Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis

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_____ S U M M A R Y

BACKGROUND: Current treatment for drug-resistant tuberculosis (DR-TB) is inadequate, and outcomes are significantly poorer than for drug-susceptible TB, particularly for patients previously treated with second-line drugs, treatment failures or extensively drug-resistant (XDR-) TB patients (complicated DR-TB). Linezolid is not recommended for routine DR-TB treatment due to the lack of efficacy data, but is suggested for patients where adequate second-line regimens are difficult to design.

OBJECTIVE: To conduct a systematic review and meta-analysis to assess existing evidence of efficacy and safety of linezolid for DR-TB treatment.

METHODS: We searched PubMed, Embase and abstracts from World Conferences of The Union for studies published through February 2011. We included all studies in which linezolid was given systematically to DR-TB patients and where treatment outcomes were reported.

RESULTS: A total of 11 studies were included in our review, representing 148 patients. The pooled proportion for treatment success was 67.99% (95%CI 58.00–78.99, τ^2 129.42). There were no significant differences in success comparing daily linezolid dose (≤600 vs. >600 mg) and mean linezolid duration (≤7 vs. >7 months). The pooled estimate for the frequency of any adverse events was 61.48% (95%CI 40.15–82.80), with 36.23% (95%CI 20.67–51.79) discontinuing linezolid due to adverse events.

CONCLUSION: Treatment success with linezolid was equal to or better than that commonly achieved for uncomplicated DR-TB, and better than previous reports for previously treated patients and those with XDR-TB. While data are limited, linezolid appears be a useful drug, albeit associated with significant adverse events, and should be considered in the treatment of complicated DR-TB.

KEY WORDS: linezolid; tuberculosis; resistance

DRUG-RESISTANT TUBERCULOSIS (DR-TB) is now found in all countries where drug susceptibility testing (DST) is available.[1] Of the estimated 440 000 cases of multidrug-resistant TB (MDR-TB) emerging each year, at least 10% are believed to be resistant to additional second-line anti-tuberculosis drugs and can be defined as extensively drug-resistant TB (XDR-TB). Treatment outcomes, even under optimal conditions, are relatively poor for MDR-TB compared to drug-susceptible TB, and are substantially poorer for XDR-TB.[2–4]

The World Health Organization (WHO) reports that among 7063 patients from 13 countries who initiated second-line treatment for MDR-TB in 2007, only 37% were successfully treated and 20% either died or failed treatment.[5] Similarly poor outcomes are reported for XDR-TB patients, many of whom were MDR-TB treatment failures.[3,6] Treatment options for patients in whom second-line treatment for MDR-TB has failed or those who have XDR-TB are extremely limited. Treatment often relies on a set of drugs with poorly established efficacy and severe adverse event profiles.[7] Poor efficacy and tolerability leads to treatment discontinuation in many settings, which carries the risk of increased mortality and transmission of highly resistant strains.

Linezolid is an oxazolidinone, a relatively new class of antibiotic primarily used for the treatment of gram-positive bacterial infections. Linezolid has demonstrated high in vitro antibacterial activity against _Mycobacterium tuberculosis_,[8,9] and has been used to treat complicated cases of resistant TB in several programmes.[10–12] Given that patients with refractory and/or XDR-TB have few treatment options, linezolid may well be a useful addition to the armamentarium. However, linezolid is a toxic drug with significant side effects, including severe neuropathies and haematological adverse events.[13] While labelled use of linezolid is restricted to 28 days, with dosage at 600 mg twice daily, DR-TB requires a much longer treatment duration, often for ≥2 years, and therefore carries an increased likelihood of severe adverse

events. The balance between potential efficacy and drug toxicity has led some to explore a dose reduction for linezolid in the treatment of DR-TB, but experience to date is limited and fragmented. To assess this further, we reviewed the existing evidence of safety and efficacy of linezolid for the treatment of DR-TB.

METHODS

This systematic review was conducted according to the guidelines for reporting systematic reviews of observational studies by the MOOSE (Meta-analysis of Observational Studies in Epidemiology) group.[14]

Search strategy and selection criteria

We searched PubMed and Embase from January 2000 (when linezolid was first approved for use for indications other than TB) to February 2011 using the key words 'linezolid', 'oxazolidinone' and 'tuberculosis'. We also searched for relevant abstracts of all electronically retrievable abstracts of the World Conferences on Lung Health of The Union (from 2004 to 2010). Reference lists of all retrieved articles and selected review articles were also searched for additional references. All potentially eligible articles were reviewed for inclusion by both authors.

Studies were included if linezolid was used as treatment for MDR-TB and final treatment outcomes were available for at least some of the patients. Case series with ⩽3 cases were excluded to limit potential outcome reporting bias. Studies were excluded if their study population comprised only patients included in a later study, or if authors reported 'substantial overlap' when contacted. No language restrictions were applied.

Data extraction

Data were extracted according to a pre-defined extraction form by the first author and verified by the second author. The following data were extracted: first author, publication year, study setting, study design, observation period, number of patients treated, patient inclusion criteria, drug resistance profile, prior treatment with second-line drugs, description of treatment regimen used in conjunction with linezolid, human immunodeficiency virus (HIV) status, starting dose of linezolid, duration of linezolid treatment and treatment outcomes. Linezolid dose was recorded as the initial starting dose, except when the regimen specified a higher lead-in dose for a set period of less than one month. Additional data on the description, incidence, timing and outcome of adverse events were also extracted. Where data on linezolid dose, dosing strategy and HIV infection were missing, and in the case of duplicate reports, authors from five studies were contacted to ascertain missing data and the extent of overlap between studies.

We assessed the following factors as determinants of methodological quality: dose of drug reported, use of individualised treatment regimens guided by DST, definition of treatment success, availability of higher generation fluoroquinolones (used for at least one patient), hospitalisation at initiation of linezolid treatment, availability of DST for linezolid, availability of adjunct surgery and whether treatment was provided free of charge for patients. The definition of treatment success utilised was considered appropriate if it was rated as similar to that recommended by the WHO: completion of treatment with at least five negative cultures in the last 12 months of therapy or completion of therapy without evidence of treatment failure.[7]

Data analysis

We calculated point estimates and 95% confidence intervals (CIs) for the proportion of patients achieving treatment success and the frequency of adverse events; our denominator included all patients who received linezolid irrespective of duration. The variance of the raw proportions was stabilised using a Freeman-Tukey type arcsine square-root transformation,[15] and estimates were pooled using a DerSimonian-Laird random effects model.[16] We calculated the τ^2 statistic to assess the proportion of overall variation attributable to between-study heterogeneity, as this is less affected by the number of studies than the more commonly used I^2 statistic.[17] Outcomes were stratified according to dose of drug used and the potential effect of duration of treatment. The definition of treatment success was assessed in univariate sensitivity analyses. All P values are two-sided, and a $P < 0.05$ was considered significant. Analyses were conducted using Stata (version 11, Stata Corp, College Station, TX, USA) and StatsDirect (version 2.5.2, StatsDirect Ltd, Cheshire, UK).

RESULTS

Our search strategy yielded 270 journal article abstracts, which ultimately yielded 49 full-text articles for review and 11 studies for final inclusion (Figure 1). The search of conference abstracts yielded five abstracts, but none reported final treatment outcomes. Of the full-text articles reviewed, two studies were excluded as they included patient data reported in subsequent studies.[18,19]

Study characteristics for the 11 included studies are summarised in Table 1.[10–12,20–27] A total of 218 patients received linezolid, of whom 148 had evaluable outcomes; the remainder were reported to have been still receiving treatment at the time of publication. All patients were adults, and all were infected with MDR-TB, of whom at least 62 (28%) were infected with XDR-TB strains. Prior TB treatment with first- and/or second-line treatment was variably reported, although several studies[12,20,21] reported median durations of
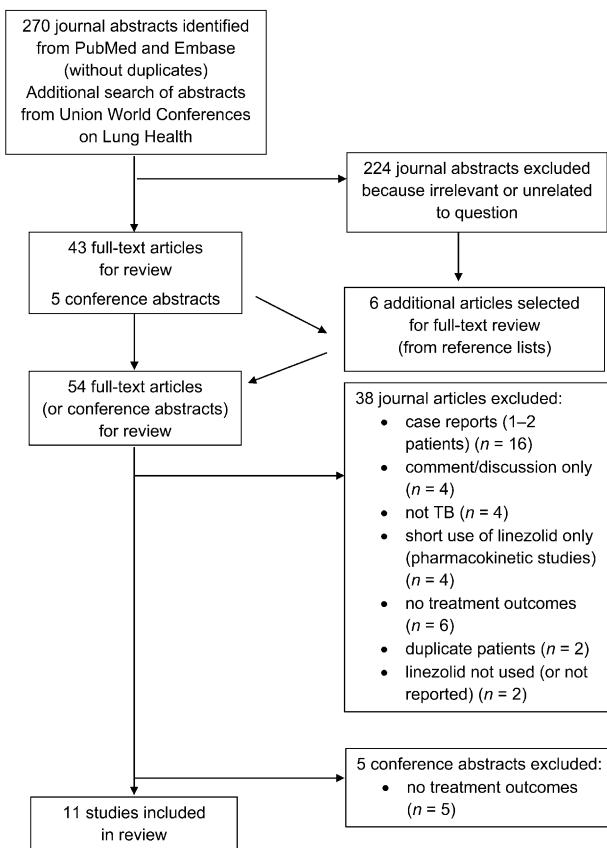
Figure 1 Diagram of abstract review and study inclusion. TB = tuberculosis.

prior treatment of years, compared to months, and previous second-line treatment was reported to have either failed or resulted in relapse for 50 patients. Indications for linezolid use included one or more of the following: failure of previous second-line treatment, use in 'salvage' regimens, the presence of extensive second-line drug resistance (variably defined, but including XDR-TB), or inability to tolerate other second-line medications. Concurrent HIV infection was reported for only eight patients (5% of total).

Linezolid dose varied considerably across studies, both at treatment initiation and after adjustment in the case of adverse events attributable to linezolid. The starting dose ranged between 300 and 1200 mg daily. The higher daily dose of 1200 mg was always delivered twice daily, whereas lower doses were given either singly or twice daily.

Overall, reporting of studies was generally poor. Only one study reported whether patients were hospitalised to receive linezolid treatment.[23] Three studies did not report treatment success according to the WHO definition,[20,23,26] and only two studies reported whether TB treatment including linezolid was provided free of charge[10,12] (Table 2). However, although reporting was poor, the quality of treatment provided was judged to be good; all studies used individualised treatment regimens guided by DST, and higher gener-

ation fluoroquinolones were reported to be available in over half of all studies. Table 2 shows the factors assessed as determinants of methodological quality.

Treatment success

Of the 148 patients with evaluable outcomes, 107 were successfully treated, giving an overall pooled proportion of treatment success of 67.99% (95%CI 58.00–78.99), with a moderate degree of heterogeneity, as expected for observational studies (τ^2 129.42; Figure 2). Among the 41 patients with poor outcomes, 18 died, treatment failed in 11, 10 defaulted and 2 were reported as a poor outcome without specification. The total duration of linezolid treatment varied considerably both within and across studies, ranging from 1 week to 28 months (Table 1).

In sensitivity analysis, the estimates of treatment success did not differ significantly from the overall estimate if only studies using a definition of treatment success rated as similar to WHO recommendations were included ($P = 0.81$). The success of treatment did not differ in studies where linezolid was given for a mean duration of $\leqslant 7$ months (67.8%, 95%CI 58.0–78.0) compared to studies where linezolid was given for >7 months (66.9%, 95%CI 52.0–81.4, $P = 0.92$), and there was no significant difference in the pooled estimates for treatment success between studies that used $\leqslant 600$ mg daily (66.9%, 95%CI 53.7–80.1) and studies that used >600 mg (61.6%, 95%CI 36.6–86.7, $P = 0.7$).

Culture conversion

Nine studies reported the proportion of patients who had converted sputum cultures from positive to negative during linezolid treatment: the pooled proportion was 97.86% (95%CI 95.19–100, τ^2 0). As the majority of these studies used doses of $\leqslant 600$ mg, a subgroup analysis by dose was not done.

Adverse events

All but one study reported overall rates of adverse events attributable to linezolid. The frequency of adverse events ranged from 30.63% (95%CI 15.93–47.72) to 79.32% (53.04–96.46), with an overall pooled proportion of 61.48% (95%CI 40.15–82.80; Figure 3). The most commonly reported adverse events were neuropathies (peripheral and optic) and bone marrow suppression, particularly severe anaemia, often requiring transfusion. Pooled proportions of the frequency of neuropathy and bone marrow suppression were respectively 36.12% (95%CI 19.09–53.16) and 28.47% (95%CI 14.80–42.14; Figure 3). The proportion of patients in whom linezolid was stopped due to adverse events ranged from 5.84% (95%CI 0.23–18.15) to 79.32% (95%CI 53.04–96.46) across nine studies, giving an overall pooled proportion of 36.23% (95%CI 20.67–51.79); the lowest rate was reported in the one study with a

Table 1 Description of included studies

Author, year, reference	Country	Study type	Inclusion criteria	No. given LZD	HIV infection	Daily LZD dose mg/day	LZD treatment duration, months	Culture conversion	No. (evaluable outcomes)	Treatment success n (%)
Fortun, 2005[22]	Spain	Retrospective case series	All consecutive MDR-TB patients treated with LZD between 1999–2004	3*	1 HIV-negative, others unknown	1200	Mean 12, median 11, range 4–24	3 of 3	2	1 (50)
von der Lippe, 2006[23]	Norway	Case series	All MDR-TB patients treated with LZD between 1998–2002	10	1 HIV-positive	1200	Mean 5, median 4, range 2–10	NR	10	9 (90)
Park, 2006[12]	Korea	Prospective non-randomised case series	MDR-TB patients who had failed at least 3 previous treatment cycles, with good adherence, given LZD from 2003	8	All HIV-negative	600	Mean 11, median 9, range 3–18	8 of 8	3	1 (33)
Yew, 2008[24]	Hong Kong	Retrospective case series	All MDR-TB patients given LZD between 2005 and 2008	6	All HIV-negative	1200	Mean 2, range <1–7	4 of 4	4	1 (25)
Jeon, 2009[25]	Korea	Retrospective case series	All XDR-TB cases diagnosed between 2001 and 2005	7	All HIV-negative	600	Mean 7, median 6, range 4–12	NR	7	5 (71)
Koh, 2009[21]	Korea	Retrospective case series	MDR-TB patients with failure to respond to second-line treatment given LZD between 2007 and 2008	24	All HIV-negative	300	Median 12	22 of 24	6	4 (67)
Migliori, 2009[11]	Belarus, Germany, Italy, Switzerland	Retrospective case series	MDR-TB cases diagnosed in participating centres given LZD between 2001 and 2007	85	3 HIV-positive	600–1200	Mean 7, median 3	74 of 85	46	36 (78)
Nam, 2009[20]	Korea	Retrospective case series	MDR-TB patients with failure to respond to second-line treatment who were given LZD	11	All HIV-negative	600	Mean 7, median 5, range 3–24	9 of 11	11	6 (55)
Udwadia, 2009[26]	India	Prospective non-randomised case series	All MDR-TB cases who received LZD between 2004 and 2007	18	All HIV-negative	600	Mean 21	NR	18	11 (61)
Anger, 2010[10]	USA	Retrospective case series	All MDR-TB patients given LZD for ≥1 month between 2000 and 2006	16	3 HIV-positive	400–1200	Mean 15, median 17, range 1–29	11 of 11	16	11 (69)
Schecter, 2010[27]	USA	Retrospective case series	All MDR-TB cases treated with LZD between 2003 and 2007	30	17 HIV-negative, others unknown	600	Mean 19, median 22, range 1–36	29 of 29	25	22 (88)

* 2 patients infected with *M. bovis* were excluded.
LZD = linezolid; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant; NR = not reported.
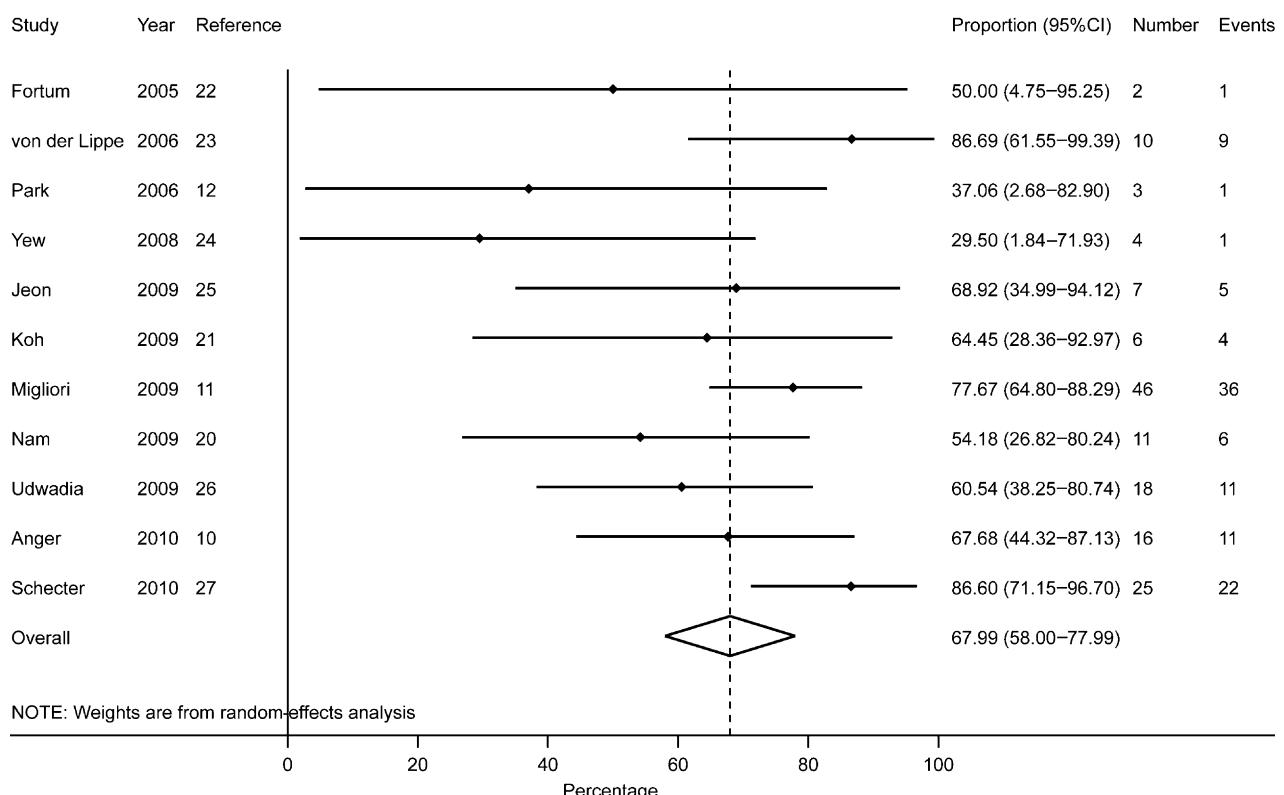
Table 2 Methodological quality assessment

Author, year, reference	Dose reported	Individualised treatment regimens guided by DST	Availability of higher generation fluoroquinolones	Hospitalisation at initiation of LZD treatment	DOT during treatment	DST for LZD available	Definition of treatment success similar to WHO	All treatment given free of charge to patients	Adjunct surgical resection available
Fortun, 2005[22]	Yes	Yes	No	NR	NR	Yes	Yes	NR	NR
von der Lippe, 2006[23]	Yes	Yes	No	Yes	Yes	Yes	No	NR	NR
Park, 2006[12]	Yes	Yes	Yes	NR	NR	Yes	Yes	No	NR
Yew, 2008[24]	Yes*	Yes	NR	NR	NR	NR	Yes	NR	NR
Jeon, 2009[25]	Yes*	Yes	Yes	NR	No	No	Yes	NR	Yes
Koh, 2009[21]	Yes	Yes	Yes	NR	NR	Yes	Yes	NR	Yes
Migliori, 2009[11]	Yes	Yes	NR	NR	NR	NR	Yes	NR	NR
Nam, 2009[20]	Yes	Yes	Yes	NR	NR	Yes	No	NR	Yes
Udwadia, 2009[26]	Yes	Yes	NR	NR	NR	NR	NR	NR	NR
Anger, 2010[10]	Yes	Yes	Yes	NR	Yes (6 months)	Yes	Yes	Yes	Yes
Schecter, 2010[27]	Yes	Yes	Yes	NR	Yes	NR	Yes	NR	Yes

*Data provided by authors.
DST = drug susceptibility testing; LZD = linezolid; DOT = directly observed treatment; WHO = World Health Organization; NR = not reported.

starting dose of linezolid of 300 mg/day for the majority of patients.[21] One study did not describe adverse events attributable to linezolid,[25] and one study, although it reported significant adverse events attributed to linezolid, did not state in how many patients treatment with linezolid was discontinued due to adverse events.[26] Overall, adverse events were the main reason for discontinuation of linezolid prior to treatment completion, although one study reported that treatment was discontinued after 3 months for some patients due to limited drug availability.[11]

Eight studies reported adverse events according to the dose of linezolid. A sensitivity analysis of the frequency of adverse events among patients receiving a linezolid dose of $\leqslant$600 mg daily compared to those receiving >600 mg daily suggests a trend towards a lower frequency of adverse events among patients receiving lower doses: 34.40% (95%CI 23.02–45.77) for $\leqslant$600 mg vs. 49.85% (37.31–62.38) for >600 mg ($P = 0.07$). The proportion of adverse events necessitating treatment discontinuation was significantly different by dose: 29.49% (95%CI 3.24–55.74) for

Study	Year	Reference	Proportion (95%CI)	Number	Events
Fortum	2005	22	50.00 (4.75–95.25)	2	1
von der Lippe	2006	23	86.69 (61.55–99.39)	10	9
Park	2006	12	37.06 (2.68–82.90)	3	1
Yew	2008	24	29.50 (1.84–71.93)	4	1
Jeon	2009	25	68.92 (34.99–94.12)	7	5
Koh	2009	21	64.45 (28.36–92.97)	6	4
Migliori	2009	11	77.67 (64.80–88.29)	46	36
Nam	2009	20	54.18 (26.82–80.24)	11	6
Udwadia	2009	26	60.54 (38.25–80.74)	18	11
Anger	2010	10	67.68 (44.32–87.13)	16	11
Schecter	2010	27	86.60 (71.15–96.70)	25	22
Overall			67.99 (58.00–77.99)		

NOTE: Weights are from random-effects analysis

Percentage

Figure 2 Plot of treatment success, individual and pooled (random effects).

Study	Year	Reference		Proportion (95%CI)	Number	Events
Any						
Fortum	2005	22		62.94 (17.10–97.32)	3	2
von der Lippe	2006	23		68.27 (39.24–91.10)	10	7
Park	2006	12		72.40 (40.61–94.96)	8	6
Yew	2008	24		64.45 (28.36–92.97)	6	4
Koh	2009	21		37.99 (20.36–57.44)	24	9
Migliori	2009	11		41.28 (31.14–51.80)	85	35
Nam	2009	20		79.32 (53.04–96.46)	11	9
Udwadia	2009	26		60.54 (38.25–80.74)	18	11
Anger	2010	10		98.51 (87.58–98.68)	16	16
Schecter	2010	27		30.63 (15.93–47.71)	30	9
Subtotal				61.48 (40.15–82.80)		
Treatment discontinuation						
Fortum	2005	22		37.06 (2.68–82.90)	3	1
von der Lippe	2006	23		68.27 (39.24–91.10)	10	7
Park	2006	12		27.60 (5.04–59.39)	8	2
Yew	2008	24		64.45 (28.36–92.97)	6	4
Koh	2009	21		5.84 (0.23–18.15)	24	1
Migliori	2009	11		22.67 (14.50–32.06)	85	19
Nam	2009	20		79.32 (53.04–96.46)	11	9
Anger	2010	10		32.32 (12.87–55.68)	16	5
Schecter	2010	27		11.24 (2.73–24.51)	30	3
Subtotal				36.23 (20.67–51.79)		
Neuropathy						
Fortum	2005	22		6.70 (5.12–46.64)	3	0
von der Lippe	2006	23		59.13 (30.19–84.97)	10	6
Park	2006	12		50.00 (19.61–80.39)	8	4
Yew	2008	24		35.55 (7.03–71.64)	6	2
Koh	2009	21		33.99 (17.11–53.30)	24	8
Migliori	2009	11		4.05 (0.94–9.21)	85	3
Nam	2009	20		79.32 (53.04–96.46)	11	9
Udwadia	2009	26		39.46 (19.26–61.75)	18	7
Anger	2010	10		44.11 (22.04–67.48)	16	7
Schecter	2010	27		20.94 (8.70–36.76)	30	6
Subtotal				36.12 (19.09–53.16)		
Bone marrow suppression						
Fortum	2005	22		62.94 (17.10–97.32)	3	2
von der Lippe	2006	23		50.00 (22.14–77.86)	10	5
Park	2006	12		16.28 (0.78–45.67)	8	1
Yew	2008	24		35.55 (7.03–71.64)	6	2
Koh	2009	21		5.84 (0.23–18.15)	24	1
Migliori	2009	11		27.32 (18.48–37.18)	85	23
Nam	2009	20		20.68 (3.54–46.96)	11	2
Udwadia	2009	26		7.69 (0.31–23.47)	18	1
Anger	2010	10		79.49 (57.74–94.70)	16	13
Schecter	2010	27		7.99 (1.22–19.92)	30	2
Subtotal				28.47 (14.80–42.14)		

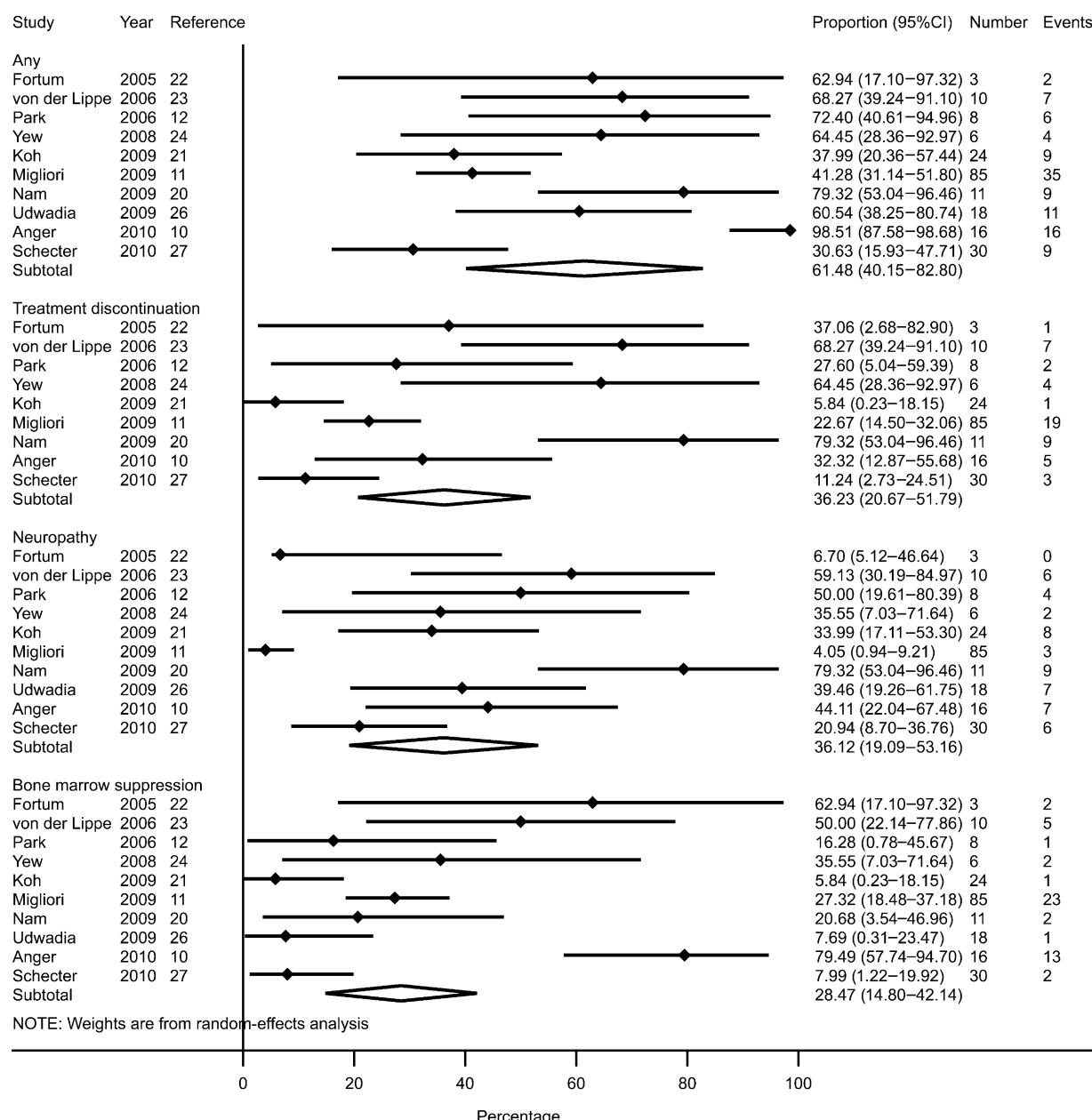NOTE: Weights are from random-effects analysis

Figure 3 Plot of adverse events, any, neuropathies and bone marrow toxicity, and discontinuation of linezolid due to adverse events.

≤600 mg vs. 60.75% (95%CI 42.69–78.81) for >600 mg ($P = 0.05$).

DISCUSSION

The poor safety profile associated with long-term use of linezolid and the lack of evidence of clinical efficacy has led linezolid to be used primarily for patients considered to have 'intractable' or 'complicated' DR-TB, including those in whom treatment using recommended second-line drugs has failed or those with XDR-TB, with susceptibility to few available drugs. This systematic review and meta-analysis has shown a high proportion of treatment success when linezolid is used to treat these complicated MDR-TB patients.

Our pooled proportion of 68% treatment success is in line with outcomes for MDR-TB treatment in general: two recent meta-analyses both reported a pooled proportion of 62% treatment success for patients with uncomplicated MDR-TB.[2,4]

As linezolid has been used as part of a multidrug regimen in the studies included in this review, this level of treatment success may not be solely attributed to linezolid use. A number of included studies also used higher generation fluoroquinolones that have been shown to be efficacious in DR-TB treatment, particularly for XDR-TB.[3,6] Determining the independent contribution of linezolid is therefore problematic, as is the case for any drug used for DR-TB treatment. However, in the majority of included

studies, few drugs with demonstrated susceptibility were able to be included in treatment regimens, and this patient group has been shown to have particularly poor outcomes: 44% treatment success for XDR-TB[3] and similar or lower for MDR-TB cases previously treated with second-line drugs.[28,29] The data thus suggest a significant benefit from the inclusion of linezolid in the treatment regimen.

The high frequency of adverse events is an important limitation of linezolid. Severe adverse events —predominantly neuropathies and bone marrow suppression—lead to discontinuation of linezolid in over a third of patients and dose reduction in others. Although our analysis was limited by the small number of studies resulting in a low overall sample size, our results indicate that a reduced daily dose of ≤600 mg from treatment initiation may lower the frequency of occurrence of adverse events without impacting treatment success. In particular, reducing the daily dose may reduce the impact of bone marrow suppression, particularly severe anaemia, as has been suggested previously.[12] Linezolid has been approved for use at 800–1200 mg daily for the short-term treatment of bacterial infections, and due to the relatively short half-life of 5–7 h, 12-h dosing is recommended.[30] However, there are limited data for linezolid with regard to *Mycobacterium tuberculosis*, and lower doses, potentially given once daily for longer periods, may be sufficient against TB, particularly when used in combination as multidrug regimens.

Notably, a relatively high treatment success was demonstrated in these studies, although high proportions of patients required linezolid to be discontinued early, with no significant difference in treatment success between studies in which linezolid was given for a mean duration of less than 7 months compared to longer. However, the high initial culture conversion compared to lower overall treatment success suggests that stopping treatment early may have consequences on long-term outcome. This discrepancy highlights the need for pharmacokinetic and randomised trial data to optimise dosing and duration, not only for initial culture conversion but also for final treatment outcomes.

Our systematic review is subject to several limitations. First, reporting of included patients and outcomes was not consistent across studies, and the outcome of treatment success was often not reported by important variables such as linezolid dose and duration. Second, criteria for reporting adverse events were invariably not reported, and interpretation of adverse event rates should therefore be made with caution. Third, as with any systematic review, limitations associated with potential publication bias should be considered. Statistical methods are not appropriate for the formal assessment of publication bias, but we acknowledge the risk of such bias.[31] Fourth, a proportion of patients included in the studies did not have treatment outcomes reported, the majority of whom were still receiving treatment at the time of publication. Although these patients could be still receiving treatment while remaining culture-positive (potential treatment failure), given the high level of culture conversion reported, it is more likely that these are patients who have culture-converted and are still to complete their treatment (potential treatment success). Finally, our overall sample size was small and all data were observational, resulting in low statistical precision and a moderate degree of heterogeneity. We used a random-effects model which is more appropriate for meta-analyses in which heterogeneity is anticipated, and explored potential sources of heterogeneity in a series of subgroup analyses. The fact that point estimates for treatment success were relatively consistent across studies lends further confidence to the pooled estimates.

Overall, the available data suggest that linezolid is a potentially useful drug in treating the significant proportion of MDR-TB patients in whom second-line regimens fail or who are infected with TB strains with such significant resistance as not to allow the formulation of an appropriate second-line regimen using recommended drugs. However, the high frequency of serious adverse events suggests that linezolid should be used with some caution, in settings where adverse events can be monitored and patients hospitalised if needed. Some adverse events, such as optic or peripheral neuropathy, may be irreversible and debilitating. This risk needs to be balanced against the paucity of effective treatment options for patients with DR-TB and the possibility of cure afforded by the use of linezolid, as has been done for other MDR-TB drugs with important side effects, such as kanamycin and amikacin, which are associated with significant and often irreversible hearing loss in more than a third of patients.[32]

Adverse events are not the only barriers to linezolid use for DR-TB treatment. In South Africa, where linezolid is patent protected, linezolid costs approximately US$2500 per month of treatment (at 600 mg daily). In contrast, in India, where linezolid is not patented, generic production has reduced the cost to between US$50–70/month. In addition to lower cost, the quality of linezolid preparations, and particularly non-validated generic forms, needs to be assured before more widespread use. While some progress has been made in the development of new drugs for MDR-TB, the urgent need for better treatment regimens requires that the use of existing drugs should also be pursued more thoroughly.[33] Encouragingly, at least two randomised controlled trials are underway to assess the use of linezolid in DR-TB treatment. Preliminary results are promising, with high levels of culture conversion but as yet no published treatment outcomes.[34,35] Furthermore, a new oxazolidinone 100480 (PNU-100480) has been shown to have improved

anti-tuberculosis activity[36] and is currently in Phase 1 trials for TB. The urgent need to scale up treatment for DR-TB highlights the deficiencies in currently available second-line treatment regimens for TB and underlines the urgent need to develop new drugs and use those already available, such as linezolid, more effectively.

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_____ R É S U M É

CONTEXTE : Le traitement actuel de la tuberculose à germes résistants (TB-DR) est inadéquat et les résultats sont significativement plus médiocres que dans la TB à germes sensibles aux médicaments, particulièrement chez les patients déjà traités antérieurement par les médicaments de deuxième ligne et ceux chez lesquels le traitement a échoué ou qui sont atteints d'une TB à germes ultrarésistants (TB-XDR ; TB-DR compliquée). Le linezolide n'est pas recommandé pour le traitement de routine de la TB-DR en raison de l'insuffisance de données d'efficacité, mais il est suggéré chez les patients où des régimes de deuxième ligne adéquats sont difficiles à élaborer.

OBJECTIF : Mener une revue systématique et une métaanalyse pour évaluer les évidences existantes concernant l'efficacité et la sécurité du linezolide dans le traitement de la DR-TB.

MÉTHODES : Nous avons fait des recherches dans PubMed, Embase et dans les résumés des Conférences Mondiales de L'Union concernant les études publiées jusqu'à février 2011. Nous avons inclus toutes les études dans lesquelles le linezolide avait été administré systématique-

ment à des patients TB-DR et où les résultats du traitement étaient signalés.

RÉSULTATS : Nous avons inclus dans notre revue 11 études, correspondant à 148 patients. La proportion cumulée de succès du traitement a été de 67,99% (IC95% 58,00–78,99 ; τ^2 129,42). On n'a pas observé de différence significative en matière de succès lors de la comparaison entre les doses quotidiennes de linezolide (⩽600 vs. >600 mg), ni entre les durées moyennes du linezolide (⩽7 vs. >7 mois). L'estimation cumulée de la fréquence de tout effet indésirable a été de 61,48% (IC95% 40,15–82,80), dont 36,23% (IC95% 20,67–51,79) ont dû interrompre le linezolide par suite d'effets indésirables.

CONCLUSION : Les taux de succès du traitement par le linezolide sont égaux ou même meilleurs que ceux obtenus habituellement dans la TB-DR non compliquée, et supérieurs aux observations antérieures chez les patients déjà traités ainsi que chez ceux atteints de TB-XDR. Bien que les données soient limitées, le linezolide s'avère un médicament utile. Quoi qu'associé à des effets indésirables significatifs, il devrait être pris en considération dans le traitement de la TB-DR compliquée.

_____ R E S U M E N

MARCO DE REFERENCIA: El tratamiento actual de la tuberculosis resistente a los medicamentos (TB-DR) es inadecuado y sus resultados son mucho menos favorables que los desenlaces de la TB normosensible, sobre todo en los pacientes que han recibido un tratamiento previo con antituberculosos de segunda línea, los pacientes que tuvieron un fracaso terapéutico o los pacientes con tuberculosis extremadamente drogorresistente (TB-XDR; TB-DR complicada). El linezolid no se recomienda en el tratamiento corriente de la TB-DR debido a la falta de datos sobre su eficacia, pero se propone a los pacientes en quienes es difícil de formular una pauta adecuada con medicamentos de segunda línea.

OBJETIVO: Llevar a cabo una reseña sistemática de la bibliografía y un metanálisis, con el fin de evaluar los datos existentes sobre la eficacia y la seguridad toxicológica del linezolid en el tratamiento de la TB-DR.

MÉTODOS: Se buscaron estudios publicados hasta febrero del 2011 en las bases de datos PubMed, Embase y en los resúmenes de la Conferencia Internacional sobre Salud Respiratoria de La Unión. Se incluyeron todos los estudios en los cuales se administró linezolid en forma

sistemática a los pacientes con TB-DR y se notificaron los desenlaces terapéuticos.

RESULTADOS: Se incluyeron en la reseña 11 estudios, con un total de 148 pacientes. La proporción combinada de tratamiento exitoso fue 67,99% (IC95% 58,00–78,99; τ^2 129,42). No se observaron diferencias significativas en la eficacia del tratamiento cuando se comparó la posología diaria de linezolid (⩽600 mg contra >600 mg) o el promedio de duración de su administración (⩽7 contra >7 meses). El cálculo acumulado de la frecuencia de reacciones adversas fue 61,48% (IC95% 40,15–82,80), con un 36,23% (IC95% 20,67–51,79) de interrupción del linezolid debido a estos efectos.

CONCLUSIÓN: El éxito terapéutico obtenido con el linezolid fue equivalente o mejor que el que se logra con frecuencia en la TB-DR no complicada y mejor que los informes anteriores sobre pacientes con tratamiento previo y con TB-XDR. Si bien los datos existentes son limitados, el linezolid aparece como un medicamento útil, aunque se asocie con reacciones adversas considerables y se debe considerar su administración en el tratamiento de la TB-DR complicada.