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Linezolid for drug-resistant tuberculosis (Protocol)

Singh B, Cocker D, Ryan H, Sloan DJ

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[Intervention Protocol]

Linezolid for drug-resistant tuberculosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy of linezolid when used as part of a second-line regimen for treating people with multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) pulmonary tuberculosis (TB), and to assess the prevalence and severity of adverse events associated with linezolid use in this patient group.

BACKGROUND

Description of the condition

Tuberculosis (TB) is caused by infection with bacteria of the *Mycobacterium tuberculosis* complex. It remains one of the leading infectious causes of death worldwide despite significant reductions in incidence; there were 1.4 million deaths from TB worldwide in 2015, with an additional 0.4 million deaths from TB amongst people living with human immunodeficiency virus (HIV) (WHO TB Report 2016). Pulmonary TB is the most common form of TB, and the most important from a public health point of view because TB is transmitted by aerosolized droplets from people with active pulmonary TB when they cough (Vashishtha 2013). It is estimated that around one third of the world's population is infected with TB, although of these only one in ten will develop active TB disease (WHO 2009).

Most people with TB are infected with strains of *M. tuberculosis* that are treatable with the standard first-line drugs recommended by the World Health Organization (WHO) guidelines: rifampicin, isoniazid, pyrazinamide, and ethambutol (WHO 2010). Early diagnosis and treatment with effective drugs is one of the mainstays of TB disease control, as well as being a life-saving intervention for people with TB.

Multidrug-resistant TB (MDR-TB) is TB disease that is caused by *M. tuberculosis* strains that have acquired resistance to two important drugs in the first-line regimen: rifampicin and isoniazid (Sharma 2006). Extensively drug-resistant TB (XDR-TB) occurs when *M. tuberculosis* strains are resistant to rifampicin, isoniazid, and any of the antibiotics in the fluoroquinolone class, as well as any of the three injectable drugs used in the second-line treatment of TB: amikacin, kanamycin, and capreomycin (WHO 2016).

The WHO estimates that 480,000 cases of MDR-TB occurred in 2015, with 190,000 people dying of MDR-TB worldwide, and an estimated 9.5% of people with MDR-TB actually have XDR-

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TB (WHO TB Report 2016). Detection of drug-resistant TB is challenging and currently requires costly laboratory services, and access to effective treatment is far from universal. Though there has been rapid progress, only 12% of new TB cases were tested for drug resistance in 2014, with case detection at only 41% (WHO 2015). Over the last decade treatment success rates have remained static at around 50% (WHO 2015), and the international TB community has recognized that new drugs and drug regimens with improved efficacy are urgently needed to improve cure rates. The WHO End TB Strategy outlines measures for post-2015 TB control, including aims to detect and treat everyone with drug-resistant TB, which will require significant scaling up of resources and efforts (WHO 2014).

Constructing MDR-TB therapy regimens is recognized as a difficult balancing act, with several of the agents available being expensive and toxic, and of uncertain antituberculous efficacy due to limited evidence from clinical trials (Chang 2013a). This is especially true for XDR-TB. This has led to efforts being channeled towards investigation of new and existing drugs and regimens, with a drive to standardize trial design and reporting (Mitnick 2015), and focus on low-resource settings which are disproportionately affected by TB and MDR-TB globally (Sloan 2016).

Description of the intervention

The recently updated WHO guidelines for treatment of drug-resistant TB suggest linezolid as a "group C: other core second-line agent", and recommend that two such drugs are required within a core drug-resistant TB regimen (WHO 2016). However, concerns about serious adverse effects prompt the guidelines to state that, where close monitoring for adverse events is not available, "linezolid would best be reserved for MDR-TB patients who have additional drug resistance...or who are intolerant to other components of the core regimen" (WHO 2016).

This upgrades the status of linezolid, which in the previous iteration of the WHO drug-resistant TB guidelines was a "group 5" drug (WHO 2011). Evidence of efficacy and safety of group 5 drugs was deemed insufficient to recommend their use as core drugs within a regimen. In fact, the number of cases treated was so small that the evidence for linezolid was not analysed separately for the WHO 2011 guidelines.

Subsequent publications have suggested linezolid may have a more significant role in regimens, especially in the context of XDR-TB. The International Union Against TB and Lung Disease guidelines recommend it should be the third drug to consider within group 5 (Caminero 2013).

Three meta-analyses have examined the evidence for linezolid in drug-resistant TB (Cox 2012; Sotgiu 2012; Zhang 2015). They include mostly observational data, much of it retrospective, and few randomized trials have been undertaken. There is much debate surrounding linezolid, without consensus, due to the lack of high quality evidence. Many suggest it should be more widely used, hence its upgrade in the recent WHO guidelines (Caminero 2015; WHO 2016).

Inclusion of retrospective data for treatment outcome may well have exacerbated the effect of confounders in the meta-analyses of treatment efficacy (Cox 2012; Sotgiu 2012; Zhang 2015). These reviews focus on efficacy more than safety, with selection of studies based on the former. Safety is a major area of concern with linezolid (Ramachandran 2015).

How the intervention might work

Linezolid is an oxazolidinone antibiotic that disrupts protein synthesis by binding to the 70S initiation complex of bacterial ribosomes (Sloan 2016). It also binds to human mitochondria and inhibits protein synthesis, which is the mechanism of toxicity in clinical use (De Vriese 2006). It is active against most Gram-positive bacteria, with extensive evidence of in vitro activity against isolates of *M. tuberculosis*, including those resistant to first-line drugs (Erturan 2005; Huang 2008).

Linezolid can be taken orally or intravenously, with excellent oral bioavailability, and therefore does not require ongoing injections throughout a regimen (Dryden 2011). Though an adult dose of 600 mg twice daily is most commonly used to treat infections due to Gram-positive bacteria, a variety of dosing strategies have been used for linezolid in the context of drug-resistant TB. These have ranged from 300 mg to 1200 mg, as once- or twice-daily regimens, and lower doses have been tried in an attempt to increase tolerability and reduce toxicity (Park 2006; Migliori 2009; Yew 2009; Koh 2012). A thrice-weekly intermittent dosing regimen has also been tried in limited cohorts to prolong linezolid duration for as long as possible, with the suggestion of promising outcomes (Chang 2013b). The optimal dosing and duration of linezolid remains unclear from the perspective of preventing emergence of resistance, as well as efficacy, tolerability, and toxicity.

Adverse effects of linezolid include suppression of the bone marrow causing anaemia and thrombocytopenia, peripheral neuropathy and optic neuropathy leading to disability and blindness which is usually irreversible, and most commonly gastrointestinal upset which may lead to difficulties with adherence to treatment (Ramachandran 2015). Adverse events with courses of linezolid longer than one month appear to be common, affecting over 80% of participants in some studies (Lee 2012, Tang 2015).

Why it is important to do this review

Uncertainties about the balance between benefits and risks of linezolid use in drug-resistant TB mean a systematic review that assesses the efficacy and adverse events related to linezolid is highly desirable. Its recent inclusion as a core agent in second-line regimens in WHO guidance, with a warning regarding availability of monitoring for adverse events and lack of firm guidance on dos-

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ing, means that clinicians and policy makers will need an up-to-date appraisal of the evidence (WHO 2016). It should assist policy makers who are deciding on the place of linezolid in their national and regional drug-resistant TB programmes, as well as individual clinicians trying to interpret the wide variety of published data on how effective, safe, and tolerable linezolid is in people being treated for MDR-TB and XDR-TB.

OBJECTIVES

To assess the efficacy of linezolid when used as part of a second-line regimen for treating people with multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) pulmonary tuberculosis (TB), and to assess the prevalence and severity of adverse events associated with linezolid use in this patient group.

METHODS

Criteria for considering studies for this review

Types of studies

To assess the efficacy of linezolid we will include randomized controlled trials (RCTs) and quasi-RCTs.

To assess the prevalence and severity of adverse events associated with the use of linezolid, we will include RCTs and quasi-RCTs, and both prospective and retrospective cohort studies, as defined by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), where some participants receive linezolid and others do not.

Types of participants

Adults and children with a diagnosis of multidrug-resistant (MDR-) or extensively drug-resistant (XDR-) pulmonary tuberculosis (TB).

Types of interventions

Intervention

Antituberculous treatment (ATT) regimens that contained linezolid at any dose and for any duration.

Control

ATT regimens that did not contain linezolid.

Types of outcome measures

These outcome measures are based on those specified by the WHO for TB programme outcome reporting in MDR- and XDR-TB (WHO 2013).

Primary outcomes

- All-cause death: all deaths that occurred during each included study and until the end of follow-up.
- TB-associated death: all deaths attributed to TB by the study investigators that occurred during each study and until the end of follow-up.
- Treatment failure: participants who did not show sputum culture conversion by the end of the intensive phase of ATT, or who had reverted from culture negative to culture positive, or who had failed to respond clinically to treatment as defined by the study investigators.
- Cure: participants who completed ATT as planned without evidence of failure and had at least three consecutive negative sputum cultures in specimens taken at least 30 days apart after the intensive phase of treatment.

Secondary outcomes

- Treatment interrupted (default): participants who stopped taking ATT for one month or more at any point in the course of treatment.
- Treatment completed: participants who completed ATT as planned but did not have at least three consecutive negative sputum cultures in specimens taken at least 30 days apart after the intensive phase of treatment..
- Time to sputum culture conversion: the length of time between starting treatment and conversion from sputum culture positive to sputum culture negative.

Adverse events

- All adverse events.
- All serious adverse events.
- Adverse events that led to discontinuation of antituberculous drugs or dose reduction.
- Adverse events attributed to linezolid, particularly peripheral and optic neuropathy, anaemia, thrombocytopenia, lactic acidosis, and serotonin syndrome.

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

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Electronic searches

We will search the following databases for relevant studies: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); and LILACS, using the search terms detailed in Appendix 1. We will also check the WHO International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) for ongoing trials using the terms: "linezolid" and "tuberculosis".

Searching other resources

We will also contact researchers in the field to identify unpublished or ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (BS and DC) will screen the titles and abstracts of the search results independently and code them as either 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (BS and DC) will independently screen them for inclusion and will record the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author. We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will contact study authors for clarification if a study's eligibility is unclear. We will resolve any disagreements through discussion and list the excluded studies and the reasons for their exclusion in the 'Characteristics of excluded studies' table. We will record the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management

We will design and pilot a data extraction form, and modify the form based on the results of the pilot. Two review authors (BS and DC) will independently extract data from each included study using the finalized data extraction form. BS and DC will compare the extracted data to identify any possible errors, and will resolve any discrepancies through discussion and by referring to the original study articles. We will extract the following data from each included study.

- Country and clinical setting, start and end dates of the study, study design, inclusion and exclusion criteria applied, number of participants eligible for inclusion and number of participants allocated to each group.
- Participant characteristics: age, sex, history of previous TB treatment, known contact with MDR-TB patient, duration of symptoms at presentation, comorbidity (human immunodeficiency virus (HIV) infection, other immunosuppression and other diseases), diagnostic methods used (for example, culture-based drug susceptibility testing, Xpert MTB/RIF, line probe assay for drug susceptibility), drug susceptibility profile of participants at entry to the study.
- Intervention data: description of drugs, dose, route of administration in both the intensive and continuation phase, and duration of all drugs for both phases. Administration of other drugs or therapeutic procedures, including surgery.

Primary outcomes

For the primary outcomes we will extract the following data.

All-cause death

- Number of deaths, stratified by drug susceptibility profile, age and HIV status, if available.
- Timing of death after start of treatment.

TB-associated death

- Number of deaths attributed to TB by the investigators, stratified by drug susceptibility profile, age and HIV status, if available.

Treatment failure

- Number of participants who have not shown sputum culture conversion by the end of the intensive phase of ATT, stratified by drug susceptibility profile, age and HIV status, if available.
- Number of participants who have reverted from culture negative to culture positive, stratified by drug susceptibility profile, age and HIV status, if available.
- Number of participants who have failed to respond clinically to treatment as defined by the investigators, stratified by drug susceptibility profile, age and HIV status, if available.
- Method of monitoring treatment and defining treatment failure.
- Time between start of treatment and treatment failure.
- Outcome following classification as treatment failure.

Cure

- Number of participants who have completed ATT as planned and have had at least three negative sputum cultures in specimens taken at least 30 days apart during the last months of treatment, stratified by drug susceptibility profile, age, and HIV status, if available.

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Secondary outcomes

For the secondary outcomes we will extract the following data.

Treatment interrupted

- Number of participants who stopped taking ATT for one month or more at any point in the course of treatment, stratified by drug susceptibility profile, age and HIV status, if available.
- Method of monitoring treatment adherence.
- Reasons for treatment interruption, if available.

Treatment completed

- Number of participants who completed ATT as planned but did not have at least three negative sputum cultures in specimens taken at least 30 days apart during the last months of treatment.
- Method of monitoring treatment.

Time to sputum culture conversion

- Time between starting treatment and conversion from sputum culture positive to sputum culture negative.
- Method of monitoring treatment, including frequency of sputum sampling.

Follow-up

Length of follow-up, follow-up methods, number and characteristics of losses to follow-up.

Adverse events

We will extract information on the total number of the following.

- Adverse events.
- Serious adverse events.
- Participants experiencing adverse events.
- Adverse events that led to discontinuation of antituberculous drugs or dose reduction.
- Adverse events that attributed to linezolid, particularly peripheral and optic neuropathy, anaemia, thrombocytopenia, lactic acidosis, and serotonin syndrome.

For each outcome, we will extract the number of participants assigned and the number of participants analysed in each treatment group. For dichotomous outcomes, we will extract the number of participants who experienced the event. For count data outcomes, we will extract the number of events in the intervention and control group.

Assessment of risk of bias in included studies

For randomized controlled trials (RCTs) and quasi-RCTs, two review authors will independently assess the methodological quality of each included trial using the Cochrane 'Risk of bias' tool and report the results in a 'Risk of bias' table (Higgins 2011a). We will resolve any disagreements through discussion. Regarding generation of allocation sequence and allocation concealment, we will classify each as either adequate, inadequate, or unclear in each included trial according to Jüni 2001. We will report who was blinded in each included trial, and we will assess the risk of bias associated with blinding separately for each primary outcome. If at least 90% of participants were followed up to the trial's completion we will classify inclusion of all randomized participants as adequate; otherwise we will classify inclusion as inadequate. We will attempt to contact the trial authors if information is unspecified or unclear.

For non-randomized studies, we will use the ROBINS-I risk of bias tool (Sterne 2016), and will adapt and pilot it before we use it to assess all included non-randomized studies. The following are areas of confounding that we expect to be relevant to all or most included studies.

- Extent of drug resistance: number of effective drugs available.
- Severity of TB disease at start of treatment.
- HIV co-infection.
- Timing of addition of linezolid to the regimen.
- Duration of linezolid treatment.
- Background antituberculous therapy regimen.
- Supportive care available in study setting.

Measures of treatment effect

We will use relative risk as the measure of treatment effect for analysis.

Unit of analysis issues

We do not anticipate that any cluster-RCTs will meet the inclusion criteria of the review.

For multi-armed studies, where we wish to include more than one intervention study arm, we will split the control group to avoid including the same participants more than once.

Dealing with missing data

The primary analysis is an intention-to-treat analysis where all participants randomized to treatment are included in the denominator. This analysis assumes that all losses to follow-up have good outcomes. We will carry out a sensitivity analysis to explore the impact of the missing data on the summary effect estimate for all-cause death and cure.

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Assessment of heterogeneity

We will assess heterogeneity by visually inspecting the forest plots to determine closeness of point estimates with each other and overlap of confidence intervals (CIs). We will use the Chi² test with a P value of 0.10 to indicate statistical significance, and the I² statistic to assess heterogeneity with a value of 50% taken to indicate significant statistical heterogeneity.

Assessment of reporting biases

We will conduct visual inspection of the funnel plot of the trials for any obvious asymmetry that could be evidence of publication bias.

Data synthesis

Using Review Manager 5 (RevMan 5) (RevMan 2014), we will perform a meta-analysis on the data in included trials. We will not combine data from RCTs and non-RCTs. As we anticipate significant variability in the samples of participants across the different studies, we will use a random-effects model for meta-analysis, unless there is a very small number of included studies with low heterogeneity, in which case we will use a fixed-effect model.
For non-randomized data, we will not perform a meta-analysis. We will report these data descriptively in a table that includes how the data is collected, and the reported outcomes (unadjusted). If the study authors have adjusted data, we will provide this estimate with a short description of the adjustments the study authors made.
We will assess the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We will use GRADEpro GDT software to construct 'Summary of findings' tables (GRADEpro GDT 2014).

Subgroup analysis and investigation of heterogeneity

We plan to investigate heterogeneity through the following subgroup analyses.

- Drug resistance profile, determined by: (a) % XDR, (b) % fluoroquinolone-resistant (resistant to any fluoroquinolone, but susceptible to injectables), (c) % injectable-resistant (resistant to any injectable, but susceptible to fluoroquinolones).
- HIV status (seropositive and seronegative).
- Age (adults and children).
- Daily dose of linezolid (600 mg or less and over 600 mg adult equivalent).
- Duration of linezolid (six months or less and longer than six months).
- Total cumulative dose of linezolid.
- Other drugs within the background antituberculous drug regimen.

Sensitivity analysis

We will perform a worst-case scenario analysis by imputing the missing data as poor outcomes in the linezolid group and good outcomes in the control group, and by comparing this to an available-case analysis to explore the effect of missing data on the primary outcomes all-cause death and cure.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR	CENTRAL	MEDLINE	Embase	LILACS
1	Tuberculosis OR TB	Tuberculosis OR TB ti, ab	Tuberculosis OR TB ti, ab	Tuberculosis OR TB ti, ab	Tuberculosis OR TB
2	Multi-drug resistant	drug resist* OR MDR OR DR OR XDR ti, ab	drug resist* OR MDR OR DR OR XDR ti, ab	drug resist* OR MDR OR DR OR XDR ti, ab	Multi-drug resistant
3	MDR-TB	1 and 2	1 and 2	1 and 2	MDR-TB
4	Drug-resistant	DR-TB OR MDR-TB OR XDR-TB ti, ab	DR-TB OR MDR-TB OR XDR-TB ti, ab	DR-TB OR MDR-TB OR XDR-TB ti, ab	Drug-resistant

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(*Continued*)

5	XDR-TB	Tuberculosis, Multidrug-Resistant"[Mesh] OR "Extensively Drug-Resistant Tuberculosis"[Mesh]	Tuberculosis, Multidrug-Resistant"[Mesh] OR "Extensively Drug-Resistant Tuberculosis"[Mesh]	Multidrug resistant tuberculosis [Emtree] OR "extensively drug resistant tuberculosis" [Emtree] OR "drug resistant tuberculosis" [Emtree]	XDR-TB
6	2 or 3 or 4 or 5	3 or 4 or 5	3 or 4 or 5	3 or 4 or 5	2 or 3 or 4 or 5
7	1 and 6	"Oxazolidinones"[Mesh]	"Oxazolidinones"[Mesh]	Linezolid ti, ab OR "Linezolid" [Emtree]	1 and 6
8	linezolid	"linezolid" [Supplementary Concept]	"linezolid" [Supplementary Concept]	LZD OR Zyvox ti, ab	linezolid
9	7 and 8	Linezolid OR LZD OR Zyvox ti, ab	Linezolid OR LZD OR Zyvox ti, ab	"oxazolidinone derivative" [Emtree]	7 and 8
10	-	7 or 8 or 9	7 or 8 or 9	7 or 8 or 9	-
11	-	6 and 10	6 and 10	6 and 10	-
12	-	-	Limit 11 to Humans	Limit 11 to Human	-

CONTRIBUTIONS OF AUTHORS

BS and HR wrote the protocol with input from DC and DS. All protocol authors read and approved the final version of the protocol.

DECLARATIONS OF INTEREST

BS and HR work for the Royal Liverpool University Hospital, UK, and have no known conflicts of interest.

DC is a PhD candidate supported by a Wellcome Trust Training Fellowship in Tropical Medicine based at the Liverpool School of Tropical Medicine, UK, and has no known conflicts of interest.

DS is a Senior Clinical Lecturer at the University of St. Andrews, UK, and is a principal or co-investigator on projects funded through grants from the Cunningham Trust, the Wellcome Trust, MRC-Newton Fund, and EDCTP, and has no known conflicts of interest.

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