Linezolid to treat extensively drug-resistant TB: retrospective data are confirmed by experimental evidence

To the Editor:

Extensively drug-resistant tuberculosis (XDR-TB) (defined as TB caused by *Mycobacterium tuberculosis* strains with *in vitro* resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the second-line injectable drugs, amikacin, capreomycin or kanamycin) on top of being a growing public health concern, represents a nightmare for the clinician [1–4]. The crucial therapeutic issue is the difficulty of identifying at least four available ''active'' anti-TB drugs, to ensure treatment success as well as to prevent the emergence of additional drug resistance [1–4].

After more than 40 years without new anti-TB drugs appearing on the horizon, new chemical compounds (*i.e.* bedaquiline, PA-824 and delamanid) seem promising for these difficult-to-treat cases of TB [4, 5].

While the necessary experimental studies will prove how to use them, more and more interest is currently focused on existing antibacterial drugs with new indications for drug-resistant TB, particularly linezolid, meropenem, clofazimine and cotrimoxazole [6–9].

Based on *in vitro* and pharmacological data, suggesting that linezolid (an oxazolidinone antibiotic) could be efficacious in treating mycobacterial infections, and on anedoctal evidence of its effectiveness in the smallest groups of patients, it was used off-label, despite its high price, to treat multidrug-resistant (MDR) TB cases in several countries. The little scientific supporting data on the efficacy, safety and tolerability of linezolid came from *ad hoc* randomised, controlled clinical trials, as well as from large observational studies [7].

The *European Respiratory Journal* recently published a systematic review and a meta-analysis of individual patients focused on the main published epidemiological observational studies (n=12), describing cohorts of TB patients (n=121) treated with linezolid-containing regimens in 11 countries [7]. The selected papers had the following inclusion criteria: description of at least five culture- and drug-susceptibility testing confirmed MDR- or XDR-TB patients treated with linezolid-containing regimens; proportion of childhood patients less than 25% of the total sample; available evidence on efficacy, safety and tolerability.

Individual data were extracted from the manuscripts and collected in an *ad hoc* electronic form containing variables related to the efficacy, safety and tolerability profiles. The information retrieved was confirmed and/or updated, when possible, by the responsible authors of the selected papers. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed.

A high proportion of MDR-TB cases achieved sputum smear (86 out of 93; 92.5%) and culture (100 out of 107; 93.5%) conversion after treatment with individualised linezolid-containing therapeutic schemes and 99 out of 121 (81.8%) achieved treatment success, with no differences in efficacy between those treated with a daily linezolid dosage $\leqslant$600 mg *versus* $>$600 mg.

Unfortunately, adverse events were observed in 58.9% (63 out of 107) of the cases (68.4% of them reported major adverse events); moreover, the frequency was significantly higher when the daily linezolid dose exceeded 600 mg.

More recently, a study by Lee *et al.* [10] provided, for the first time, the prospective experimental evidence needed on the efficacy, safety and tolerability of linezolid to treat XDR-TB.

Out of 39 XDR-TB, patients 87% showed a negative sputum culture after 6 months of treatment with linezolid-containing regimens. Linezolid (600 mg) was prescribed daily to the enrolled cohort at the beginning of the clinical trial; after 4 months of exposure to linezolid or after sputum smear conversion, a subgroup was administered a 300 mg daily dosage. Adverse events, potentially attributable to linezolid, occurred in 31 out of 38 (82%) patients, with a smaller proportion in those randomised to a 300 mg daily dosage (11 out of 16; 69%).

The aim of the present study was to analyse the safety, tolerability and efficacy of linezolid in the XDR-TB subgroup of the meta-analytic cohort [7] and to compare these results with those described by Lee *et al.* [10].

Statistical analyses were carried out using Stata 9.0 (StataCorp, College Station, TX, USA).

TABLE 1 Retrospective evaluation of the safety and tolerability of linezolid in 39 extensively drug-resistant tuberculosis cases

Adverse event		Subgroup analysis		
		LNZ ⩽600 mg	LNZ >600 mg	p-value
Total adverse events presumably due to linezolid	22/34 (64.7)	14/20 (70.0)	8/14 (57.1)	0.49
Major adverse events	21/28 (75.0)	16/20 (80.0)	5/8 (62.5)	0.37
Anaemia	9/29 (31.0)	5/21 (23.8)	4/8 (50.0)	0.21
Leukopenia	4/29 (13.8)	1/21 (4.8)	3/8 (37.5)	0.05
Thrombocytopenia	5/29 (17.2)	2/21 (9.5)	3/8 (37.5)	0.11
Peripheral neuropathy	16/29 (55.2)	11/21 (52.4)	5/8 (62.5)	0.70
Optic neuritis	5/25 (20.0)	2/17 (11.8)	3/8 (37.5)	0.28
Gastro-intestinal disorders	5/28 (17.9)	2/21 (9.5)	3/7 (42.9)	0.08
Exposure to linezolid days	315 (178–540)	270 (93–720)	330 (270–490)	0.64

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

The XDR-TB patients enrolled in the meta-analysis were 39 out of 120 (32.5%) cases; most of them were male (24 out of 39; 61.5%), with a median (interquartile range) age of 36 (28–42) years. A daily dose of linezolid ⩽600 mg and >600 mg were prescribed to 25 out of 39 (64.1%) and 14 out of 39 (35.9%) patients, respectively. The safety and tolerability profile is summarised in table 1.

The proportion of adverse events in 34 XDR-TB patients was >60%, with 75% determining an interruption of treatment. After a median exposure to linezolid of 315 days, peripheral neuropathy was the most common adverse effect (55.2%), followed by anaemia (31.0%) and optic neuritis (20.0%). Although the proportion of adverse events was higher in the group of individuals treated with a linezolid daily dosage of ⩽600 mg, the difference was not statistically significant.

The XDR-TB meta-analytic observational cohort [7] and the experimental group of Lee *et al.* [10] seem to be not statistically different in terms of proportions of adverse events attributable to linezolid prescribed at the daily dose of ⩽600 mg (14 out of 20, 70% *versus* 31 out of 38, 82%; p=0.30), as well as of culture converters after 4 and 6 months of linezolid exposure (14 out of 25, 56% *versus* 15 out of 19, 79%; p=0.11; 18 out of 25, 72% *versus* 34 out of 38, 89%; p= 0.08, respectively).

On top of sharing the same conclusions (linezolid is effective but, due to adverse events, patients need careful monitoring), the rough statistical comparison between the two studies confirms that the dosage ⩽600 mg·day^{-1} has the best risk–benefit profile [7, 10]. It has demonstrated an equal observational and experimental clinical efficacy in a difficult-to-treat group of TB patients, even if the limited sample size could represent a methodological shortcoming. More experimental evidence is urgently needed, preferably based on strong indicators, predictive of high efficacy, after a short period of drug exposure, following the example of randomised clinical trials on new anti-HIV and anti-hepatitis C drugs.

A growing amount of data from linezolid-exposed cohorts more and more clearly supports the rationale of prescribing the drug daily at a low dose, tailored to the pharmacokinetic profile obtained through therapeutic drug monitoring [7].

The identification of the adequate daily exposure to linezolid will prevent occurrence of adverse events, both life-threatening (*e.g.* determining the physician's decision to stop the drug) and non-serious (*e.g.* lowering the patient's motivation to continue the prescribed treatment).

The obvious consequence will be improved patient adherence and an increased chance of achieving treatment success.

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Results of the recent *ERJ* meta-analysis on linezolid to treat XDR-TB have been confirmed by a trial published in NEJM http://ow.ly/kslan

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