

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

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Background: Linezolid containing regimens have been proposed as potentially valuable alternatives for the treatment of patients with multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant TB (XDR-TB).

Methods: A systematic review and meta-analysis was conducted to assess the efficacy, safety and tolerability of linezolid for drug-resistant TB (DR-TB) treatment. We searched the Cochrane Controlled Trial Registry, PubMed, Embase, Science Citation Index Expanded (SCI) and China National Knowledge Infrastructure (CNKI), database up to May 2014 to identify studies providing data of the use of linezolid for the treatment of DR-TB.

Results: The search yielded 15 studies (367 patients) including one randomized controlled trial (RCT), covering 239 patients who could be evaluated for effectiveness; 83% [95% confidence interval (CI), 75-90%; $I^2=62.8\%$] had a favorable outcome, defined as either cure or treatment completion. The pooled rate of culture conversion was 89% (95% CI, 83-95%; $I^2=49.6\%$). Between the group receiving daily linezolid doses of ≤ 600 or >600 mg, the mortality was considerably lower in patients treated with less than 600 mg/day (P value <0.001). Of 367 patients for whom data on safety was available, peripheral neuropathy (31%, 95% CI, 19-42%; $I^2=81.7\%$) and anemia (25%, 95% CI, 15-34%; $I^2=76.6\%$) were the main adverse effects. Patients receiving less than 600 mg/day were more likely to experience nervous system adverse events (P value <0.01).

Conclusions: The available evidence suggests that linezolid could be considered as a promising option as treatment of MDR/XDR TB. Randomized trials are warranted to define the dose and frequency of administration.

Keywords: Multidrug-resistant tuberculosis (MDR-TB); extensively drug-resistant TB (XDR-TB); treatment; linezolid; meta-analysis

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Introduction

Tuberculosis (TB) has attracted increasing public health attention due to the alarming rates of multidrug-resistant TB (MDR-TB, defined as resistance to at least isoniazid and rifampicin) and extensively drug-resistant TB (XDR-TB, defined as MDR-TB with additional bacillary resistance to any fluoroquinolone and at least one second-line injectable

anti-TB drug) (1,2). MDR accounts for about 3.6% of new TB patients worldwide, accounting for an estimated 450,000 new cases in 2012. By September 2013, 92 countries had reported at least one case of XDR-TB. Among the developing countries, India and China has the two highest prevalence of TB in the world and troublingly high rates of MDR and XDR-TB (3,4). Furthermore, the treatment of

MDR-TB requires a longer duration, is considerably more complicated, expensive and toxic. The longer treatment course of MDR-TB results in poor treatment outcome, leading to the emergence of XDR-TB. XDR-TB treatment is much more difficult and costly and will stress national health budgets even more than MDR-TB treatment (5-8).

Recently a number of promising novel strategies for the management of drug-resistant TB have also been explored, including treatment with linezolid, fluoroquinolones, high-dose isoniazid and phenothiazines (9). A linezolid-containing regimen for drug-resistant TB (DR-TB) is one of the off-label uses of linezolid that has not yet been approved by the licensing agencies. Excellent activity against drug-resistant Mycobacterium TB was in fact discovered at the early stage of *in vitro* studies of linezolid. However, in contrast with other protein synthesis inhibitors, linezolid's mechanism of action involves inhibition of protein synthesis at its early stages (10-13).

So far, the efficacy of linezolid for the treatment of TB has never been documented by clinical trials. Current treatment for MDR-TB lasts 20 months at least (14). The currently approved time for licensed treatments using linezolid is up to 28 days; however, this is an insufficient length of time for treatment of DR-TB. Thus the potential effectiveness of a linezolid-containing regimen for DR-TB must be clinically assessed against the dangers of drug toxicity caused by extended use (10). However, since the outcome of patients with DR-TB is generally poor (15), other treatment options need to be considered. Linezolid has excellent activity against DR mycobacteria and its effectiveness and safety have been evaluated in several small studies, including a randomized controlled trial (RCT) with a small number of patients and a suboptimal study design. In the present systematic review and meta-analysis we sought to pool the clinical evidence regarding the effectiveness and safety of linezolid for the treatment of DR-TB.

Methods

Search strategy

We searched the Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure (CNKI) and Science Citation Index Expanded (SCI) database from January 2000 to May 2014, using combinations of the key words: "linezolid", "MDR-TB", "XDR-TB", "multidrug-resistant tuberculosis" and "extensively drug-resistant tuberculosis". In addition, the references of the chosen

articles and relevant review papers were hand-searched and reviewed. The review was not restricted by language.

Selection strategy

Two investigators (X Zhang and R Qin) independently searched the literature and examined relevant studies for further assessment of data on effectiveness and safety of linezolid for the treatment of patients with DR-TB. We included peer-reviewed reports of studies from which the treatment outcomes of the patients could be clearly extracted. A number of criteria were required for inclusion in our analysis: (I) confirmation that patients had MDR-TB by drug-susceptibility testing (DST) of *M. tuberculosis* cultures; (II) any individualized treatment could be given to patients, provided linezolid was included in a regimen after the study enrolment; (III) detailed treatment outcomes and follow-up data or definitions of treatment success similar to that outlined by World Health Organization (WHO) were provided; (IV) the proportion of patients with pulmonary TB was not less than 90%. Exclusion criteria of studies for our analysis were: (I) experimental trials and trials focused solely on pharmacokinetic or pharmacodynamic variables; (II) animal studies; (III) reports that appeared in conference abstracts with no further information obtainable from personal correspondence with the authors.

Data extraction

Data were extracted independently by two investigators (R Qin and X Zhang), and differences were resolved by discussion with a third investigator (R Wang). The corresponding authors of selected papers were contacted to obtain any missing data, including those for the assessment of the effectiveness, safety and tolerability of linezolid-containing treatment regimens. Basic study information, including the first author, publication year, country in which the study was conducted, clinical center, study period and study design, the number of MDR- and XDR-TB patients, the proportion of XDR-TB patients, the rates of infection related to gender, average age and the history of previous anti-TB treatment was extracted.

For evaluation of linezolid effectiveness, safety and tolerability, the following variables were collected: the dosage of linezolid, the final treatment outcome, adverse events, and the rate of sputum culture conversion and the duration of exposure to the linezolid-containing regimen.

Definitions

According to the recommendations of the WHO, we defined the final treatment outcome as either favorable (cured and treatment completed) or unfavorable (died, treatment failed) (16). Safety and tolerability end-points are classified as major and minor adverse events. A major adverse event was defined as any adverse reaction that brought about temporary or permanent discontinuation of linezolid, whereas a minor adverse event required only dose adjustment and/or addition of concomitant treatment (17).

Qualitative assessment

This systematic review and meta-analysis of studies on the use of linezolid for DR-TB was performed according to guidelines established by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (18). Discrepancies for the study selection and data extraction from the included studies were resolved by consensus (X Zhang and R Qin).

Data analysis

We pooled the proportions of patients who had a favorable outcome (cured and treatment completed), sputum culture conversion, or failed and died across the selected studies for a meta-analysis, using available detailed data from patients. The 95% score interval method was used to calculate the 95% CI. Random-effects models were applied for assigning weights according to the methods described by DerSimonian and Laird (19).

The heterogeneity of outcome within and between each group of studies were assessed using the Cochrane Q test (P value <0.1 denoting the presence of heterogeneity) and the I^2 statistic in forest plots described by Higgins *et al.* (20,21). The I^2 statistic estimates the percent of observed between-study variability due to heterogeneity rather than to chance and ranges from 0 to 100 percent (values of 25%, 50% and 75% were considered representing low, medium and high heterogeneity respectively) (22). A value of 0% indicates no observed heterogeneity while 100% indicates significant heterogeneity. For this review we determined that I^2 values above 75 percent were indicative of significant heterogeneity. This heterogeneity was further explored through subgroup analyses and meta-regression. Subgroup analyses were performed based on the potential clinical factors when such were available (e.g., initial daily dose

of linezolid ≤ 600 or >600 mg). A univariate approach was employed to assess the causes of heterogeneity among the selected studies. We tested the significance of these coefficients by Student's *t*-test and reported the P value for significance (23). To avoid false negative results due to the small number of studies entered in the regression analysis, a two-tailed 0.10 P value was considered as cutoff for statistical heterogeneity in a meta-regression.

To clearly define data from different statistical methods, when 95% CI is presented a meta-analysis was done; otherwise the data was added. Statistical procedures were performed using the STATA version 10 and R 2.15.2 (24).

Finally, the small study bias was appraised by graphical inspection of funnel plots and Egger test.

Results

Study selection

Of the 414 publications that we initially identified as dealing with MDR- and XDR-TB, 370 were excluded because they were reviews, commentaries, *in vitro* studies, or were irrelevant to our research objectives (Figure 1). We performed a full text review on 44 articles, 15 of which met our specified inclusion and exclusion criteria (17,25-38).

Characteristics of studies and assessment of study qualities

Table 1 summarizes the basic characteristics of the 15 studies included in the analysis. Most (46.7%) were conducted in Asian countries, such as South Korea, India and China, or in Europe (33.3%). The majority of the studies (73.3%) were retrospective and observational in design; only one was a RCT (33). All 15 studies were published in English. Of the 15 studies, four were multicenter studies (29,32,34,37).

As shown in the assessment of clinical practice quality (Table 2), the study by Lee *et al.* was a RCT (33). Two studies provided free treatment for patients (33,37). However, the quality of the treatment given to patients was judged to be good, because dosages in all the studies were recorded clearly and all patients were prescribed individualized treatment according to the DST result. The majority of studies (87%) had recorded the history of previous anti-TB treatments.

Characteristics of patients included

In the publications studied, 367 patients met the definition

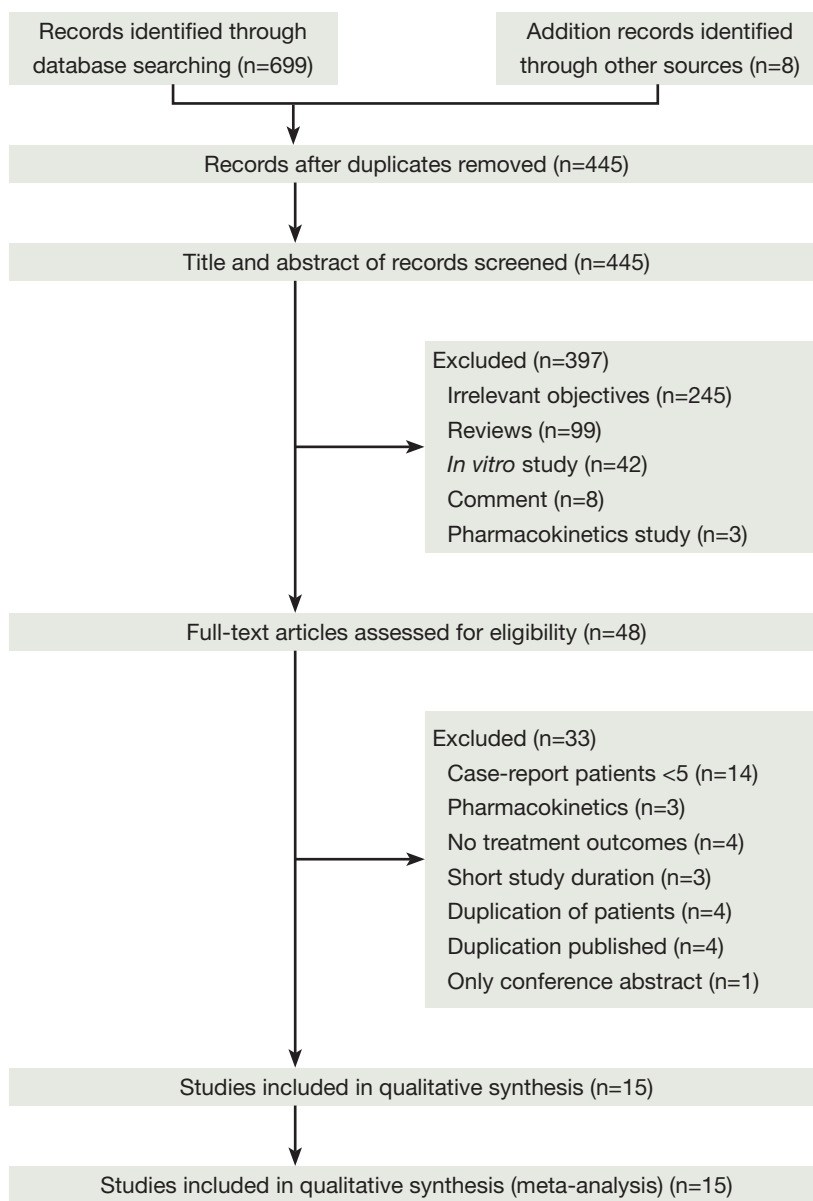


Figure 1 PRISMA flowchart of enrolled studies for systematic review.

for infection with MDR- or XDR-TB, and 239 patients had evaluable treatment outcomes (*Table 1*). None of the authors contacted via e-mail provided the additional requested data. More than half the patients were male with a median age of 35.3 (range, 24-41) years. Nearly 9% of patients were HIV-positive. The mean number of drugs included in the MDR- and XDR-TB treatment ranged from 5 to 11, but the specific antibiotics or changes in the antibiotic regimens other than linezolid were not provided in the majority of the studies. The mean percentage of patients undergoing

surgery was 18.1% (range, 0-63.6%). XDR-TB accounted for 46.3% of the included cases.

In the comparative analysis according to linezolid dose (*Table 3*), with the exception of the proportions of XDR-TB and HIV-positive patients, no statistically significant differences were detected in the characteristics of those who were treated with a daily linezolid-containing regimen of ≤ 600 mg and those with a daily dose of >600 mg. The group with a daily dose of ≤ 600 mg had a higher proportion of HIV-positive and XDR-TB patients.

Table 1 Characteristics of epidemiology and patients in the selected studies

Year	First author and year (ref.)	Country	Single/multi-center	Study duration	Study design	Paediatric patients aged <15 yrs	Daily linezolid dose	Median duration of linezolid therapy	Data set for the systematic review*	Data set for the meta-analysis#
2012	Lee (33)	South Korea	Single-center	2008-2011	Open label, randomized trial	No	600 mg OD	6 months	41	17
2012	Singla (29)	India	Single-center	2006-2011	Prospective study	No	600 mg BD, 600 mg OD	30 days	29	14
2011	Villar (27)	Portugal	Single-center	2004-2009	Prospective study	Yes, one patient	1,200 mg OD, 600 mg OD	375 days	16	9
2010	Udwadia (28)	India	Single-center	2004-2007	Prospective, non-randomised study	Not Reported	600 mg OD	20.5 months	18	15
2012	Abbate (38)	Argentina	Single-center	2002-2008	Retrospective study	No	600 mg BD	90 days	17	15
2012	Koh (34)	South Korea	Multi-center	2007-2009	Retrospective study	No	300 mg OD	413 days	51	45
2012	Xu (25)	China	Single-center	2007-2010	Retrospective study	No	600 mg BD, 900 mg OD	6 months	18	13
2012	De Lorenzo (36)	Italy	Single-center	2009-2010	Retrospective study	No	600 mg BD, 600 mg OD, 450 mg BD	63.5 days	12	3
2009	Migliori (32)	Germany, Belarus, Italy, Switzerland	Multi-center	2001-2007	Retrospective, non-randomised, unblinded observational study	No	600 mg OD, 600 mg BD	221 days	85	45
2006	von Der Lippe (26)	Norway	Single-center	1998-2002	Retrospective study	No	600 mg BD	17 months	10	7
2006	Park (31)	South Korea	Single-center	2003-2006	Retrospective study	No	600 mg OD, 600 mg BD	9 months	8	3
2005	Fortún (35)	Spain	Single-center	1999-2004	Retrospective study	No	600 mg BD, 300 mg BD	24 months	5	4
2010	Anger (37)	US	Multi-center	2000-2006	Respective study	Yes, one patient.	600 mg BD, 300 mg BD	16 months	16	15
2010	Schechter (30)	US	Multi-center	2003-2007	Respective study	No	600 mg OD	21.5 months	30	23
2009	Nam (17)	South Korea	Single-center	NR	Respective study	No	600 mg OD, 300 mg BD	5 months	11	11

*, treatment outcome: definite (cured, treatment completed, died, failure), still on treatment, default, transfer out; #, Treatment outcome: definite only (cured, treatment completed, died, failure), NR, not reported.

Table 2 Assessment of clinical practice quality of the studies

Year	First author (ref.)	Dose reported	Individualized regimen based on DST result	History of previous anti-tuberculosis treatment	Explicit definition of success treatment based on the WHO recommendation	The description of included and excluded criteria	Free treatment	Setting of the control group
2012	Lee (33)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2012	Singla (29)	Yes	Yes	Yes	Yes	Yes	No	No
2011	Villar (27)	Yes	Yes	Yes	Yes	No	NR	No
2010	Udwadia (28)	Yes	Yes	No	NR	No	No	Yes
2012	Abbate (38)	Yes	Yes	Yes	Yes	Yes	NR	No
2012	Koh (34)	Yes	Yes	Yes	Yes	Yes	NR	No
2012	Xu (25)	Yes	Yes	Yes	Yes	Yes	No	No
2012	De Lorenzo (36)	Yes	Yes	Yes	NR	No	NR	No
2009	Migliori (32)	Yes	Yes	Yes	Yes	Yes	NR	Yes
2006	von Der Lippe (26)	Yes	Yes	No	Yes	Yes	NR	No
2006	Park (31)	Yes	Yes	Yes	Yes	Yes	No	No
2005	Fortún (35)	Yes	Yes	Yes	NR	No	NR	No
2010	Anger (37)	Yes	Yes	Yes	Yes	Yes	Yes	No
2010	Schechter (30)	Yes	Yes	Yes	Yes	No	NR	No
2009	Nam (17)	Yes	Yes	Yes	Yes	Yes	No	No

DST, drug susceptibility test; WHO, World Health Organization; NR, not reported.

Table 3 Demographic, epidemiological and clinical characteristics of MDR-TB or XDR-TB cases included in systematic review according to linezolid dose

Variables	Total	LNZ ≤600 mg/day	LNZ >600 mg/day	P value
Number of patients included	367	151	216	–
Male, n (%)	143/266 (53.8)	80/151 (53.0)	63/115 (54.8)	0.77
Types of countries				
Developed countries (%)	285/367 (77.7)	115/151 (76.2)	170/216 (78.7)	0.56
Developing countries (%)	82/367 (22.3)	36/151 (23.8)	46/216 (21.3)	–
Median (IQR) age at the admission, years	35.3 (24.0-41.2)	36.2 (29.0-41.2)	34.6 (24.0-40.0)	0.608
HIV-positive, n (%)	14/171 (8.2)	14/113 (12.4)	0/58 (0.0)	0.005
Surgical treatment, n (%)	37/237 (15.6)	18/133 (13.5)	19/104 (18.3)	0.319
XDR-TB, n (%)	170/367 (46.3)	81/151 (53.6)	89/216 (41.2)	0.019
Previous exposure to anti-TB therapy, years	2.53	2.77	2.43	0.835
Median (IQR) exposure to linezolid, days	340 (63.5-690.0)	618 (150.0-690.0)	224 (63.5-480.0)	0.062

MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; LNZ, linezolid.

Effectiveness of linezolid-containing regimens

The pooled rate of culture conversion of the patients who had evaluable treatment outcomes was 89% (95% CI, 83-95%; $I^2=49.6\%$) (Figure 2). Of the 239 patients who had evaluable treatment outcomes, 190 MDR-TB patients had

favorable outcomes. The weighted proportion of favorable outcome was 83% (95% CI, 75-90%; $I^2=62.8\%$, Figure 3). Death and treatment failure were observed in 9.6% and 10.9% of the enrolled subjects, respectively.

Patients receiving a lower dosage of linezolid (≤ 600 mg) had a lower death rate (1.8% vs. 16.4%, P value <0.05) but a

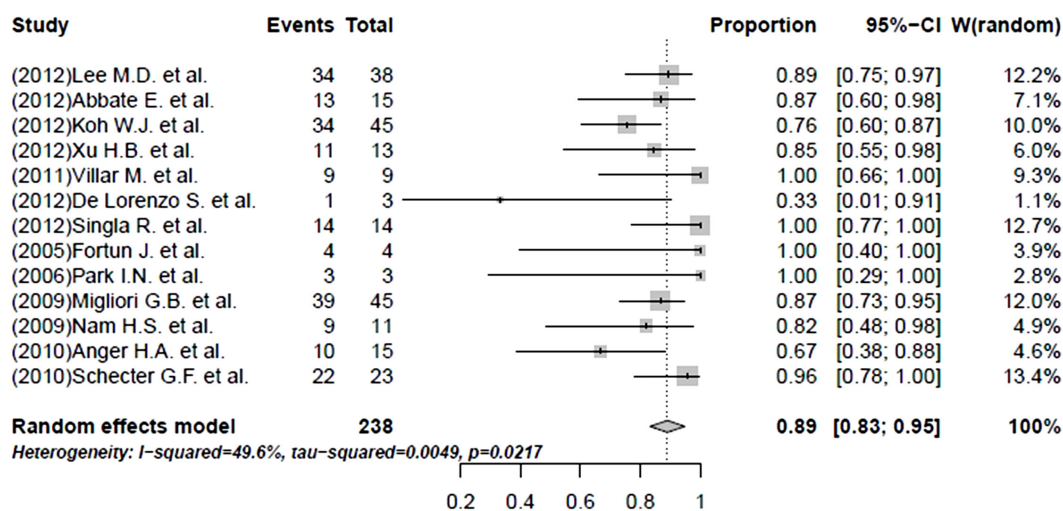


Figure 2 Forest plot showing the proportions of culture converters in the enrolled studies.

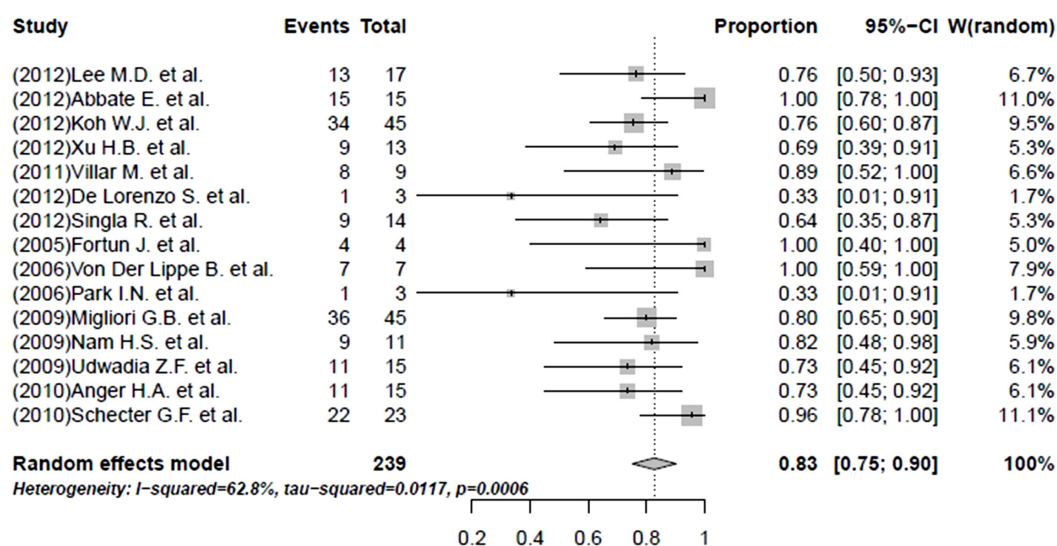


Figure 3 Forest plot showing the proportions of patients who had favorable outcome in the enrolled studies.

higher percentage of failure (18.0% *vs.* 4.7%, P value =0.001), than the group receiving the higher dosage (>600 mg) (Table 4).

Safety and tolerability of linezolid-containing regimen

Nearly half the patients treated with a linezolid-containing regimen experienced adverse events that were attributable to linezolid (Table 5). Major adverse effects, which required linezolid discontinuation, were experienced by 35% (95% CI, 22-47%; $I^2=90.1\%$) of the patients (Figure 4). Peripheral neuropathy (31%, 95% CI, 19-42%; $I^2=81.7\%$) and anemia (25%, 95% CI, 15-34%; $I^2=76.6\%$) constituted the

main adverse effects (Figures 5 and 6, respectively). Other linezolid-related adverse events with lower frequencies included gastro-intestinal disorders (28/208, 13.5%), optic neuritis (23/246, 8.0%), thrombocytopenia (20/262, 7.6%) and leucopenia (19/262, 7.3%) (Table 5).

A higher incidence of adverse events in the hematopoietic system (38.0% *vs.* 17.9%, P value <0.05) and a lower frequency of adverse events in nervous system (19.9% *vs.* 43.0%, P value <0.05) attributed to linezolid treatment were detected in the subgroup with a linezolid dosage >600 mg/day. More specifically, a statistically significantly higher risk of anemia (31.3% *vs.* 13.6%, P value =0.007) and a lower

Table 4 Treatment outcomes of MDR-TB or XDR-TB cases included in meta-analysis according to linezolid dose

Variables	Total	LNZ ≤600 mg/day	LNZ >600 mg/day	P value
The number of the patients included in meta-analysis in the meta-analysis, n (%)	239 (100.0)	111 (46.4)	128 (53.6)	–
Culture conversion, n (%)	203/238 (85.3)	99/117 (84.6)	104/121 (86.0)	0.771
Median (inter-quartile range) period from start of anti-TB therapy to culture conversion, days	87.4	57.7	106.6	0.076
Cured, n (%)	140/239 (58.6)	72/111 (64.9)	68/128 (53.1)	0.066
Treatment completed, n (%)	50/239 (20.9)	17/111 (15.3)	33/128 (25.8)	0.047
Favorable outcome, n (%)	190/239 (79.5)	89/111 (80.1)	101/128 (78.9)	0.808
Failed, n (%)	26/239 (10.9)	20/111 (18.0)	6/128 (4.7)	0.001
Died, n (%)	23/239 (9.6)	2/111 (1.8)	21/128 (16.4)	0.000

MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; LNZ, linezolid.

Table 5 Retrospective evaluation of the safety and tolerability of linezolid in the treatment of MDR-TB or XDR-TB cases included in the systematic review according to linezolid dose

Variables	Total	LNZ ≤600 mg/day	LNZ >600 mg/day	P value
The number of the patients included in the systematic review, n (%)	367 (100.0)	151 (41.1)	216 (58.9)	–
Total adverse events presumably due to linezolid, n (%)	147/269 (54.6)	49/82 (59.8)	98/187 (52.4)	0.265
Major adverse events, n (%)	108/367 (29.4)	39/151 (25.8)	69/216 (31.9)	0.206
Total adverse events in nervous system, n (%)	108/367 (29.4)	65/151 (43.0)	43/216 (19.9)	0.000
Total adverse events in hematogenic system, n (%)	109/367 (29.7)	27/151 (17.9)	82/216 (38.0)	0.000
Anemia, n (%)	74/270 (27.4)	8/59 (13.6)	66/211 (31.3)	0.007
Leucopenia, n (%)	19/262 (7.3)	8/81 (9.9)	11/181 (4.4)	0.273
Neutropenia, n (%)	3/262 (1.1)	0/81 (0.0)	3/181 (1.7)	0.244
Thrombocytopenia, n (%)	20/262 (7.6)	3/81 (3.7)	17/181 (9.4)	0.109
Pancytopenia, n (%)	4/262 (1.5)	0/81 (0.0)	4/181 (2.2)	0.178
Optic neuritis, n (%)	23/246 (8.0)	13/115 (8.6)	10/131 (7.6)	0.669
Peripheral neuropathy, n (%)	79/256 (30.9)	51/137 (37.2)	28/119 (23.5)	0.018
Gastro-intestinal disorders, n (%)	28/208 (13.5)	1/30 (3.3)	27/178 (15.2)	0.079

MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; LNZ, linezolid.

proportion of peripheral neuropathy (23.5% vs. 37.2%, P value=0.018) was found in the group with a linezolid dose of >600 mg/day, compared with the group taking a dose of ≤600 mg/day.

Heterogeneity analysis

Subgroup analyses on the effectiveness, safety and tolerability were performed based on the potential clinical factors between patients treated with a daily dose of linezolid ≤600 and >600 mg. No differences were found in

the baseline characteristics of patients between the group treated with high dose or low dose of linezolid, except in the rates of XDR-TB and HIV, which were both slightly higher in the group receiving lower linezolid dose. This may have been one of the factors that caused high heterogeneity.

A high level of statistical heterogeneity was observed in the level of adverse events ($I^2=90.1\%$) (Figure 4), peripheral neuropathy ($I^2=81.7\%$) and anaemia ($I^2=76.6\%$) across studies. A meta-regression was introduced to explore the heterogeneity between studies. This evaluated the impact of study characteristics on the outcomes. The following

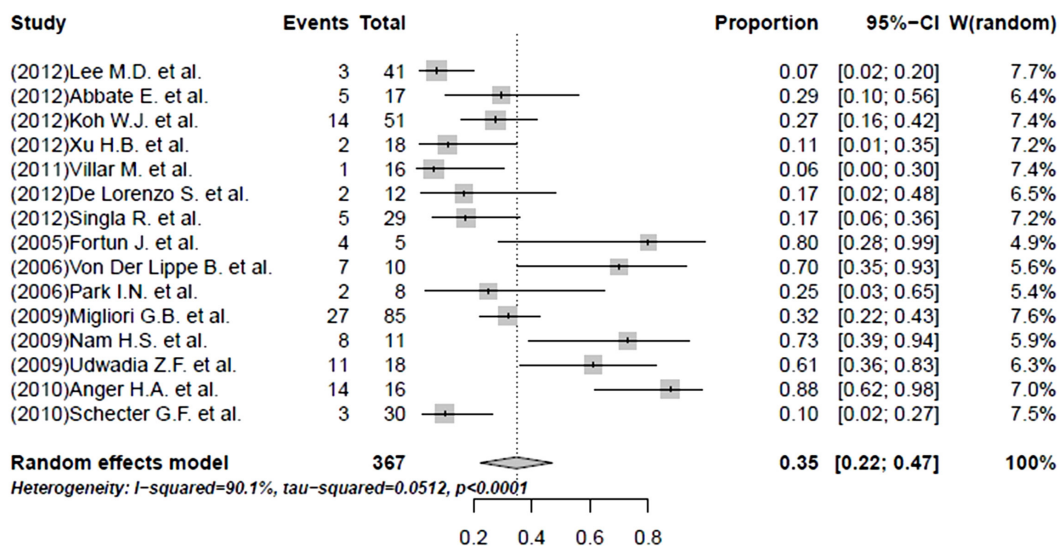


Figure 4 Forest plot showing the proportions of patients who interrupted their treatment owing to adverse events.

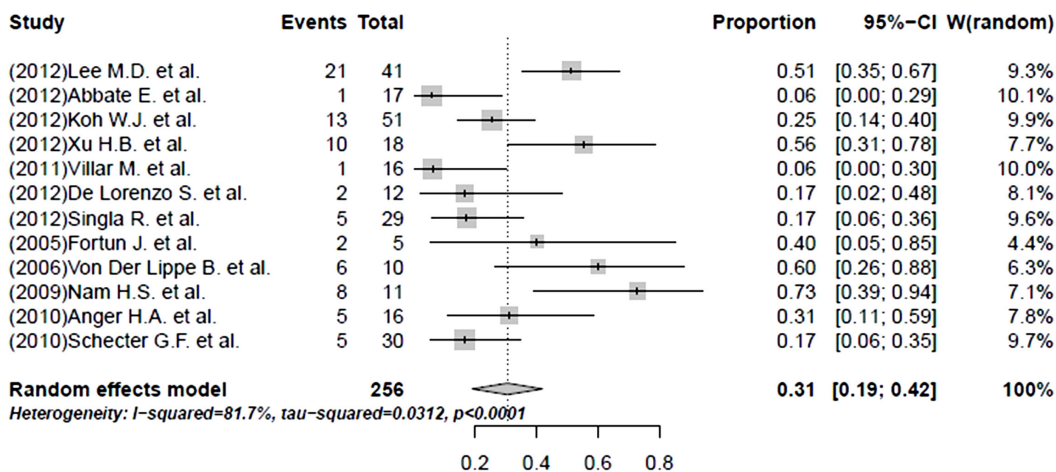


Figure 5 Forest plot showing the proportions of individuals affected by peripheral neuropathy in the enrolled studies.

variables for each study were assessed: (I) study design; (II) pediatric patients; (III) daily linezolid dose; (IV) control group; and (V) sample size. The results of the exploration of this heterogeneity are shown in Table 6. No significant differences were shown (Table 6).

Discussion

In this systematic review and meta-analysis we sought to evaluate the effectiveness and safety of linezolid as salvage treatment of patients with DR-TB. The pooled analysis showed that linezolid was associated with a promising

favorable outcome in 83% of treated patients and sputum conversion in 89% of them. The findings of the analysis were strengthened by the fact that linezolid was added in the regimen after treatment with first or second line agents had failed. Compared with previous meta-analyses, the inclusion of more clinical studies and a larger sample size (approximately 70% more patients were included) in this analysis allowed a more precise assessment of data regarding the effectiveness and safety of linezolid-containing regimens (39,40). Finally, the addition of a small RCT added further accreditation to the analysis. In addition, we explored the possible origin of heterogeneity, an aspect not previously addressed.

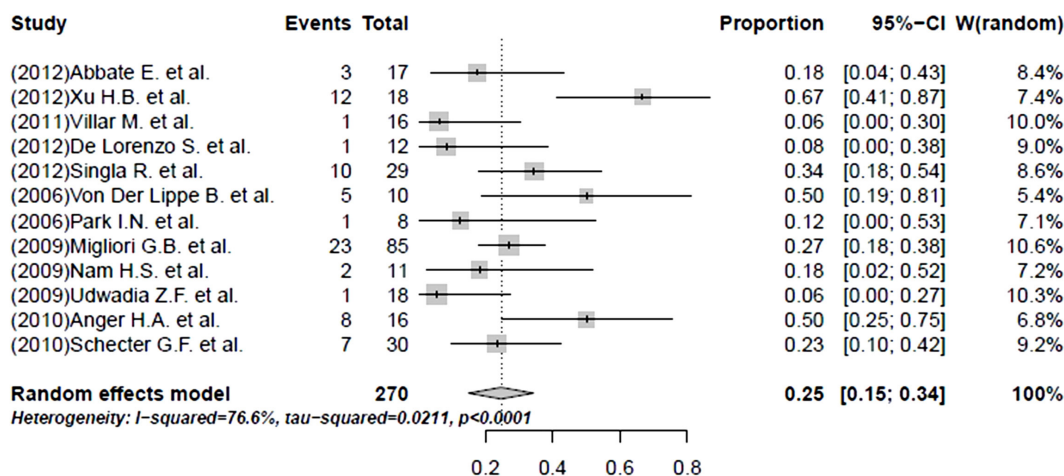


Figure 6 Forest plot showing the proportions of individuals affected by anaemia in the enrolled studies.

Table 6 Exploration of heterogeneity (meta-regression): change in adverse events, peripheral neuropathy and anaemia

Variables	Univariate P value		
	Adverse events	Peripheral neuropathy	Anaemia
Study design	0.460	0.710	0.157
Pediatric patients	0.533	0.301	0.845
Daily linezolid dose	0.926	0.108	0.059*
Control group	0.873	0.554	0.765
Sample size	0.414	0.236	0.759

*, P value <0.1 was defined as statistically significant for a meta-regression.

Effectiveness

The pooled rate of culture conversion reached almost 90% ($I^2 < 50\%$). The pooled proportion of the patients who experienced favorable outcomes was 83%, a figure higher than the treatment outcome from a recent meta-analysis of patients with DR-TB (67.99%; 95% CI, 58.00–78.99%) (39). This high level of treatment success may not be solely attributed to linezolid use but may be partly a reflection of the combination of drugs in these anti-TB regimens. All the patients included were receiving treatment with first- and second-line drugs for at least a month; data regarding specific antibiotics administered concurrently with linezolid were not available in the included studies. Furthermore, this might represent a form of publication bias. The WHO reports that the proportion of favorable outcome in patients

TB was 87% in 2011. The respective proportion for patients with MDR-TB was 48% in 2010, while only approximately 30% of countries achieved a favorable outcome higher than 75% (2). Furthermore, the estimated mortality for MDR-TB was around 38%, while these studies reported a much lower mortality (approximately 10%). Thus, it is possible that data from settings where the effectiveness of linezolid was not that pronounced have not become publicly available. However, the RCT included in the analysis showed a sputum conversion of 87% at 6 months, suggesting that when linezolid is administered such a response may be feasible (33). In this RCT, patients were randomized to immediate or late prescription of linezolid and 4 months later were re-randomized to lower linezolid dose. Patients who received linezolid immediately were more likely to have culture conversion at 4 months than patients who received linezolid at two months (79% vs. 35%, P value =0.001).

There was no significant difference in favorable outcome between the group receiving daily linezolid doses of ≤ 600 or >600 mg. However, more patients completed treatment in daily linezolid dose >600 mg, while higher mortality and lower failure rate (P value <0.001) was found in the high dose group. We were unable to study why these differences were observed. We could assume that patients assigned to higher daily doses had more severe or unresponsive forms of TB because more patients in this group had an operation for their condition than in the lower dose group (although the difference was not significant). On the other hand, more patients in the lower dose group had HIV (although they

were few in absolute numbers) and more patients had XDR TB. Data from RCTs regarding the optimal linezolid dose for DR-TB are not currently available.

The 35% incidence of major adverse effects requiring discontinuation or dose reduction of linezolid found in our analysis confirms the serious limitations of linezolid-containing treatments that were found in a previous works (40). In addition, a higher rate of toxicity in the hematopoietic system and a lower percentage of nervous toxicity (P value <0.01) were found in the group with higher linezolid dose. Furthermore, patients who received lower linezolid doses, received treatment for a longer period than those who were prescribed higher ones. Therefore, it seems that toxicity in hematopoietic system (myelosuppression) appeared to be more dose-dependent (41), while nervous system toxicity was duration-dependent (peripheral and optic neuropathy) (42,43). In accordance to the findings of this meta-analysis, the single available RCT reported that anemia developed mainly during the first 4 months, when patients were receiving mainly 600 mg daily, while neuropathy (optic and peripheral) developed mainly after 5 months of treatment, when most of patients were taking 300 mg daily (33).

The WHO suggested that the primary reasons for DR-TB are lower doses, and shorter periods of treatment or wrong antibiotics followed by transmission of DR-TB to close contacts. In addition, transmission due to diagnostic delays, and inadequate infection control programs have led to DR-TB becoming an increasing global health problem (2). Therefore, countries should be equipped to provide free access, quality medical care for M/XDR-TB among other interventions and try to improve diagnosis of latent TB infected individuals to achieve control and eventual elimination of TB (44,45). In addition, as one part of the care of patients with TB, therapeutic drug monitoring (TDM) may help the clinician make informed decisions regarding the timely adjustment of drug therapy (46). Especially, patients with M/XDR-TB, who are at risk of drug-drug interactions or have concurrent disease states, benefit more from TDM by reducing the dose of second line-drugs in order to reduce both adverse events and the cost of the drugs.

Limitations of our study

Our study was subject to several limitations. First of all, as the majority of the enrolled studies had some methodological limitations (e.g., non-randomized and

retrospective studies), selection bias and publication bias could not be avoided in original studies. We acknowledged the risks of such biases by using a random-effect model which can be employed to control for fixed but unobserved heterogeneity (R>50%). Second, the combined results were influenced by some unpublished data in part of the clinical trials. For instance, two studies did not show the outcome of sputum culture conversion (25,27), and three studies did not record the total rate of adverse effects (27,28,34). Third, owing to the observational nature of the most of enrolled studies, the effectiveness of linezolid was not weighted for some confounding factors. The most pronounced of them was the lack of data regarding the specific antibiotics contained on the treatment regimens. (e.g., drug combination regimens).

Conclusions

In conclusion, the available data suggest that linezolid is a promising and viable option for treating DR-TB patients. However, doctors should carefully weigh up the benefits and drawbacks of using a linezolid-containing regimen according to the specific needs of individual patients. Although some studies recommend that dose reduction may sustain effectiveness and limit the adverse effect of myelosuppression (47), toxicity to the nervous system, triggered by prolonged use of linezolid, should always be considered. Meanwhile, patients being currently treated with linezolid need to be carefully monitored so that appropriate and timely intervention may be taken if adverse effects occur. Adequately powered RCTs can provide more valid conclusions regarding optimal doses and duration of linezolid treatment.

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