Is delamanid a potential agent in the treatment of diseases caused by *Mycobacterium avium-intracellulare*?

To the Editor:

Delamanid, a new agent derived from the nitro-dihydro-imidazooxazole class of compounds that inhibits mycolic acid synthesis, has strong *in vitro* activity against *Mycobacterium tuberculosis*, including multidrug resistant (MDR) strains [1]. The drug has been proven to be effective in treatment of MDR tuberculosis (MDR-TB) patients [2–5]. Delamanid is pharmacologically characterised by an excellent intracellular bactericidal activity and a high accumulation rate [6].

It has been known for decades that for patients with pulmonary disease caused by *Mycobacterium avium-intracellulare* complex (MAC), the rates of failure, relapse, death and default are high [7]. Treatment options after failure of first-line drug combinations are poor and regimen with alternative drug combinations are not yet established [8]. Although scientific evidence for treatment concepts based upon drug susceptibility tests *in vitro* is not broad, such testing is recommended in case of treatment failure [8, 9].

Screening the new tuberculosis drugs, like delamanid (and bedaquiline), for activity against nontuberculous mycobacteria (NTM) was recently required [10, 11].

For decades, our laboratory routinely determines minimal inhibitory concentrations (MIC) of first- and second-line tuberculosis drugs in MDR-TB as well MAC and other NTM strains [12].

In order to evaluate a potential role of delamanid in the treatment of MAC disease, we tested 20 strains of MAC against the new compound. All samples were clinical isolates from patients with pulmonary disease treated at our centre between 2008 and 2015. MIC testing was performed with a modified agar dilution method on Middlebrook 7H10 agar as described elsewhere [13–15]. MIC was defined as the lowest drug concentration that inhibits at least 99% of the bacterial proportion after a two-fold serial dilution of the respective drug (MIC_{99}).

Results are shown in table 1. MAC strains, among those single strains with high MIC against clarithromycin, exhibited low MIC against delamanid, varying from 0.013 to 0.4 $\mu g \cdot mL^{-1}$. The MIC tend to be only slightly higher than those published about strains of *M. tuberculosis* [1]. To our knowledge, this is the first evidence that delamanid is a potential agent in the treatment of diseases caused by *M. avium-intracellulare*.

Thus, it seems worth it to evaluate delamanid in clinical studies on the treatment of patients who experience treatment failure of mycobacterial disease caused by MAC. In general, these diseases require a lengthy treatment. Therefore, a design for a clinical study of delamanid in a combination treatment of diseases caused by mycobacteria which are difficult to treat, such as MAC, should give consideration to an administration of delamanid longer than 6 months as approved for the treatment of MDR tuberculosis.

In view of the excellent intracellular accumulation of delamanid which achieves drug concentrations higher than the MIC we measured for MAC strains also with daily doses of 100 mg [6], a study on a combination treatment of patients with refractory or recurrent MAC disease with a delamanid dosage lower than the recommended daily allowance for the treatment of MDR tuberculosis (200 mg) should be discussed.

TABLE 1 Minimal inhibitory concentrations of delamanid against *Mycobacterium avium-intracellulare* complex strains

	Strains n	Minimal inhibitory concentrations $\mu g \cdot mL^{-1}$					
		0.013	0.025	0.05	0.1	0.2	0.4
Mycobacterium avium	9		1		3	5	
Mycobacterium intracelullare	11	3	3	2	1	1	1

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Delamanid shows low minimal inhibitory concentrations *in vitro* against *M. avium-intracellulare* strains http://ow.ly/xDiM304ul7O

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Specific airway resistance in preschool children: why not panting after all?

To the Editor:

Specific airway resistance (sR_{aw}) is measured with minimal cooperation in the preschool child during tidal breathing [1]. Methodological difficulties have been encountered in modern plethysmographs when the warming and humidification of the inspired gas [2] are replaced by numerical algorithms to eliminate the thermo hygrometric artefact [1, 3, 4]. Measuring sR_{aw} during panting [5] had been dismissed in preschool children based on the assumption that the ventilatory manoeuvre would be difficult to perform and