events will be collected.

**Aim:** To investigate the impact of the addition of linezolid on clinical and microbiologic outcomes in M(X) DR TB patients in Durban, South Africa

## **OBJECTIVES**

### **Primary Objectives**

Primary objectives of this study will be:

1. To determine microbiologic outcomes, including the proportion of culture-conversions.
2. To compare survival rates in those treated with linezolid-containing group and OBT

### **Secondary Objectives**

The secondary objective of this retrospective chart review is to assess the safety (significant adverse events) and tolerability (treatment discontinuation) of low dose, linezolid (600 mg p.o. daily for any duration) added to Optimized Background Therapy (OBT) for M(X)DR-TB. Optimized Background Therapy (OBT) is defined as treatment with  $\geq 4$  drugs with activity against tuberculosis to which the patient's isolate is believed to be sensitive by history or drug sensitivity testing. Specifically, the primary objectives will be defined as follows:

1. Safety by examining the cumulative rate of adverse events
2. Tolerability by examining the proportion of patients who complete at least 80% of doses in the proposed regimen.

## **STUDY CRITERIA**

### **Inclusion Criteria**

1. Pulmonary MDR and XDR tuberculosis with or without extrapulmonary TB with a *M. tuberculosis* isolate that is confirmed to be resistant to at least rifampicin and isoniazid.
2. Age  $\geq 18$  years.

## **METHODS**

### **Study Design**

Retrospective Chart Review of in-patients and out-patients initiated on Linezolid from 01 January 2014.

### **Study Population**

Adult patients, both HIV negative and HIV, positive receiving treatment for microbiologically confirmed pulmonary M(X)DR-TB, with or without extra-pulmonary disease at King DinuZulu Hospital (KDH) in Durban, South Africa.

## **STUDY IMPLEMENTATION**

### **Study Evaluations (see attached Case Report Forms)**

Using standardized data collection tools (appended to this protocol) we propose to perform a review of demographic, clinical and treatment characteristics, HIV co-infection and outcome of both TB and HIV. Data to be collected includes: demographics, clinical features, laboratory parameters, therapeutic interventions, adverse drug reactions, surgical interventions, clinical progress, and standard TB and HIV outcomes. All standard laboratory and clinical tests including chest radiographs, HIV test results, viral loads, and CD4 counts will also be captured on each patient.

While in the hospital, all patients obtain their medication from the ward nurse daily. Nursing records and doctor's progress notes are used to document any drug adverse effect. Once patients are released from the hospital, they are scheduled for monthly follow-up visits where their sputum is collected, blood may be drawn to assess hematologic, liver and kidney toxicity. Routine HIV counseling and testing and ART is offered as standard of care on every new KDH admission.

### **Patient Privacy and Confidentiality**

Permission from the necessary hospital authority will be obtained for accessing patient medical and demographic records. No patient names will appear on study data analysis forms. Patients will be represented on study data sheets with study numbers. The key to patient study ID

numbers and patient names will be kept in a secure location as hard copies by the principal investigator.

### **Regulatory and ethical review**

The study will be conducted under the oversight of the University of KwaZulu-Natal, Nelson R Mandela School of Medicine Biomedical Research Ethics Committee (BREC). The study protocol will be submitted to the ethics committee by the Principal Investigator and reviewed and approved by the ethics committee prior to study initiation. The investigator will provide progress reports and all other information required by the ethics committee to conduct its reviews.

### **Good Clinical Practice**

The study will be carried out according to ICH-GCP and South African Good Clinical Practice Guidelines (SA GCP). The Principal Investigator and/or designee will ensure that the study staff are conducting the study in accordance with SA GCP and ICH-GCP guidelines and ensure appropriate human subjects training for all study staff. The study protocol and all future revisions of the document, will be reviewed and approved by the UKZN Biomedical Research Ethics Committee (UKZN BREC) prior to implementation. A data manager will oversee the maintenance and completeness of the patient data.

## References:

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