Eur Respir J 2012; 40: 1430–1442
DOI: 10.1183/09031936.00022912

Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis

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ABSTRACT: Linezolid is used off-label to treat multidrug-resistant tuberculosis (MDR-TB) in absence of systematic evidence. We performed a systematic review and meta-analysis on efficacy, safety and tolerability of linezolid-containing regimes based on individual data analysis.

12 studies (11 countries from three continents) reporting complete information on safety, tolerability, efficacy of linezolid-containing regimes in treating MDR-TB cases were identified based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Meta-analysis was performed using the individual data of 121 patients with a definite treatment outcome (cure, completion, death or failure).

Most MDR-TB cases achieved sputum smear (86 (92.5%) out of 93) and culture (100 (93.5%) out of 107) conversion after treatment with individualised regimens containing linezolid (median (inter-quartile range) times for smear and culture conversions were 43.5 (21–90) and 61 (29–119) days, respectively) and 99 (81.8%) out of 121 patients were successfully treated. No significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage $\leqslant$600 mg *versus* $>$600 mg). Adverse events were observed in 63 (58.9%) out of 107 patients, of which 54 (68.4%) out of 79 were major adverse events that included anaemia (38.1%), peripheral neuropathy (47.1%), gastro-intestinal disorders (16.7%), optic neuritis (13.2%) and thrombocytopenia (11.8%). The proportion of adverse events was significantly higher when the linezolid daily dosage exceeded 600 mg.

The study results suggest an excellent efficacy but also the necessity of caution in the prescription of linezolid.

KEYWORDS: Efficacy, extensively drug-resistant tuberculosis, linezolid, multidrug-resistant tuberculosis, safety, tolerability

Tuberculosis (TB) is a leading cause of morbidity and death worldwide. In the past decades cases of drug-resistant TB, particularly multidrug-resistant tuberculosis (MDR-TB; defined as *in vitro* resistance to at least isoniazid and rifampicin, the two most potent first-line drugs for TB treatment) and extensively drug-resistant TB (XDR-TB; defined as *in vitro* resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the second-line injectable drugs: amikacin, capreomycin or kanamycin), have been described in almost all countries that have been surveyed [1–3]. Management of MDR-TB and XDR-TB is still a major problem from both a clinical and public health perspective [1–5]. Evidence has shown that anti-TB treatment outcomes for ''complicated'' MDR-TB (*e.g.* those with additional resistance beyond isoniazid and rifampicin) and XDR-TB cases are still sub-optimal, highlighting an urgent need for information on safety, tolerability and efficacy of new antibiotics [6–15].

In vitro and pharmacological data suggest that linezolid, an oxazolidinone antibiotic, could be

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Received:
Feb 07 2012
Accepted after revision:
March 19 2012
First published online:
April 10 2012

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

efficacious in treating mycobacterial infections, including MDR-TB [16–21].

Nevertheless, clinical experience on linezolid has been mainly restricted to case reports and small case series including both non-tuberculous mycobacterial diseases and TB [22–29].

Due to the lack of available antibiotics to treat such difficult cases, linezolid is already used off-label to treat MDR-TB in several countries, despite the absence of randomised controlled clinical trials to assess efficacy, safety and tolerability and also large retrospective and prospective observational studies [8, 13, 15].

Data on the use of linezolid to treat MDR-TB is limited. At present, only seven cohorts published on linezolid include more than 10 cases, their size ranging between 12 and 85 cases (of which only 45 had information on efficacy) [8, 30–35].

In the recent debate surrounding the use of new anti-TB drugs [36–37], the role and contribution to treatment success of linezolid has generated much interest due to several reasons. First, the limited evidence available shows that the drug is very active against *Mycobacterium tuberculosis,* although, it has a high price. Secondly, several adverse events have been attributed to linezolid: up to 41.2% of patients experienced major adverse events (mainly anaemia, thrombocytopenia and polyneuropathy) in the largest published cohort [8]. Thirdly, the correct dose, optimising efficacy and tolerability has not yet been defined [38–40]. The possible role of linezolid in future short regimens critically depends on the answer to the following questions. What is the correct dosage and necessary duration of exposure? Is it really effective? Does its safety and tolerability allow for administration over a sufficient duration to ensure efficacy?

To further support the development of evidence-based guidance on the use of linezolid in difficult-to-treat MDR-TB and XDR-TB cases, we present the results of a systematic review and a meta-analysis on efficacy, safety and tolerability of linezolid that has been based on individual data analysis.

MATERIALS AND METHODS

Search strategy

We identified clinical studies evaluating linezolid to treat MDR-TB and XDR-TB cases.

We searched computerised bibliographic databases, PubMed and EMBASE, from January 2001 through to October 2011. In addition we checked all abstracts published over the same period in the *International Journal of Tuberculosis and Lung Disease.*

Combinations of the following search terms were used: "tuberculosis", ''multidrug-resistant tuberculosis'', ''extensively drug-resistant tuberculosis'', ''MDR'', ''XDR'', ''safety'', ''tolerability'', ''efficacy'' and ''linezolid''. We restricted our search to publications in English. Unpublished sources of data were not included, as the evaluation of their quality in absence of a peer-review process could not be ensured. We also manually searched bibliographies of retrieved articles and existing systematic reviews and meta-analyses on MDR-/XDR-TB for additional references.

Study selection

We included studies that reported complete information on safety, tolerability and efficacy of linezolid in treating culture-confirmed MDR-TB and XDR-TB cases in humans involving $\geqslant$five adult individuals (proportion of paediatric patients was required to be $<$25% of the total cohort).

The following studies were excluded: 1) case reports with $<$five cases, editorials and reviews on linezolid; 2) laboratory studies; 3) animal studies; and 4) studies where MDR-TB and XDR-TB were not confirmed by *M. tuberculosis* culture and drug susceptibility testing (DST) in quality-assured laboratories.

Studies not reporting the core pieces of information necessary for the analysis were excluded in a second round of selection (*e.g.* after failing to obtain the information from the Authors, as described in the Data extraction section). In efficacy analysis bacteriological conversion and definite outcomes were defined as described in LASERSON *et al.* [41].

For safety and tolerability analysis, variables of interest included: linezolid dose and duration of exposure to linezolid-containing regimens; existing adverse events; description of adverse events (major, defined as those requiring interruption of the drug or adjustment of the dosage, and minor) [8]; and time of occurrence of the adverse events.

Citations were independently screened by three investigators (E. Zampogna (EZ), R. Centis (RC) and G. Ferrara (GF)) by examining titles and abstracts to identify potentially relevant studies, and differences were resolved by consensus (G.B. Migliori (GBM) and G. Sotgiu (GS)). These original articles were then retrieved and the full text screened for final inclusion and data extraction.

Data extraction

A standardised electronic *ad hoc* form for data extraction was designed. Three reviewers (EZ, RC and GF) analysed and crosschecked all selected articles independently and extracted data. In case of deviations, final documentation of data was based on consensus (GBM and GS). The inter-rater agreement obtained for the data from the included studies was ~100%.

Senior and/or correspondence authors of the selected papers were contacted by email in order to verify the accuracy of the abstraction and obtain missing information in the texts; including potentially useful information for the evaluation of the efficacy, safety, and tolerability profiles of the linezolid-based regimens.

Anonymous individual data were extracted and confirmed by the senior and/or correspondence authors of the included manuscripts. For the efficacy analysis the following variables were collected: time to sputum smear conversion and culture conversion, and final treatment outcome.

For the safety and tolerability analysis the recorded covariates were: daily linezolid dosage and duration of exposure to linezolid-containing regimens; adverse events; description of the adverse event; and time of occurrence of the adverse event.

In addition, the following variables were collected: calendar period of the study; country in which the study was conducted; sex; age; multidrug regimen prescribed in combination or in addition to linezolid (drugs, dose and duration); drug resistance profile; history of previous treatment; number of previous treatment regimens longer than 30 days.

No ethical clearance was requested for this anonymous epidemiological analysis, since all selected studies had previously received approval from local institutional review boards.

Study quality assessment

This systematic review and meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [42].

The inter-rater agreement obtained for the study selection and data extraction from the included studies was >95%; discrepancies were resolved by consensus (GBM and GS).

Statistical analysis

Descriptive, both qualitative and quantitative, variables were summarised with proportions, medians and interquartile ranges (IQR); they were compared using the Chi-squared test and the Wilcoxon Mann–Whitney test, respectively.

Meta-analytic computations were performed using individual data taken from patients with a definite treatment outcome (cure, treatment completion, death, or treatment failure) [41]. Random-effects models were used to account for the predicted between-study dispersion. Forest plots were used to graphically evaluate both the variability (*i.e.* 95% CI) of the point estimates for the efficacy/safety-related covariates and the weight of every cohort size in the computation of the pooled estimates. Inconsistency among included studies was assessed by the Chi-squared test for heterogeneity; the inconsistency (I^2) statistic assesses the role of true variability rather than sampling error on the overall variation.

Subgroup analyses focused on the safety, efficacy and tolerability of linezolid and were performed between patients treated with a daily regimen of ⩽600 mg linezolid *versus* those treated with a daily regimen of >600 mg linezolid. p-values <0.05 were regarded as statistically significant. Statistical analyses were performed with the Stata 9.0 (StataCorp LP, College Station, TX, USA) and Meta-Disc Version 1.4 [43] software.

RESULTS

Selection of the studies

The scientific literature search identified 88 citations. 12 clinical studies were selected, as summarised in the PRISMA flowchart (fig. 1). The characteristics of the studies and the number of cases analysed in the systematic review and meta-analysis are summarised in table 1. The senior and/or correspondence author of 10 (83.3%) out of 12 studies [8, 30–35, 44–47] responded to the electronic invitation to provide demographic, epidemiological and clinical information missing in the full texts of the retrieved manuscripts.

Characteristics of the selected studies

Six (50%) out of the 12 studies [8, 22, 33, 35, 44, 47] were conducted in Europe, four (33.3%) out of the 12 in Asia [31, 32, 45, 46], and two (16.7%) out of the 12 in the USA [30, 34] (table 2). Eight (66.7%) out of 12 were retrospective observational studies [8, 22, 30, 34–35, 44–46] while four (33.3%) out of 12 were prospective [31–33, 47]. The majority (66.7%, eight out of 12) of the studies were performed in single, university or tertiary, in/outpatient settings [22, 31–32, 35, 44–47].

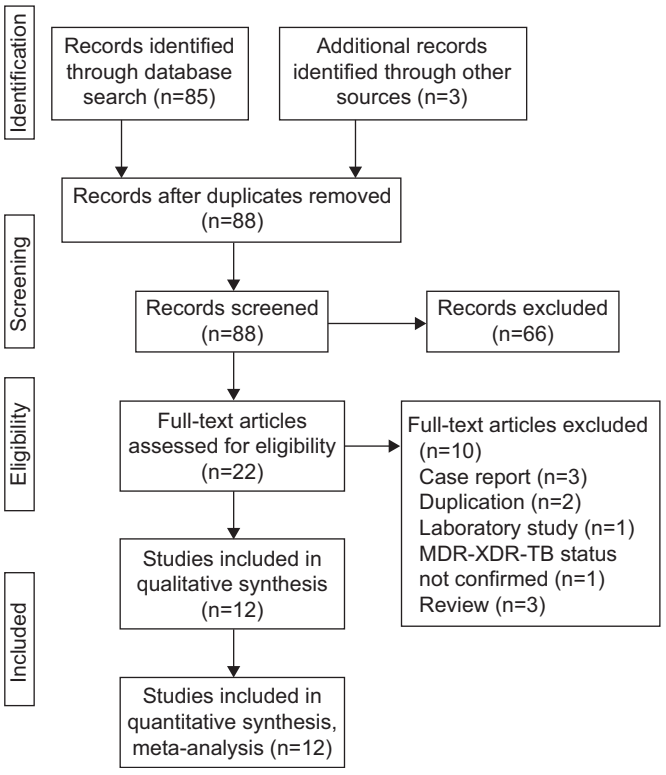


FIGURE 1. PRISMA flowchart of enrolled studies for systematic review. MDR: multidrug-resistant; XDR-TB: entensively drug-resistant tuberculosis.

Linezolid treatment was administered in an unblinded and nonrandomised manner; all study designs were planned without a control group (table 3) except the multicentre study by MIGLIORI *et al.* [8]; one (8.3%) out of 12. All but two TB patients who were enrolled in the prospective or retrospective studies were aged ⩾15 yrs [8, 22, 30–32, 35, 44–47] and all were given individualised anti-TB therapy based on the results of the DST [8, 22, 30–35, 44–47]. Linezolid dosages ranged from 300 mg *b.i.d.* [22, 46, 47] to 400 mg *q.d.* or *b.i.d.* [34], and 450 mg *q.d.* [30] to 600 mg *q.d.* [8, 30–33, 34, 35, 45, 46], *b.i.d.* [8, 22, 31, 33–35, 44, 47] or three times a week [30].

Characteristics of the international cohort

Individual data from 121 patients treated with linezolid in clinical settings located all over the world (*i.e.* Europe, North America, and Asia) [8, 22, 30–35, 44–47] were collected (tables 1 and 4). More than half were males (53.7%) and were born in Asian countries (69.3%), with a median (IQR) age at treatment onset of 32 (25–41) yrs. Known risk factors favouring the development of TB and MDR-/XDR-TB were detected in several patients: 35.4% were migrants from high TB-burden countries; 8.7% were HIV positive; and 76.9% were previously treated with anti-TB therapy >30 days (median (IQR) for the number of times exposed to anti-TB drugs was 1 (0–4)). Almost all individuals with pulmonary TB were sputum smear-positive (102 (92.7%) out of 110) and showed cavitary lesions at the baseline chest-radiograph examination (79 (74.5%). out of 106). XDR-TB was diagnosed in 32.5% of the individuals (I^2=67.0%; fig. 2). One fourth of the cases underwent surgery because of the lack of sufficient active drugs or as adjunct intervention. Of the

TABLE 1 Cases included in the systematic review and meta-analysis in the 12 studies selected

First author [ref.]	Systematic review treatment outcome: definite#, still on treatment, default, transferred out	Meta-analysis treatment outcome: definite# only
Alffenaar [47]	8	8
Anger [34]	16	15
De Lorenzo [35]	12	3
Fortún [22]¶	5	4
Nam [46]	11	11
Migliori [8]+	44	4
Park [45]	8	7
Schecter [30]	30	23
Singla [31]	29	14
Udwadia [32]	18	13
Villar [33]	16	9
von der Lippe [44]¶	10	10
Total number of cases	207	121

Data are presented as n. #: definite was defined as: cured, treatment completed, died or failure; ¶: authors of the studies meeting the inclusion criteria, where individual data was available in the manuscript but the correspondence/senior author did not provide the individual data-set; +: data from the German cohort were not included in the meta-analysis.

51 patients with data on hospital stay, discharge occurred after a median (IQR) duration of hospital stay of 39 (15–82) days.

No statistically significant demographic, epidemiological and clinical characteristics were detected between those treated with a daily dosage of linezolid ⩽600 mg (72 (59.5%) out of 121), and those treated with a daily dosage >600 mg (49 (40.5%) out of 121) except for the covariates ''migration'', ''HIV positivity'' and ''surgery'', which were significantly more frequent in the group of patients exposed to a daily dose >600 mg.

Efficacy of regimes containing linezolid

The majority of individuals converted to sputum smear (86 (92.5%) out of 93; I^2=22.9%) and culture (100 (93.5%) out of 107; I^2=18.2%) negativity after the exposure to individualised linezolid-containing regimens (table 5 and fig. 3); median (IQR) time to sputum smear and culture conversion was 43.5 (21–90) and 61 (29–119) days, respectively.

More than 80% were successfully treated (99 (81.8%) out of 121; I^2=44.8%), while death and treatment failure were observed in 14.1% and 4.1% of the enrolled subjects, respectively (fig. 4) [41].

No statistically significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage ⩽600 mg *versus* >600 mg); proportion of cure was ~80% in both groups and the rate of death and treatment failure occurred in less than one-fourth in both groups, respectively.

Safety and tolerability of linezolid

Approximately one out of every two patients (63 (58.9%) out of 107; I^2=82.2%) experienced adverse events attributed to linezolid including 54 (68.4%) out of 79 patients (I^2=73.1%) with major adverse events, *i.e.* they required linezolid treatment interruption or dosage reduction (table 6 and fig. 5). The main adverse events were anaemia (38.1%; I^2=69.7%) and peripheral neuropathy (47.1%; I^2=44.0%) (fig. 6); other haematological and non-haematological adverse events occurred in a lower proportion of cases, *i.e.* gastro–intestinal disorders (16.7%), optic neuritis (13.2%) and thrombocytopenia (11.8%).

A statistically significant higher risk of adverse events attributed to linezolid treatment was detected in the cohort treated with a linezolid daily dosage >600 mg (74.5% *versus* 46.7%). In particular, a statistically significant higher probability of anaemia (60% *versus* 2.5%; p=0.0005), leukopoenia (17.1% *versus* 2.0%; p=0.012) and gastrointestinal symptoms (29.4% *versus* 8.0%; p=0.01) was found despite a lower statistically significant

TABLE 2 Epidemiological characteristics of the selected studies

First author [ref.]	Country	Study design	Clinical setting	Study duration yr
Alffenaar [47]	The Netherlands	Open-label, prospective, pharmacokinetic	Monocentre, university medical centre	2007–2008
Anger [34]	USA	Retrospective	Multicentre, public and private clinics	2000–2006
De Lorenzo [35]	Italy	Retrospective	Monocentre, tuberculosis reference centre	2009–2010
Fortún [22]	Spain	Retrospective	Monocentre, Ramon y Cajal Hospital (Madrid, Spain)	1999–2004
Nam [46]	South Korea	Retrospective	Monocentre, university medical centre	2004–2007
Migliori [8]	Belarus, Germany, Italy, Switzerland	Retrospective, controlled, nonrandomised, unblinded	Multicentre, 21 public hospitals and tuberculosis reference centres	2001–2007
Park [45]	South Korea	Retrospective	Monocentre, university medical centre	2003–2006
Schecter [30]	USA	Retrospective	Multicentre, public clinics	2003–2007
Singla [31]	India	Prospective	Monocentre, tertiary centre	2006–2011
Udwadia [32]	India	Prospective, nonrandomised	Monocentre, private tertiary centre	2000–2007
Villar [33]	Portugal	Prospective	Multicentre, public clinics	2004–2009
von der Lippe [44]	Norway	Retrospective	Monocentre, university medical centre	1998–2002

TABLE 3 Characteristics of the patients and of the anti-tuberculosis (TB) treatment in the selected studies

First author [ref.]	Paediatric population aged <15 yrs	Standard or individualised anti-TB treatment	Linezolid dosage mg	Control group
Alffenaar [47]	No	Individualised	300 twice daily 600 twice daily	No
Anger [34]	Yes one patient	Individualised	600 twice daily 400 twice daily 600 once daily 400 once daily	No
De Lorenzo [35]	No	Individualised	600 twice daily 600 once daily	No
Fortún [22]	No	Individualised	600 twice daily 300 twice daily	No
Nam [46]	No	Individualised	600 once daily 300 twice daily	No
Migliori [8]	No	Individualised	600 twice daily 600 once daily	Yes
Park [45]	No	Individualised	600 once daily	No
Schecter [30]	No	Individualised	600 once daily 600 three times a week 450 once daily	No
Singla [31]	No	Individualised	600 twice daily 600 once daily	No
Udwadia [32]		Individualised	600 once daily	No
Villar [33]	Yes one patient	Individualised	600 twice daily 600 once daily	No
von der Lippe [44]	No	Individualised	600 twice daily	No

TABLE 4 Demographic, epidemiological and clinical characteristics of 121 multidrug-resistant tuberculosis (TB) cases enrolled in the meta-analysis

	Total	LNZ daily dose ⩽600 mg	LNZ daily dose >600 mg	p-value
Male	65/121 (53.7)	40/72 (55.6)	25/49 (51.0)	0.62
Age at admission yrs	32 (25–41)	30.5 (22.5–41)	33 (27–42)	0.42
Country of birth				
Europe	12/75 (16.0)	2/45 (4.4)	10/30 (33.3)	0.0008
Asia	52/75 (69.3)	37/45 (82.2)	15/30 (50.0)	0.003
Africa	6/75 (8.0)	3/45 (6.7)	3/30 (10.0)	0.61
Other geographical areas	5/75 (6.7)	3/45 (6.7)	2/30 (6.7)	
Migrant	29/82 (35.4)	9/45 (20.0)	20/37 (54.1)	0.001
HIV positive	9/104 (8.7)	0/55 (0.0)	9/49 (18.4)	0.0009
Previous exposure to anti-TB therapy >1 month	93/121 (76.9)	51/72 (70.8)	42/49 (85.7)	0.06
Number of times treated with anti-TB drugs for >1 month	1 (0–4)	1 (0–4)	1 (0–3)	0.81
Sputum-smear positive	102/110 (92.7)	66/72 (91.7)	36/38 (94.7)	0.56
Pulmonary TB	116/120 (96.7)	71/72 (98.6)	45/48 (93.8)	0.15
Extra-pulmonary TB	12/95 (12.6)	4/53 (7.6)	8/42 (19.1)	0.09
Radiological findings				
Cavitary lesions	39/106 (36.8)	21/69 (30.4)	18/37 (48.7)	0.06
Bilateral pulmonary involvement with cavitary lesions	40/106 (37.7)	26/69 (37.7)	14/37 (37.8)	0.99
Bilateral pulmonary involvement	6/106 (5.7)	5/69 (7.3)	1/37 (2.7)	0.33
Non-cavitary unilateral pulmonary involvement	21/106 (19.8)	17/69 (24.6)	4/37 (10.8)	0.09
XDR-TB	39/120 (32.5)	25/71 (35.2)	14/49 (28.6)	0.45
Surgical treatment	27/108 (25.0)	12/72 (16.7)	15/36 (41.7)	0.005
Hospital stay days	39 (15–82)	37 (12–79)	60 (19–159)	0.37

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. LNZ: linezolid; XDR-TB: extensively drug-resistant TB.

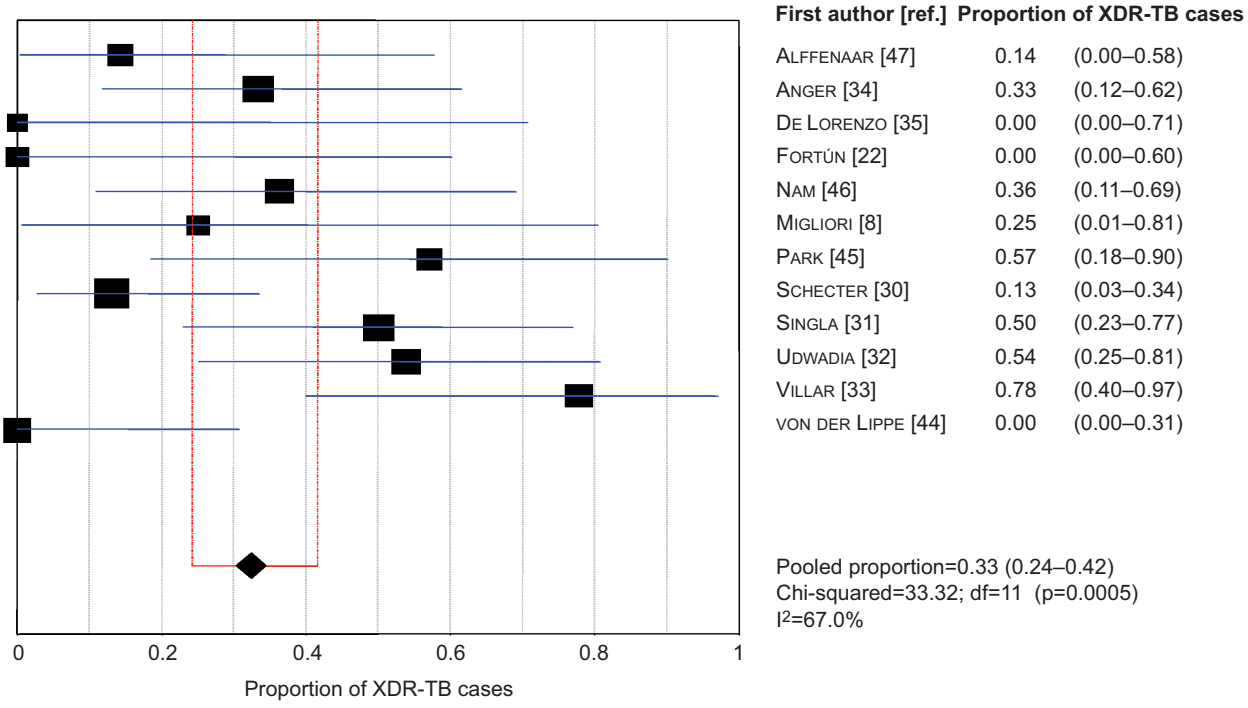


FIGURE 2. Forest plot showing the proportions of extensively drug-resistant tuberculosis (XDR-TB) patients in the enrolled studies. Data are presented as n (95% CI); I^2: inconsistency statistics; df: degrees of freedom.

exposure duration to linezolid (median (IQR) time of exposure: 252 (120–540) days *versus* 589.5 (154.5–750) days).

DISCUSSION

The main results of our study shed light on several areas relevant for the clinical use of linezolid, not described in previous observational studies: dosage and duration from one side and efficacy, safety and tolerability on the other side. The large sample size allowed more analyses and more robust inferences, not performed in the past.

This systematic review and meta-analysis of the efficacy, safety and tolerability of the linezolid-containing regimes is designed to support the development of future evidence-based guidance on the use of linezolid in difficult-to-treat MDR- and XDR-TB cases.

Dosage and duration

10 of the 12 clinical studies evaluated in the present analysis used linezolid at 600 mg·day^{-1}. This meta-analysis of data collected in different settings found no statistical difference in terms of treatment success, proportions of sputum smear or of

TABLE 5 Treatment outcomes of 121 multidrug-resistant tuberculosis (TB) cases enrolled in the meta-analysis

	All treatments	LNZ daily dose ⩽600 mg	LNZ daily dose >600 mg	p-value
Patients treated with linezolid		72 (59.5)	49 (40.5)	
XDR-TB		25/71 (35.2)	14/49 (28.6)	0.45
Sputum smear conversion	86/93 (92.5)	54/59 (91.5)	42/44 (95.5)	0.43
Culture conversion	100/107 (93.5)	54/59 (91.5)	46/48 (95.8)	0.37
Period from start of anti-TB therapy to sputum smear conversion days	43.5 (21–90)	45.5 (28–91)	92.5 (35–120)	0.02
2-month culture conversion	37/72 (51.4)	18/42 (42.9)	19/30 (63.3)	0.09
Period from start of anti-TB therapy to culture conversion days	61 (29–119)	28 (20–45)	60 (42–115)	0.07
Definite treatment outcomes				
Cured	98/121 (81.0)	59/72 (81.9)	39/49 (79.6)	0.75
Treatment completed	1/121 (0.8)	1/72 (1.4)		
Died	17/121 (14.1)	9/72 (12.5)	8/49 (16.3)	0.56
Failed	5/121 (4.1)	3/72 (4.2)	2/49 (4.1)	0.98

Data are presented as n (%), n/N (%) or median (interquartile range), unless otherwise stated. LNZ: linezolid; XDR-TB: extensively drug-resistant TB.

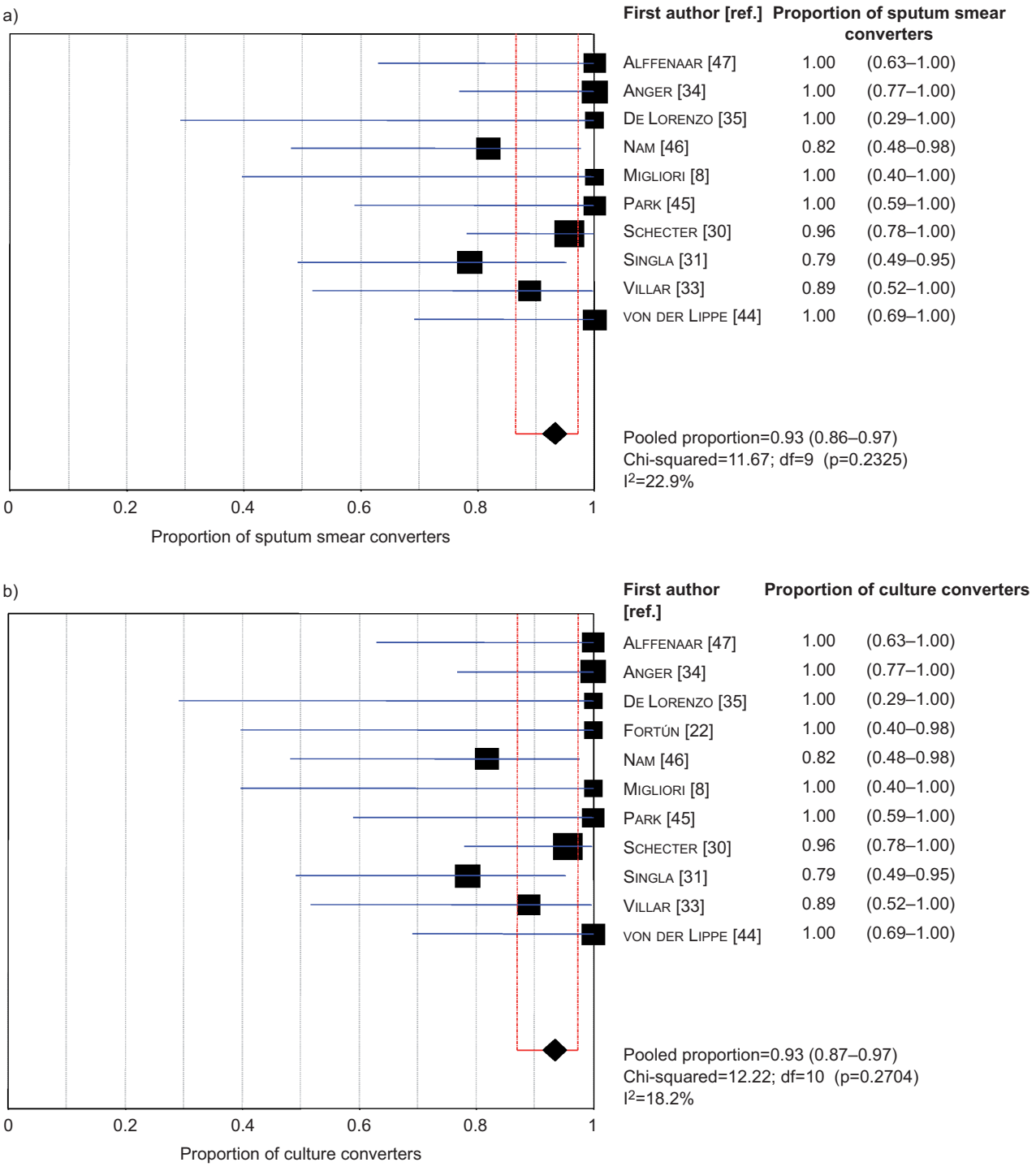


FIGURE 3. Forest plots showing the proportion of a) sputum smear converters and b) culture converters in the enrolled studies. Data are presented as n (95% CI); I^2: inconsistency statistics; df: degrees of freedom.

culture converters between those treated with ⩽600 mg *q.d.* *versus* those treated with >600 mg *b.i.d.*

Building on the evidence that a 600 mg daily dose may decrease the occurrence of adverse events, while not compromising efficacy, a study by ALFFENAAR *et al.* [47], provided a rationale for sub-dividing the total daily dose of 600 mg, in order to prevent the blood peaks probably responsible for the haematological and non-haematological related adverse events.

ALFFENAAR *et al.* [47] demonstrated that the serum concentrations of linezolid obtained following each 300 mg administration *b.i.d.* are well above the minimum inhibitory concentration ((MIC), *i.e.* 0.125–0.5 $mg \cdot L^{-1}$ against *M. tuberculosis*) and that the serum

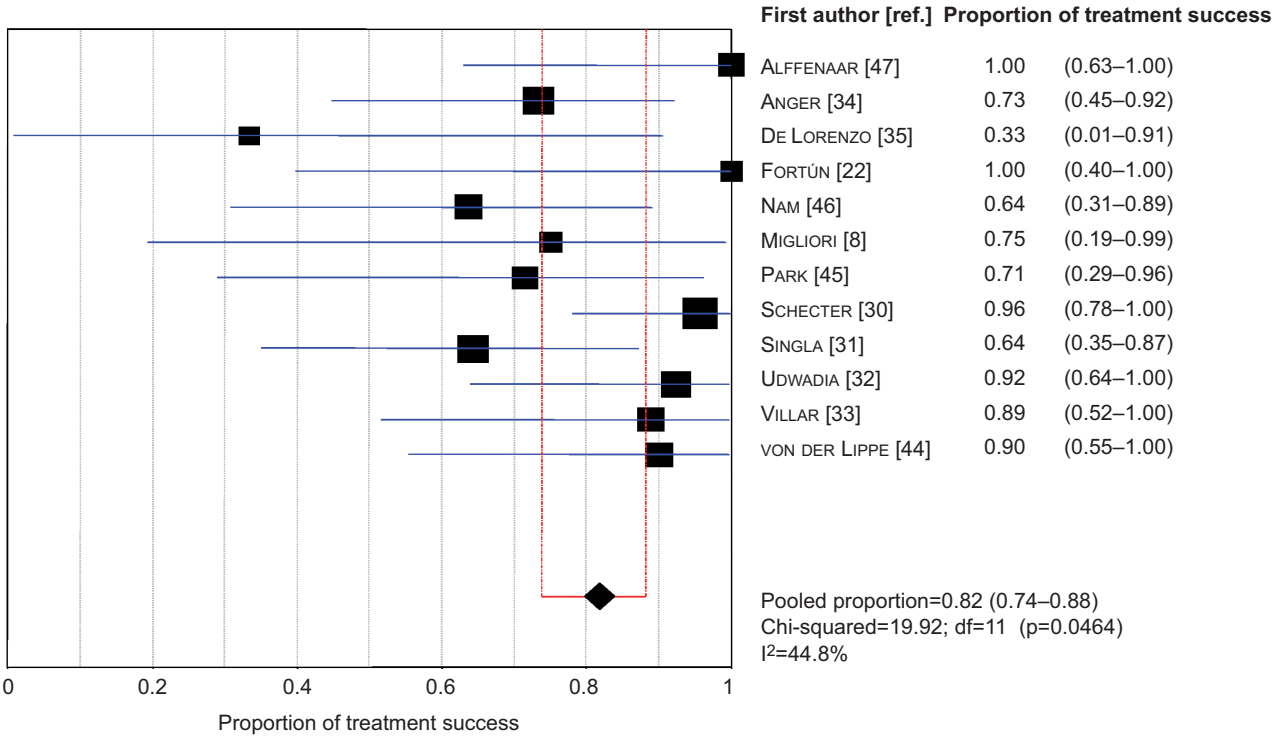


FIGURE 4. Forest plot showing the proportion of patients who were successfully treated in the enrolled studies. Data are presented as n (95% CI); I^2: inconsistency statistics; df: degrees of freedom.

concentration–time curve over 24 h/MIC ratios were sufficiently high (>100) to predict efficacy in seven out of the eight patients studied. This study provides evidence that a 300 mg *b.i.d.* dosage may be used to prolong treatment with linezolid, with sustained efficacy and limitation of adverse events.

While properly designed randomised pharmacokinetic studies on larger samples (including comparison of outcomes) will give a final answer on the ideal dose of linezolid, it seems rational to perform kinetics on all cases exposed to the drug [35].

Although very expensive, linezolid is used off-label, with extremely prolonged duration of exposure, beyond its licensed prescription length of 28 days [47]. In this international cohort the median duration of linezolid treatment was 300 days (589.5 days *versus* 252 days in the group treated with linezolid ⩽600 mg *q.d.* and >600 mg *b.i.d.*, respectively). In two studies linezolid was prescribed for the entire treatment duration, *e.g.* from 18.6 months to 20.6 months [30, 32]. The optimum duration of linezolid use is still unknown. Administration of linezolid for a shorter duration of time is likely to reduce the occurrence of

TABLE 6 Retrospective evaluation of the safety and tolerability of linezolid in 121 multidrug-resistant tuberculosis cases

	Total	LNZ daily dose ⩽600 mg	LNZ daily dose >600 mg	p-value
Patients exposed to LNZ		72 (59.5)	49 (40.5)	
Adverse events attributed to LNZ	63/107 (58.9)	28/60 (46.7)	35/47 (74.5)	0.004
Major adverse events	54/79 (68.4)	27/44 (61.4)	27/35 (77.1)	0.14
Anaemia	32/84 (38.1)	11/49 (22.5)	21/35 (60.0)	0.0005
Leukopoenia	7/85 (8.2)	1/50 (2.0)	6/35 (17.1)	0.012
Thrombocytopenia	10/85 (11.8)	5/50 (10.0)	5/35 (14.3)	0.55
Peripheral neuropathy	40/85 (47.1)	20/50 (40.0)	20/35 (57.1)	0.12
Optic neuritis	10/76 (13.2)	4/41 (9.8)	6/35 (17.1)	0.35
Gastro-intestinal disorders	14/84 (16.7)	4/50 (8.0)	10/34 (29.4)	0.01
Exposure to LNZ days	300 (140–690)	589.5 (154.5–750)	252 (120–540)	0.031

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. LNZ: linezolid.

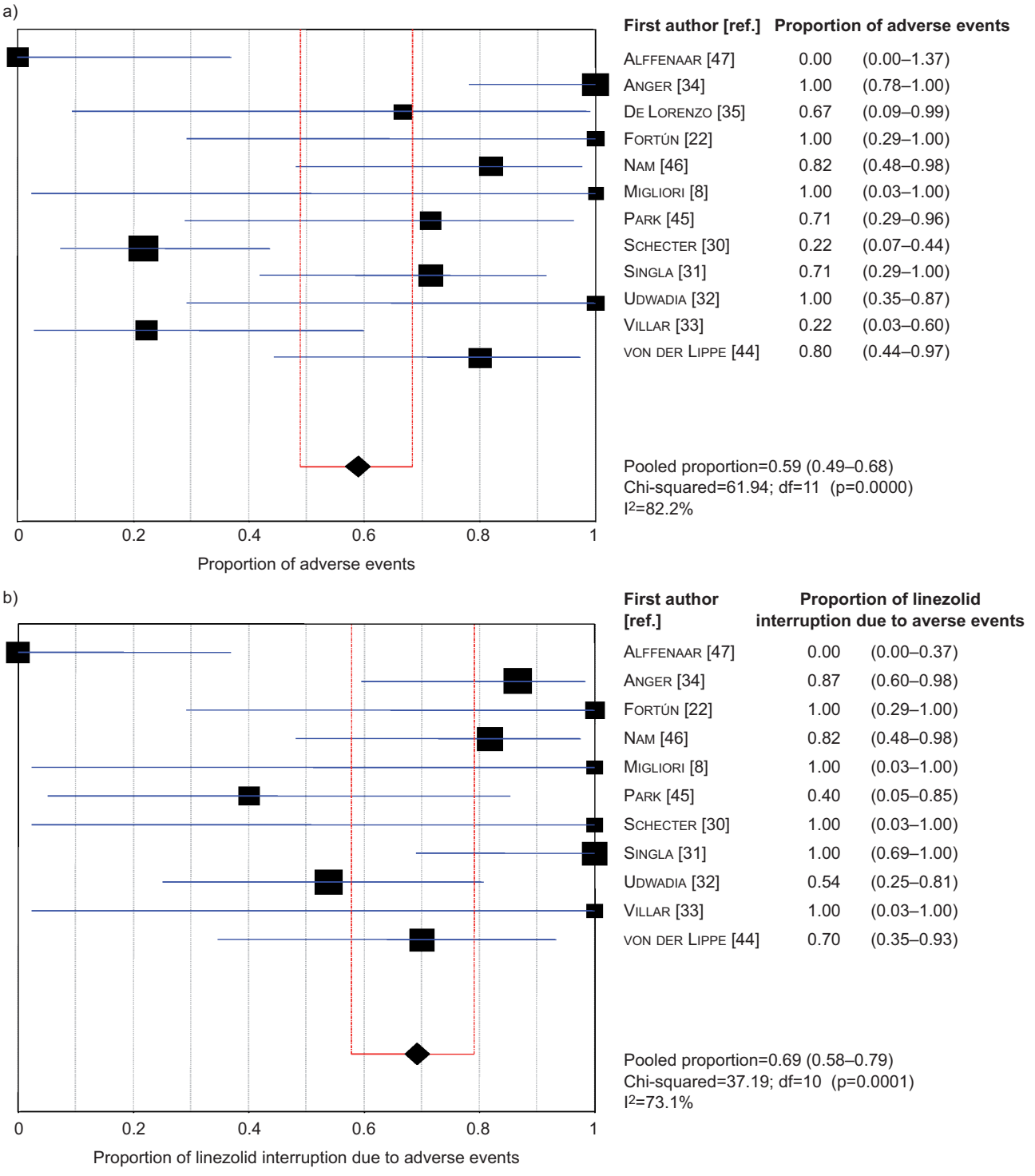


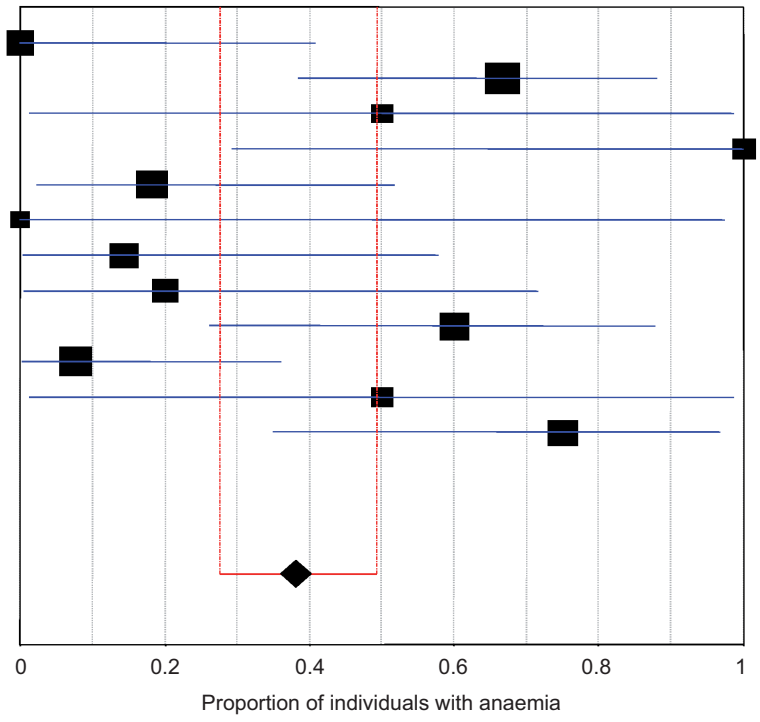
FIGURE 5. Forest plots showing a) the proportion of patients affected by adverse events and b) the proportion of patients who interrupted their treatment owing to adverse events in the enrolled studies, respectively. Data are presented as n (95% CI); I^2: inconsistency statistics; df: degrees of freedom.

adverse events, but may compromise efficacy and/or increase likelihood of acquired resistance. More information on this topic is needed and cannot be drawn from the observational studies carried out to date.

Efficacy, safety and tolerability

Linezolid proved to be successful when added to a DST-tailored, individualised treatment regimen composed of several drugs. The pooled estimates of anti-TB treatment success and

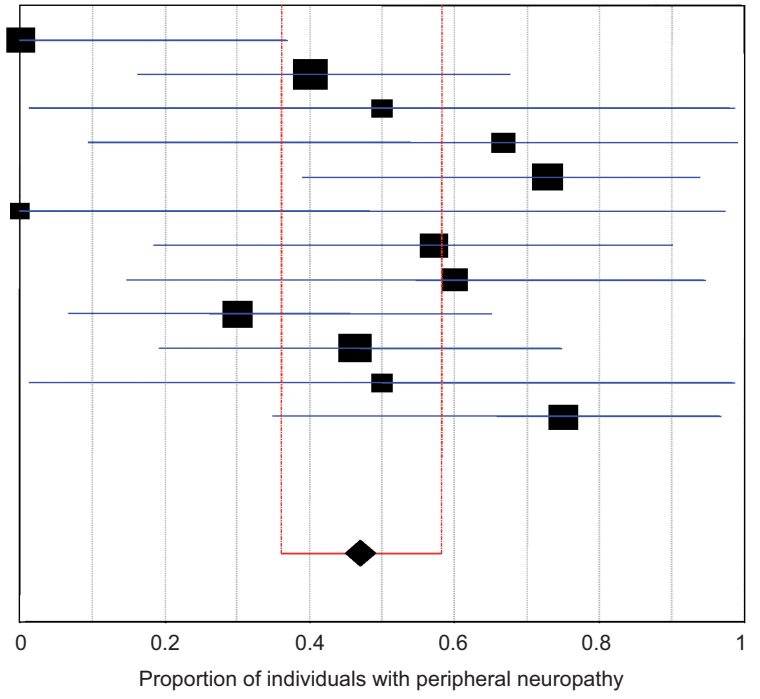
a)



First author [ref.]	Proportion of individuals with anaemia	
Alffenaar [47]	0.00	(0.00–0.41)
Anger [34]	0.67	(0.38–0.88)
De Lorenzo [35]	0.50	(0.01–0.99)
Fortún [22]	1.00	(0.29–1.00)
Nam [46]	0.18	(0.02–0.52)
Migliori [8]	0.00	(0.00–0.98)
Park [45]	0.14	(0.00–0.58)
Schecter [30]	0.20	(0.01–0.72)
Singla [31]	0.60	(0.26–0.88)
Udwadia [32]	0.08	(0.00–0.36)
Villar [33]	0.50	(0.01–0.99)
von der Lippe [44]	0.75	(0.35–0.97)

Pooled proportion=0.38 (0.28–0.49)
Chi-squared=36.31; df=11 (p=0.0001)
I^2=69.7%

b)



First author [ref.]	Proportion of individuals with peripheral neuropathy	
Alffenaar [47]	0.00	(0.00–0.37)
Anger [34]	0.40	(0.16–0.68)
De Lorenzo [35]	0.50	(0.01–0.99)
Fortún [22]	0.67	(0.09–0.99)
Nam [46]	0.73	(0.39–0.94)
Migliori [8]	0.00	(0.00–0.98)
Park [45]	0.57	(0.18–0.90)
Schecter [30]	0.60	(0.15–0.95)
Singla [31]	0.30	(0.07–0.65)
Udwadia [32]	0.46	(0.19–0.75)
Villar [33]	0.50	(0.01–0.99)
Voh der Lippe [44]	0.75	(0.35–0.97)

Pooled proportion=0.47 (0.36–0.58)
Chi-squared=19.64; df=11 (p=0.0505)
I^2=44.0%

FIGURE 6. Forest plots showing a) the proportion of individuals affected by anaemia and b) the proportion of individuals affected by peripheral neuropathy in the enrolled studies. Data are presented as n (95% CI); I^2: inconsistency statistics; df: degrees of freedom.

culture conversion were 82% and 93%, respectively. Median time to sputum smear and culture conversion were 43.5 days and 61 days, respectively.

In spite of some variability, all studies included high percentages of severe MDR-TB cases and XDR-TB patients; the pooled proportion of XDR-TB cases was 32.5% with an inconsistency of 67.0%, reflecting the different prescription habits of the settings where the studies were performed. Success was comparable between patients receiving a daily linezolid dose $\leqslant$600 mg and those having a higher dose, notwithstanding the finding that patients with definitional XDR-TB, and who would be expected to have a lower likelihood of success than other MDR-TB patients, were similarly distributed between the two treatment groups.

On the other side, the study results confirm that administration of linezolid is hampered by several toxic effects, although a large variation in major adverse events has been observed. As discussed previously, toxicity was dose–dependent, being lower when a dose $\leqslant$600 mg *q.d.* was used [47]. In eight out of the 12 studies analysed $\geqslant$25% of the cases reported major adverse events, making interruption of the drug (or re-adjustment of its dosage) necessary. The meta-analysis showed that the pooled proportion of any adverse event was 59%, of which 69% were major adverse events.

Strengths and weaknesses

The systematic review was based on a sample size of 207 cases taken from three continents and 11 countries (Belarus, Germany, India, Italy, South Korea, the Netherlands, Norway, Portugal, Spain Switzerland and USA).

The meta-analysis on individual data included a large sample size (n=121 cases), representing all the cases having a definite outcome (with the single exception of the Germany cases, which belonged to the largest data-set [8]). Although no specific cohort from Africa and Latin America is available, a proportion of cases born in these continents were included in our study (8% and 6.7%, respectively).

The individual data-set allowed the analysis of all the variables planned, so that the final conclusions were sufficiently robust and, although not necessarily representative, they could be cautiously generalised. Furthermore, subgroup analyses were performed in two comparable cohorts, apart from a few statistically significant differences of some demographic, epidemiological and clinical variables. The meta-analysis is based non-controlled, nonrandomised, unblinded observational data; consequently, a selection bias cannot be excluded in the original studies, as well as publication bias.

Furthermore, owing to the retrospective nature of the majority of the enrolled studies, the efficacy of linezolid was not weighted for the anti-TB drug-combinations and for other clinical and epidemiological confounding variables. The proportion of favourable outcomes is likely to be under-represented if linezolid has been used as a salvage drug, than if it has been prescribed in less compromised patients who could better tolerate adverse events.

In addition the wide time span in which the reviewed studies occurred is unlikely to have biased the results. Consequently this global study adds new information, which was not available in either the largest single study to date [8] or in the other selected smaller studies [30–35, 44–47].

Conclusions

The results of our study suggest an excellent efficacy but also the necessity of caution in the prescription of linezolid for treatment of MDR-TB. Although effective in treating MDR-TB and XDR-TB cases, its administration should be limited to severe cases when an additional active anti-TB drug is needed. Its role in the future generation of shorter regimens needs to be further assessed, although the drug characteristics do not support an easy outpatient-based use in combination with the new drugs, which are expected to be launched onto the market in the near future. A dosage of $\leqslant$600 mg per day (either as a single dose or divided into two doses) seems the best recommendation, as it minimises the occurrence of adverse events while not compromising efficacy. The high proportion of cases experiencing adverse events and requiring drug interruption or dosage reduction suggests that the use of linezolid should be limited to specialised MDR-TB reference centres, where both inpatients and outpatients can be carefully monitored for any occurrence of serious adverse events and where facilities are well equipped to manage any serious problem (including the possible need for blood transfusion).

SUPPORT STATEMENT

Current Research Funds from participating institutions and European Community's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement FP7-223681.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

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