well put young people at an unacceptable risk. A young person most likely needs higher absolute values to qualify for safe resection; in other words, a 25-yr-old patient with 20% ppo function for FEV1 has much more unhealthy lungs than a 70-yr-old patient with a ppo value of 30%, although in absolute values they both have 0.9 L.

The current use of percent of predicted values has been shown to work well and, generally speaking, guidelines should suggest cut-off values which err on the side of safety. The trend to include more patients with marginal cardio-pulmonary functional reserves for resection will continue [4], but must be based on evidence.

C.T. Bolliger*, A. Brunelli[#] and A. Charloux[¶]

*Internal Medicine, University of Stellenbosch, Faculty of Health Sciences, Cape Town, South Africa, [#]Dept of Thoracic Surgery, Umberto I Regional Hospital, Ancona, Italy, and [¶]Physiologie et Explorations Fonctionnelles, Hôpitaux Universitaires de Strasbourg, Strasbourg, France.

Correspondence: C.T. Bolliger, Internal Medicine, University of Stellenbosch, Faculty of Health Sciences; 7505 Tygerberg, Cape Town, South Africa, 75505. E-mail: ctb@sun.ac.za

Statement of Interest: None declared.

REFERENCES

1 Brunelli A, Charloux A, Bolliger CT, *et al.* ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 2009; 34: 17–41.
2 Bolliger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. *Eur Respir J* 1998; 11: 198–212.
3 Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilator flows. Report Working Party Standardization of Lung Function Tests. European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, S5–S40.
4 Bolliger CT. Functional reserve before lung resection. How low can we go? *Respiration.* 2009; 78: 20–22.

DOI: 10.1183/09031936.00187109

Assessment of linezolid efficacy and safety in MDR- and XDR-TB: an Indian perspective

To the Editors:

We read with interest the analysis of the efficacy, tolerability and safety profile of linezolid in multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) in the retrospective TBNET (Tuberculosis Network European Trials group) study by MIGLIORI *et al.* [1]. Before this publication, scattered case reports and small case series have been the only source of data on the efficacy and safety of this drug in the treatment of MDR- and XDR-TB cases.

Linezolid is the first oxazolidinone to be developed and introduced in clinical use. *In vitro* studies have shown good activity against different species of mycobacteria, including resistant strains. The linezolid minimum inhibitory concentration to inhibit the growth of 90% of organisms for *Mycobacterium tuberculosis* is in the range of 1–2 $mg \cdot L^{-1}$ [2]. However, clinical experience with the use of linezolid in the management of mycobacterial infection is still sparse.

The use of linezolid is especially relevant in a country like India, which bears the burden of a third of the world's MDR-TB patients. The most recent, *i.e.* fourth, World Health Organization global resistance report, released in February 2008, estimated there were 110,132 cases of MDR-TB from India in 2006. This accounted for 20% of the world's MDR-TB burden. Between them, India and China accounted for 50% of the global MDR-TB burden [3].

Acquired drug resistance, not just to isoniazid and rifampicin, but also to other second-line drugs is also common in India and XDR-TB strains have been increasingly reported since the first report from India was published in 2007 [4]. Physicians increasingly need to fall back on newer (Group V) and experimental drugs in order to make up the minimum recommended number of active drugs (ideally four or five) to ensure a successful regime. Linezolid has been increasingly used in this role. It is relatively cheap, available off-patent and there are currently 10 generic preparations available in the Indian market. Little is known about its efficacy or toxicity in the Indian context.

We report our clinical experience with the use of linezolid in a cohort of 78 Indian MDR- and XDR-TB patients (36 males and 42 females) being treated at the chest outpatient department of a large private tertiary referral hospital in Mumbai (India). In this prospective, non-randomised study from 2000 to 2007, 18 out of the 78 patients received linezolid. Of these 18 patients, seven harboured XDR-TB and 11 were MDR-TB patients. The mean duration of therapy with the drug was as long as 20.6 months. All 18 patients received the drug only in a dose of 600 mg, once a day. Of these 18 cases, 11 patients were cured, four failed treatment and three were lost to follow-up. In our cohort, the use of linezolid was not associated with any difference in treatment outcome.

In comparison with the TBNET cohort (table 1), we noticed a higher incidence of major adverse reactions (61%) in our patients. Chief among these was a severe peripheral neuropathy. 16 patients were affected by sensory-motor neuropathy.

TABLE 1 Comparison of the TBNET cohort (MIGLIORI *et al.* [1]) and the present (Udwadia) cohort

Variables	TBNET cohort	Udwadia cohort
Study design	Retrospective	Prospective
Time of study	2001–2007	2004–2007
Setting	Centres: multicentre; 21 participating centres in Belarus, Germany, Italy and Switzerland	Single centre: the chest outpatient department of a single, large, private, tertiary referral hospital in Mumbai, India
Sample size	195 subjects	78 subjects
Mean age of patients yrs	Not mentioned	29 yrs
Sex	Not mentioned	36 male, 42 female
Linezolid arm	85 out of 195 patients	18 out of 78 patients
MDR-TB	41 (91.1%) out of 45	11 (61.1%) out of 18
XDR-TB	4 (8.9%) out of 45	7 (38.8%) out of 18
Methodology	Retrospective, nonrandomised, unblinded, study evaluating the safety and tolerability of linezolid at 600 mg, once a day or twice a day, in MDR-/XDR-TB treatment. Efficacy evaluation compared end-points of 45 linezolid-treated against 110 linezolid-nontreated cases	Prospective, nonrandomised addition of linezolid to the treatment regimes of 78 consecutive MDR- and XDR-TB patients to assess outcome and safety, 18 of whom received linezolid
Linezolid dosage	600 mg once a day in 28 patients, 600 mg twice a day (1200 mg·day^{-1}) in 57 patients	600 mg once a day in all patients
Linezolid administration time	32 weeks	20.6 months
Regimen used	Individualised	Individualised
Treatment outcome in linezolid group		Cured: n=11; treatment failure: n=4; lost to follow-up: n=3
Mean sputum smear conversion	102 days	
Mean culture conversion	109 days	
Cured	23 subjects	
Completed	13 subjects	
Death	9 subjects	
Failure	0 subjects	
Efficacy end-points (sputum conversion)	600 mg *q.d.*, 10 (71.4%) out of 14; 600 mg *b.i.d.*, 21 (67.7%) out of 31	Data on time to sputum smear and culture conversion are not available due to financial constraints.
Sputum smear conversion	600 mg *q.d.*, 13 (92.9%) out of 14	
Culture conversion	600 mg *b.i.d.*, 26 (83.9%) out of 31	
Safety (adverse effects)	600 mg *q.d.*, 4 (14.3%) out of 28; 600 mg *b.i.d.*, 23 (40.4%) out of 57	600 mg *q.d.*, 11 (61%) out of 18
Time duration after which the adverse effects occurred	After 60 days of treatment	Within 1–3 months
Main adverse effect	Anaemia in 44%	Peripheral neuropathy in 38.88%
Conclusions	Risk of adverse effects but safer dosage could be prescribed without losing the potential benefits; use for only the most complicated MDR/XDR-TB cases [5]	Linezolid proved to be effective but highly toxic in Indian patients with MDR/XDR-TB. This warrants extreme caution when this drug is used for prolong periods of time in MDR/XDR-TB patients

TBNET: Tuberculosis Network European Trials; MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

Nerve conduction study was performed in nine of the 16 patients, revealing axonopathy in all cases studied. The adverse event was always affecting the lower limbs. Neuropathy was often disabling and crippling and persisted for several years after stopping the drug. The higher incidence of neuropathy in our series could have been due to the fact that our Indian MDR-TB patients are likely to have been more malnourished than their European counterparts. 16 out of the 18 patients in the linezolid group were malnourished with BMI <18 kg·m^{-2}.

One of our patients developed bilateral blindness secondary to a linezolid-induced bilateral optic neuropathy. This developed 3 months after the drug was initiated and reversed completely within 1 month of stopping linezolid. Only one other case report is available in literature documenting optic neuropathy after the use of linezolid [6]. Only one patient developed anaemia severe enough to need transfusion.

In conclusion, linezolid proved to be an effective but highly toxic drug in Indian patients with MDR-TB. We have learned

to use it with caution, in a dose never exceeding 600 mg, once a day, in patients with MDR- and XDR-TB, who have few other drug options. All of our patients were given written instruction on the side-effects that they are likely to encounter and, at each follow-up, these were diligently checked for. In all patients treated with linezolid, clinical, haematological and neurological evaluations are mandatory on a monthly basis, as well as frequent opthalmological tests.

To conclude, the high frequency of adverse effects to linezolid warrants extreme caution when this drug is used for prolonged periods of time in MDR-TB patients. Thus, prospective, randomised and multicentre evaluations are needed in order to test the efficacy of linezolid as well as the short- and long-term tolerability of the drug in TB patients.

Z.F. Udwadia, T. Sen and G. Moharil
Dept of Pulmonary medicine, P.D.Hinduja National Hospital and Medical Research Centre, Veer Savarkar Marg, Mahim, Mumbai, India.

Correspondence: Z.F. Udwadia, Dept of Pulmonary Medicine, P.D.Hinduja National Hospital And Medical Research Centre. Veer Savarkar Marg, Mumbai, Maharashtra, 400016, India. E-mail: zfudwadia@gmail.com

Statement of Interest: None declared.

REFERENCES

1 Migliori GB, Eker B, Richardson MD, *et al.* A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009; 34: 387–393.
2 Alcala L, Ruiz-Serrano MJ, Perez-Fernandez Turegano C, *et al. In vitro* activities of linezolid against clinical isolates of *Mycobacterium tuberculosis* that are susceptible or resistant to first-line antituberculous drugs. *Antimicrob Agents Chemother* 2003; 47: 416–417.
3 World Health Organization. Anti-tuberculosis drug resistance in the world: The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Geneva, The World Health Organization, 2008.
4 Jain S, Rodrigues C, Mehta A, *et al*. High prevalence of XDR-TB from a tertiary care hospital in India. *PATS* 2007; 4: A510.
5 Sotgiu G, Lange C, Richardson MD, *et al.* Comment on: daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. *J Antimicrob Chemother* 2009; 64: 879–884.
6 Rucker JC, Hamilton SR, Bardenstein D, *et al.* Linezolid-associated toxic optic neuropathy. *Neurology* 2006; 66: 595–598.

DOI: 10.1183/09031936.00132009

From the authors:

We read with much interest the letter by Z.F. Udwadia and co-workers reporting interesting data on the Indian experience in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) with linezolid.

Murine studies performed a decade ago demonstrated efficacy of linezolid and other oxazolidinones against *Mycobacterium tuberculosis* [1], despite its low early bactericidal activity [2]. Few clinical reports on selected case series have been made available in the recent past for this specific, presently off-label, indication [3–6]. The profile of this drug in the treatment of MDR-/XDR-TB is at present low, as it is included in Group 5, *e.g.* the group of drugs with limited or substantially unknown activity against *M. tuberculosis* [7, 8].

Preliminary evidence indicated a high toxicity profile for its long-term use at the dose of 600 mg *b.i.d.*, as up to 25–45% of cases reported severe anaemia and/or thrombocytopenia and peripheral and optic neuropathy [3–6]. The use of the drug is also limited by its high cost, being in the order of €100 per vial in Western Europe.

The *European Respiratory Journal* has recently become a forum for discussing potentialities of this drug in the treatment of MDR-/XDR-TB cases by publishing the TBNET (Tuberculosis Network European Trials group) study on 85 cases [5] performed in four European countries (including Belarus in Eastern Europe), the Indian experience presented by Z.F. Udwadia and co-workers from Mumbai, India of 18 cases, and the two case reports of YEW *et al.* [9] regarding the use of linezolid 800 mg *q.d.*

The aim of the present study is to discuss the key findings of the TBNET [5] and Indian studies and to draw further conclusions, focusing on the available evidence on linezolid safety.

The table included in the study by Z.F. Udwadia and co-workers was revised, including a statistical comparison between the main results of the two studies whenever possible.

Data were analysed using Stata 9.0 (StataCorp, College Station, TX, USA). Comparisons between proportions were performed using the Chi-squared test; unpaired t-tests were used for continuous variables when appropriate. Differences were considered to be significant when $p<0.05$.

The comparison between the two studies suggests the following three main conclusions.

Representativeness and study design: the study by Z.F. Udwadia and co-workers was performed at a single tertiary hospital in India, whereas the study by MIGLIORI *et al.* [5] included patient data from more than 20 hospitals in four European countries. Genetic differences between the patient populations could have a role in explaining the different proportions of adverse events found in the two studies. While the European study was retrospective, the Indian one is prospective, allowing for collection of more variables, including, for example, body weight. This allowed the calculation of the body mass index and discussion of the potential role played by malnutrition in increasing the proportion of cases facing adverse events.

Drug dosage, treatment duration and adverse events: the duration of linezolid treatment was longer in the Indian than in the European study (table 1). 600 mg *q.d.* was prescribed in the Indian study, while either 600 or 1,200 mg was used in the European one. While in the European study the patients who were prescribed 600 mg had significantly fewer major adverse events (14.3%), in the Indian study, at the same dosage, the proportion of major side effects was significantly higher than that of the overall sample in Europe (61% *versus* 40.4%; $p<0.001$) (table 1). While in Europe anaemia was the main