LINEZOLID IN COMPLICATED DRUG-RESISTANT TUBERCULOSIS

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ABSTRACT

BACKGROUND

The treatment for Drug-Resistant Tuberculosis (DR-TB) is not adequate and outcomes are poorer than for drug-susceptible TB, particularly for patients treated for 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 lack of efficacy data but is indicated in case where 2nd line regimens are difficult to design.

MATERIALS AND METHODS

We searched PubMed,Embase and Abstracts from World Conferences of The union for Studies published through February 2011. In these Linezolid was given systematically to DR-TB Patient and outcomes were reported.

RESULTS

A total of 11 studies were included representing 148 patients. The pooled proportion for treatment success was 67.99%. There was 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 patient and those with XDR-TB while data are limited. Linezolid appears to be a useful drug albeit associated with significant adverse events and could be considered for the treatment of complicated DR-TB.

KEYWORDS

Linezolid, Tuberculosis, Resistance.

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BACKGROUND

Linezolid is an Oxazolidinone, a relatively new class of antibiotic primarily used for treatment of Gram-positive bacterial infection. It has demonstrated high activity against mycobacterium tuberculosis invitro[1-2] and is used to treat complicated cases of resistant TB in several programmes. Given that patient with refractory and/or XDR-TB have few treatment options, Linezolid may be a useful addition to the armamentarium. However, Linezolid is a toxic drug with significant side effects including severe neuropathies and haematological side effects[3]while labelled use of Linezolid is restricted to 28 days, dose of 600 mg twice daily. DR-TB requires much longer treatment duration, often for ≥2 years and therefore carries an increased likelihood of severe adverse events.[4] The balance between potential efficacy and drug toxicity has led to explore a dose reduction for Linezolid in the treatment of DR-TB, and experience/knowledge to date is limited and fragmented.

DR-TB (Drug resistance TB) is found in almost all countries of the world globally.[5] In 2015, the World Health Organization (WHO) observed 3-9% new cases and 25% previously treated tuberculosis. There were an estimated 580,000 incident cases of MDR-TB in 2015. The countries with the largest number of MDR/RR-TB cases account for 45% of the total, maximum number of cases from Chinese, India and Russian federation. There were estimated 250,000 deaths MDR/RR-TB in 2015. More than half of these patients were in India, China and Russian Federation. By the end of 2015,(extensively drug resistant) XDR-TB had been reported in 117 countries. A total of 51% of patients with MDR-TB were resistant to fluoroquinolones or second-line injectable agents or both. An estimated 9.7% of people with MDR have XDR-TB.[6,7,8,9] Similarly, outcomes are reported to be poorer in XDR patients.[10] Poor efficacy and tolerability lead to treatment discontinuation in many settings and carries a risk of increased mortality and treatment of resistant strains.

Aims and Objectives

To assess efficacy and safety of Linezolid for complicated DR-TB treatment and observe its adverse effects.

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MATERIALS AND METHODS

This systemic review was conducted according to guidelines for reporting systematic review of observational studies by MOOSE (Meta-analysis of observational study in epidemiology group).[11]

Search Strategy and Selection Criteria

We searched PubMed and Embase from January 2000 (When Linezolid was first approved for use for indication other than TB) to February 2015 using the keywords "Linezolid", Oxazolidinone and tuberculosis. We also searched for relevant abstracts of all electronically retrievable abstracts or World Conferences on Lung Health (from 2004-15) references.

Inclusion Criteria

All potential eligible articles were reviewed for inclusion by the author. Studies were included if Linezolid was used as treatment for MDR-TB and final outcomes were available in at least some of the patients. The other inclusion criteria include data for drug resistant TB patients, prior treatment with second-line drugs, treatment regimen used for Linezolid, and HIV status (human immunodeficiency virus).

Exclusion Criteria

Case series with ≤3 cases were excluded to limit potential outcome. Studies were excluded if Linezolid was used as treatment for MDR-TB and final treatment outcomes were available for at least some of the patients. Studies were excluded if their study population comprised only patients included in a later study or if author reported 'substantial overlap' when contacted. No language restrictions were applied. Patients who received high dose Linezolid <one month were excluded.

Data Extraction

Data were extracted according to predefined extraction by the author. The following data were extracted: Publication year, study setting, study design, observation period, number of patients treated, drug-resistant patients, prior treatment with second-line drugs, description of treatment regimen used in conjunction with Linezolid, number of HIV patients, starting dose of Linezolid, duration of Linezolid treatment outcomes. Linezolid dose was recorded as initial starting dose except when the regimen specified higher loading dose for a set of period of less than one month. Additional data on the description, incidence timing and outcome of adverse events were also extracted. Where the data on Linezolid dose, dosing strategy and HIV Infection were missing, and in the cases of duplicate reports, author from five studies were contacted to ascertain missing data and the extent of overlap between studies.

We assess 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 at least on 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 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 one to twelve months of therapy or completion of therapy without evidence of treatment failure.

Data Analysis

We calculated point estimate and 95% confidence intervals (CIs) for the proportion of patient's achieving treatment success and the frequency of adverse events. Our denominator included all patients who received Linezolid irrespective of duration. The variance of proportion was stabilised using Freeman-Tukey type arcsine square root transformation.[12] Estimates were pooled using a DerSimonian-Laird random effect model.[13] We calculated the I^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 p0.05 was considered significant.

RESULTS

Our search strategy yielded 270 journal articles' abstracts which ultimately yielded 49 full text articles for review and 11 studies for final outcomes. (Figure1). The search of conference abstract yielded five abstracts but none reported final treatment outcomes. Of the full text articles reviewed, two studied were excluded as they included patient data reported in subsequent studies.[15,16]

Study characteristics for the 11 included studies are summarised in Table 1.[17,18,19,20,21,22,23,24,25,26,27] A total of 218 patients received Linezolid, of whom 148 had evaluable outcomes; the remainder were reported to have been still receiving treatment. 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[19,20,21] reported median durations of 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 include one or more of the following: failure of previous second-line treatment, use of '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 only in eight patients (5% of total).

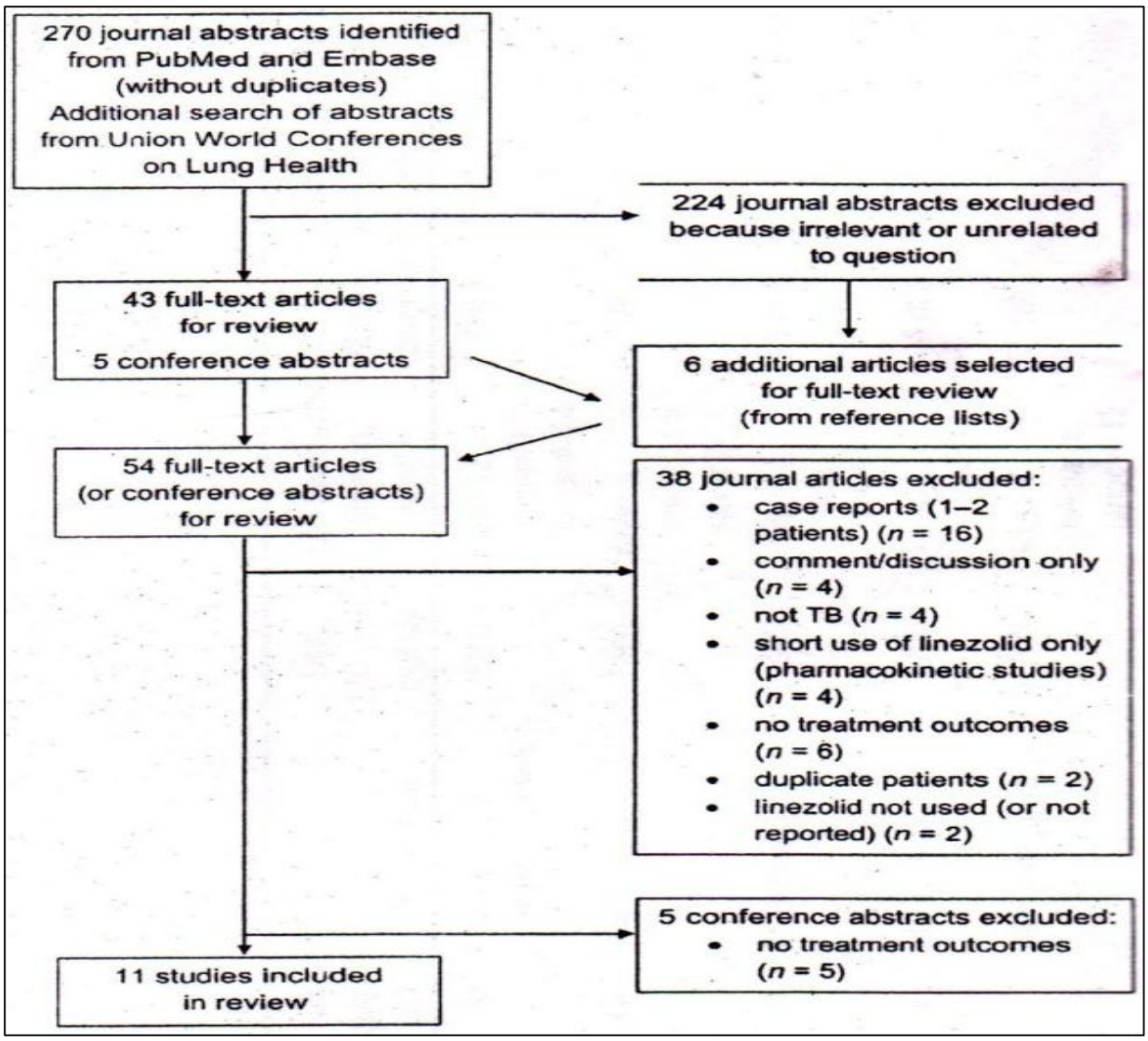

Figure 1. Diagram of Abstract Review and Study Inclusion. TB= Tuberculosis.

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 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] and only two studies reported whether TB treatment including Linezolid was provided free of charge. (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 generation fluoroquinolones reported to be available in over half of studies. Table2 shows the factors assessed as determinants of methodological quality.

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 1. Description of Included Studies

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.

Table 2. Methodological Quality Assessment

Treatment Outcomes

Of the 148 patients with evaluable outcomes, 107 were successfully treated, giving an overall pooled proportion of treatment outcomes of 67.99% (95%CI) 58.00-78.99), with a moderate degree of heterogeneity, as expected for observational studies ($\chi^2$129.42; Figure 2). In 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 (Table1).

In sensitivity analysis, the outcome did not differ significantly from the overall estimate if only studies using a definition of treatment outcomes rated as similar to WHO recommendations were included (P=0.81). The outcomes of treatment did not differ in studies where Linezolid was given

for a mean duration of ≤7 months (67.8%, 95 CI 58.0-78.0) compared to studies where Linezolid was given for >7months (66.9%, 95%CI 52.0-81.4, P=0.92), and there was no significant difference in the pooled estimate for treatment success between studies that used ≥ 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).

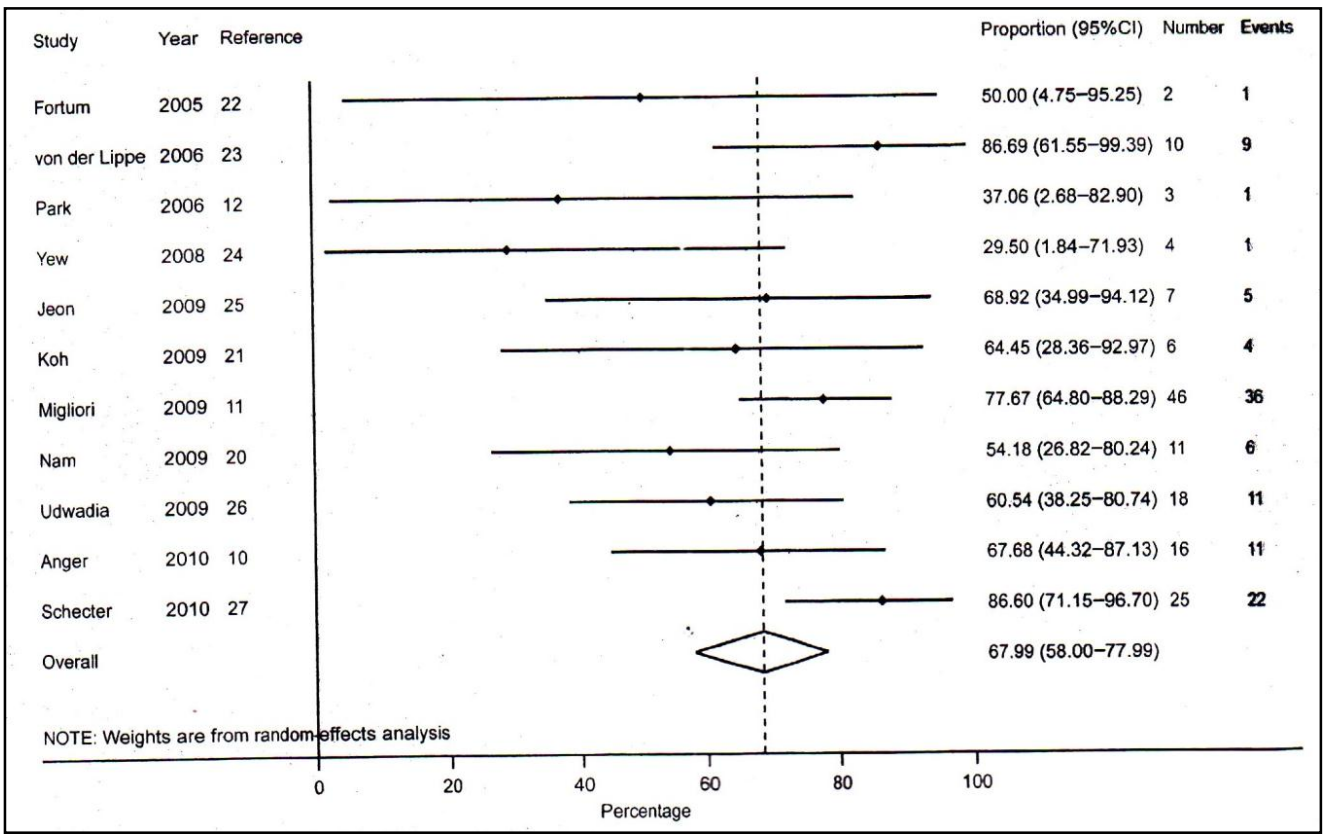

Figure 2. Plot of Treatment Success, Individual and Pooled (Random Effects)

Culture Conversion

Nine studies reported the proportion of patients with converted sputum cultures from positive to negative during Linezolid treatment: the pooled proportion was 97.86%(95%CI 95.19-100,$I^2$0). As the majority of these studies used doses of ≤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 effects 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 percentage of patients in whom Linezolid was stopped due to adverse events ranged from 5.84% (95%CI 0.23-18.15) to79.32% (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 one study with a starting dose of Linezolid of 300mg/day for the majority of patients.[21] One study did not describe adverse events to Linezolid. One study reported significant adverse events to Linezolid, but did not state in how many patients treatment with Linezolid was discontinued due to adverse events. 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.

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 ≤600 mg daily compared to those receiving >600mg daily suggests a trend towards a lower frequency of adverse events among patients receiving lower doses: 34.40% (5%CI 23.02-45.77) for ≤600 mg vs. 49.85% (37.31-62.38) for >600 mg (P=0.07).

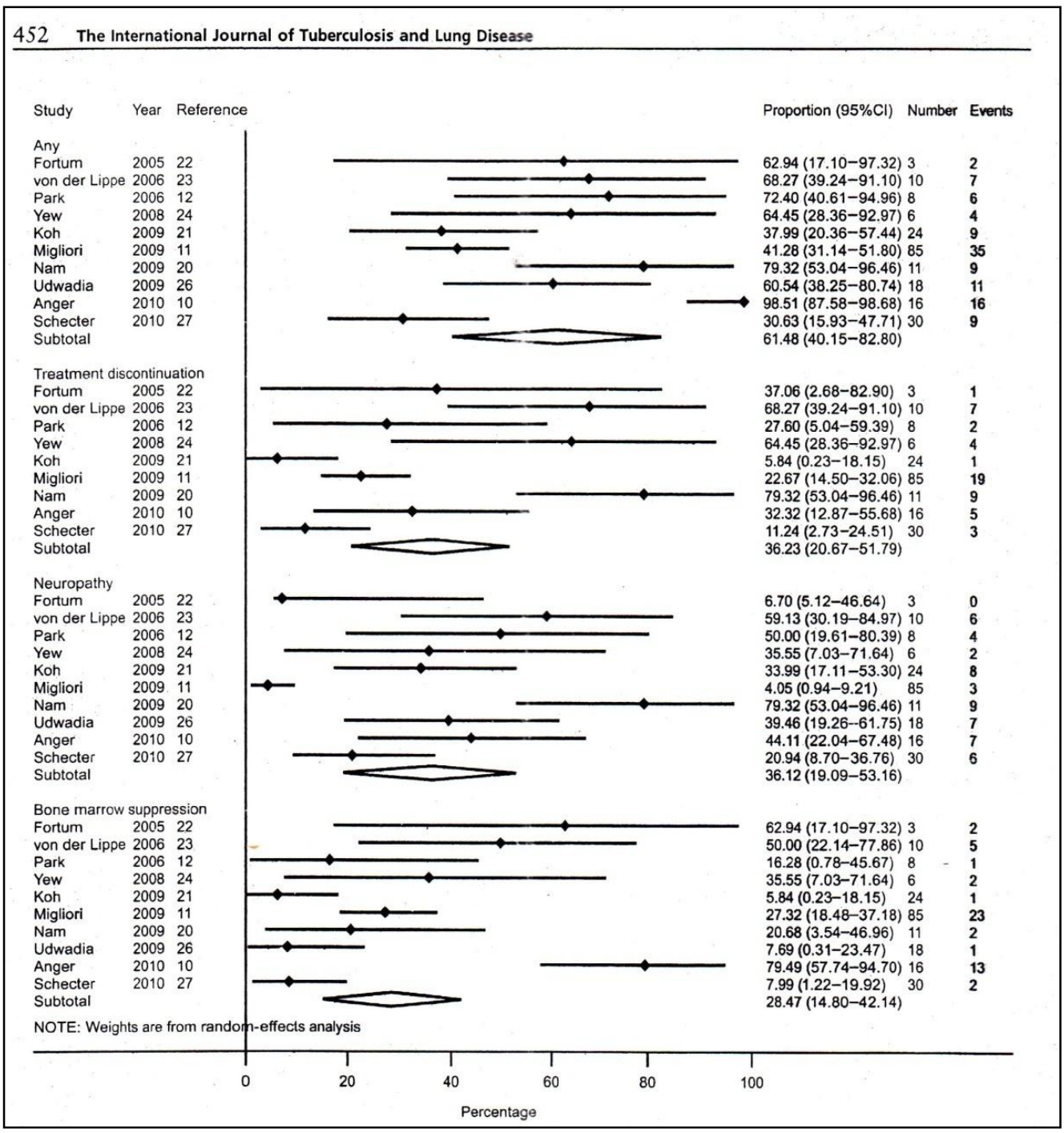

Figure 3. Plot of Adverse Events, Neuropathies and Bone Marrow Toxicity, and Discontinuation of Linezolid Due to Adverse Events

DISCUSSION

The poor safety profile 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 discussion shows a high proportion of treatment success when Linezolid is used to treat 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.

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. 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 regimen, and this patient

group has been shown to have particularly poor outcomes i.e. 44% treatment success for XDR-TB 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. (Predominantly neuropathy, bone marrow suppression). This leads to discontinuation of Linezolid in over a third of patients and dose reduction in others. Our analysis was limited by the small number of studies resulting in a low overall sample size, our results indicate that 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. Linezolid has been approved for use at 800-1200mg daily for the short-term treatment of bacterial infections, and due to the relatively short half-life of 5-7 hrs., 12-hr. 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 period may be sufficient against TB particularly when used in combination as multidrug regimen.

Notably, a high treatment success was demonstrated in these studies, although high proportion of patients required Linezolid to be discontinued early, with no significant difference in treatment success between studies in which Linezolid was given for mean duration of less than 7 months compared to longer duration. However, the high initial culture conversion compared to lower overall treatment success suggests that stopping treatment early may have consequences on longterm 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 outcomes.

Our systematic review is subject to several limitations. First reporting of included patients and outcomes was not consistent across studies, and the outcome to 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, limitation 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. Finally overall sample size was small and all data was observational resulting in low statistical suppression and a moderate degree of heterogeneity.

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 event suggests the 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 option 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 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/month (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, need to be assured before 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 and no published treatment outcomes.[34,35] Furthermore, Oxazolidinone 100480 (PNU-100480) has 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 treatments for TB and underlines the urgent need to develop new drugs and use those already available, such as Linezolid, more effectively.

CONCLUSION

The Linezolid should be used in low doses in Complicated MDR-TB in whom second-line regimens fail or who are infected with significant TB resistant bacteria as not to allow the formulation of an appropriate second-line regimen using recommended drug.

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