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What is the optimal dosage of linezolid in treatment of complicated multidrug-resistant tuberculosis?

To the Editors:

In a retrospective study, MIGLIORI *et al.* [1] have elegantly shown that linezolid 600 mg daily or twice daily added to an individualised multidrug regimen was efficacious in treating multidrug-resistant tuberculosis (MDR-TB). Once-daily dosing was associated with less major adverse effects than twice-daily dosing, corroborating the results of an earlier study in South Korea [2]. As a result of the potentially serious side-effects, MIGLIORI *et al.* [1] have appropriately recommended reserving linezolid treatment for the most complicated cases of MDR-TB. We concur with these views and would like to share our experience regarding the use of linezolid 800 mg once daily in the treatment of extensively drug-resistant tuberculosis (XDR-TB) and fluoroquinolone-resistant MDR-TB.

Table 1 shows the clinical profiles of two patients. The first is a 41-yr-old male smoker with smear-positive XDR-TB following a long history of treatment for chronic tuberculosis overseas. His chest radiograph initially showed an extremely large cavity involving the right upper lobe and the apical segment of the right lower lobe. Despite apparent sputum culture conversion after treatment for 12 weeks, drug susceptibility testing (DST) revealed an increase in the minimum inhibitory concentration of linezolid against *Mycobacterium tuberculosis* from 0.5 $mg \cdot L^{-1}$ to 4 $mg \cdot L^{-1}$ for the last positive-culture isolate after 2 months of therapy. Besides reflecting the activity of the oxazolidinones against *M. tuberculosis*, this phenomenon might represent transitional bacillary resistance prior to bacteriological conversion from positivity to negativity. The second patient is a 60-yr-old diabetic male with smear-positive fluoroquinolone-resistant MDR-TB and a high possibility of sequestered lung disease due to a thick-walled cavity in the left upper lobe. He has received two main periods of linezolid administration of varying dosages; the second period is still ongoing. Compared to the experience with linezolid 600 mg twice-daily dosing, his tolerance was better with 800 mg once daily. In addition, to date, there is no evidence of bacillary resistance to linezolid from serial DST. Both patients have apparently achieved lowering of bacillary load after administration of linezolid, together with shrinkage of cavities even when the dose of linezolid was 800 mg once daily. Surgery after achieving sputum culture conversion was contemplated in both cases, but the thought was abandoned by patients and surgeons in view of the high risk of post-operative morbidity and mortality. However, without surgery, reversion of bacteriological status to positivity would be very likely.

Our data corroborate previous findings of good diffusion of linezolid into tuberculosis cavities [3]. An *in vitro* pharmacodynamic model in *Bacillus anthracis* has suggested that an optimised once-daily dose of linezolid might prevent emergence of drug resistance, in addition to conferring antibacterial efficacy [4]. Linezolid has a reasonably low mutant prevention concentration that would theoretically help to restrict the development of mycobacterial resistance [5]. Thus, more exploration is required to delineate an optimal dose of linezolid in the treatment of ''complicated'' or ''difficult'' MDR-TB.

W.W. Yew*, K.C. Chang[#] and C.H. Chau*
*Tuberculosis and Chest Unit, Grantham Hospital, Aberdeen, and [#]Dept of Health, Tuberculosis and Chest Service, Wanchai, Hong Kong.

Correspondence: C.H. Chau, Tuberculosis and Chest Unit, Grantham Hospital, 125 Wong Chuck Hang Road, Aberdeen, Hong Kong. E-mail: chau_ch@hotmail.com

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TABLE 1 Clinical profile of two patients

	Resistance pattern	Current tuberculosis treatment[#]	Linezolid dosage	AFB smear	AFB culture	Adverse events due to linezolid
Patient 1	All except cycloserine, capreomycin and ethionamide	Oct 2008 to Dec 2008: Amikacin (5 times·week^{-1}), levofloxacin, ethambutol, cycloserine, prothionamide and linezolid	800 mg *q.d.* 7 weeks	+	+	
		Dec 2008 to Feb 2009: Capreomycin (5 times·week^{-1}), levofloxacin, cycloserine prothionamide and linezolid	800 mg *q.d* 9 weeks	+/-	+/-	Peripheral neuropathy
		Feb 2009 to April 2009: Isoniazid and capreomycin (both 3 times·week^{-1}), levofloxacin, cycloserine and prothionamide		-	-	
		April 2009 to present: Isoniazid and capreomycin (both 3 times·week^{-1}), levofloxacin, cycloserine and prothionamide		-	?	
Patient 2	Streptomycin, isoniazid, rifampicin and levofloxacin	Feb 2008 to April 2008: Levofloxacin, prothionamide, cycloserine, para-aminosalicylic acid, linezolid and kanamycin (3 times·week^{-1})	600 mg *b.d.* 7 weeks	+	+	Anaemia[§], leukopenia[§], anorexia
	Streptomycin, isoniazid, rifampicin and levofloxacin	April 2008 to May 2008: levofloxacin, prothionamide cycloserine, para-aminosalicylic acid and kanamycin (3 times·week^{-1})		+	+	
	Streptomycin, isoniazid, rifampicin and levofloxacin	May 2008 to June 2008: Levofloxacin, prothionamide, cycloserine, para-aminosalicylic acid, linezolid and kanamycin (3 times·week^{-1})	600 mg *b.d.* 5 weeks	+/-	+/-	Pancytopenia[f], anorexia
	Streptomycin, isoniazid, rifampicin and levofloxacin	June 2008 to July 2008: Levofloxacin, prothionamide, cycloserine, para-aminosalicylic acid and kanamycin (3 times·week^{-1})		-	-	
	Streptomycin, isoniazid, rifampicin and levofloxacin	July 2008 to Oct 2008: Levofloxacin, prothionamide, cycloserine and para-aminosalicylic acid		-/+	-/+	
	Streptomycin, isoniazid, rifampicin and levofloxacin	Oct 2008 to Feb 2009: Levofloxacin, prothionamide, cycloserine and para-aminosalicylic acid		+	+	
	Streptomycin, isoniazid, rifampicin and levofloxacin	Feb 2009 to April 2009[¶]: Levofloxacin, prothionamide, linezolid, cycloserine, isoniazid and pyrazinamide (both 3 times·week^{-1}), and capreomycin (twice a week)	800 mg *q.d* 9 weeks	+	+	Anaemia[##]
	Streptomycin, isoniazid, rifampicin and levofloxacin	April 2009 to May 2009[¶]: Levofloxacin, prothionamide, linezolid, cycloserine, isoniazid and pyrazinamide (both 3 times·week^{-1}), and capreomycin (twice a week)	800 mg *q.d* 5 weeks	+/-	+	Anaemia[##]
	Streptomycin, isoniazid, rifampicin and levofloxacin	May 2009 to June 2009[¶]: Levofloxacin, prothionamide, linezolid, cycloserine, isoniazid and pyrazinamide (both 3 times·week^{-1}), and capreomycin (twice a week)	600 mg *q.d* 2 weeks	-	?	
	Streptomycin, isoniazid, rifampicin and levofloxacin	June 2009 to present: Levofloxacin, prothionamide, cycloserine, isoniazid and pyrazinamide (both 3 times·week^{-1}), and capreomycin (twice a week)	1200 mg three times a week	-	?	

AFB: acid-fast bacilli. +: positivity; -: negativity; +/-: a change from positivity to negativity; -/+: a change from negativity to positivity; ?: pending results. [#]: all administered daily, unless otherwise stated; [¶]: daily treatment was given six times per week; [§]: lowest haemoglobin level 6.2 g·dL^{-1} (transfusion required), lowest counts for leukocytes and neutrophils 3.1 and 1.1, respectively; [f]: lowest haemoglobin level 7.5 g·dL^{-1} (transfusion not required), lowest counts for leukocytes, neutrophils and platelets 2.3, 0.5, and 74, respectively; [##]: lowest haemoglobin level 8.7 g·dL^{-1} (good recovery without transfusion), normal counts for leukocytes, neutrophils and platelets.

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Small airway obstruction in severe pulmonary arterial hypertension correlates with increased airway CD8+ T-cells and fractalkine expression

To the Editors:

Pulmonary arterial hypertension (PAH) is primarily a disease of lung small arteries. However, several studies have documented mild-to-moderate peripheral airflow obstruction in most adults [1–3] and children [4] with PAH, which could be significantly reversed with β_2-agonist administration [5]. Although peribronchial infiltrates have been scarcely reported in PAH [1], it is still unclear whether airway dysfunction occurs as a result of lung vascular disease or from a direct impairment of the airways.

In lung specimens from six patients with severe group I PAH [6] undergoing lung transplantation (and who did not display signs of cardiopulmonary decompensation at that time), we assessed airway inflammatory cell infiltration and PAH-related chemokine expression in comparison with specimens from nine nonsmoking controls (sampled as far as possible from the tumour) and correlated findings to lung function data. Patient's characteristics and lung function tests are summarised in table 1.

No impairment of routine lung function tests was observed in PAH patients, except a trend for lower forced expiratory volume in 1 s and increased residual volume. However, among indices of small airway function, corrected mean maximal expiratory flow (MEF_{50}) [2] was significantly decreased in severe PAH patients compared with controls (table 1; $p<0.05$). Highly significant increases in CD3+ T-cells were observed within the epithelium of large and small airways of PAH patients ($p<0.01$), as well as in submucosal glands and in lamina of bronchioles. CD4/CD8 immunohistochemistry indicated that these T lymphocytes consisted mainly of CD8+ T-cells (fig. 1). In contrast, no significant changes were observed for neutrophils and macrophages, except a modest increase of macrophages in small airways ($p=0.03$). In addition, intraepithelial infiltration of CD8+ T-cells correlated with corrected MEF_{50} ($r_s= -0.81$, $p=0.05$) in small airways; a functional parameter of small airway obstruction in these patients (fig. 2). Moreover, immunoreactive cells for fractalkine were observed in small pulmonary arteries of lung sections from PAH patients, as well as in large ($p=0.003$) and small airways ($p=0.002$) that consisted of structural cells such as epithelial cells and subepithelial inflammatory cells, in contrast to RANTES which did not significantly differ between groups (fig. 3).

In three out of 10 PAH patients for whom lung specimens were available, FERNANDEZ-BONETTI and LUPI [1] described the existence of airway narrowing, bronchial wall thickening and mononuclear infiltrates dominated by lymphocytes with some plasma cells, as well as a few granulocytes. Accordingly, we showed that this inflammatory infiltrate mainly consists of CD3+ T-cells and, to a marginal extent, macrophages, and that large airways are also consistently infiltrated by T-cells. Although we can not formally exclude a difference in sensitivity of CD8 *versus* CD4 tissue immunodetection, T-cell infiltrates seem to predominantly consist of CD8+ lymphocytes. It is tempting to speculate that fractalkine, which

TABLE 1 Patients' characteristics with hemodynamic and lung function tests

	PAH	Controls
Subjects n	6	9
Age yrs	45±14	62±7
Male:female n	4:2	4:5
$\bar{P}_{pa}$ mmHg	73±9	ND
FEV_1 % pred	81±10	107±3
FEV_1/VC %	70±6	76±5
TLC % pred	98±5	111±4
RV % pred	136±31	80±7
MEF_{50} % pred	82	86
Corr MEF_{50} $s^{-1\#}$	1.5±0.5*	1.9±0.2
$D_{L,CO}$ % pred	80±24	86±10

Data are presented as mean± SD, unless otherwise stated. PAH: pulmonary arterial hypertension; $\bar{P}_{pa}$: mean pulmonary artery pressure; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; VC: vital capacity; TLC: total lung capacity; RV: residual volume; MEF_{50}: mean maximal expiratory flow; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; ND: not determined. #: MEF_{50} corrected for remaining VC fraction, corr $MEF_{50}=MEF_{50}\times(0.50\times VC)^{-1}$. *: $p<0.05$.