Bedaquiline as a potential agent in the treatment of *Mycobacterium abscessus* infections

To the Editor:

Mycobacterium abscessus is increasingly being recognised as a significant human pathogen, especially in patients with cystic fibrosis, and the specific *M. abscessus* subspecies seems to influence the clinical outcome [1]. The pulmonary manifestation of this nontuberculous mycobacteria (NTM) infection is one of the most difficult to treat forms, leading to substantial morbidity and mortality in this population [1, 2]. *M. abscessus* strains are highly resistant to most antibacterial drugs [2]. The recent development of liposomal amikacin for inhalation for patients with cystic fibrosis suggested a therapeutic breakthrough. However, even though sputum conversion was improved in a phase 2 study, the primary end-point (change from baseline to day 84 on a semi-quantitative mycobacterial growth scale) was not reached [3]. We analysed the minimal inhibitory concentration (MIC) of another promising new anti-tuberculous drug, bedaquiline, using 20 clinical isolates of *M. abscessus*. No systematic studies on the distribution of MIC for *M. abscessus* have been performed previously.

Bedaquiline is a diarylquinoline drug recently licensed for the treatment of multidrug-resistant *Mycobacterium tuberculosis* infections. It acts through inhibition of the mycobacterial F_1F_0-ATP synthase, [4] and is characterised by excellent intracellular bactericidal activity and a high accumulation rate [4]. In previous studies, bedaquiline showed excellent *in vitro* activity against *M. tuberculosis*, including multidrug-resistant strains [5]. The new drug has been successfully and safely used in the treatment of both adult and paediatric multidrug-resistant and extensively drug-resistant tuberculosis alike [6, 7], even over extended periods of as long as 18 months [8].

As for other NTM, *in vitro* drug susceptibility testing of *M. abscessus* strains using conventional drugs is recommended only after treatment failure occurs [2]. We present the *in vitro* bedaquiline MIC results of 20 clinical strains of *M. abscessus* isolated in our centre between 2011 and 2016 from patients with pulmonary NTM disease, including three patients with cystic fibrosis. In this study, 4/20 strains (20%) were classified as *M. abscessus* subspecies *bolletii*, while all others belonged to the *M. abscessus* subspecies *abscessus*. The third*M. abscessus* subspecies, *M. abscessus* subspecies *massiliense* was not identified among our strains. MIC was determined by a modified agar dilution method on Middlebrook 7H10 agar, as described previously [9]. MIC was defined as the lowest drug concentration that inhibited at least 99% of the bacterial proportion after a two-fold serial dilution of the respective drug (MIC99).

Results are shown in table 1. All *M. abscessus* strains tested exhibited a MIC for bedaquiline of $\leqslant 1$ μg·mL^{-1}, and 17/20 (85%) had a MIC of $\leqslant 0.5$ μg·mL^{-1}. Median MIC for all *M. abscessus* strains was 0.5 μg·mL^{-1}, only slightly higher than that for *M. tuberculosis* (0.4 μg·mL^{-1}) [10]. For each of the three *M. abscessus* strains isolated from patients with cystic fibrosis, the MIC was also 0.5 μg·mL^{-1}. *M. abscessus* subspecies *bolletii* showed a trend towards lower MIC values than *M. abscessus* subspecies *abscessus* (chi-squared test: p=0.135). To our knowledge, this is the first series of published MIC values for clinical *M. abscessus* strains tested against bedaquiline. The single strains tested by Obregón-Henao *et al.* [11] and Andries *et al.* [12] revealed MICs of 1.0 μg·mL^{-1} and 0.25 μg·mL^{-1}, respectively, both similar to ours. The European Committee on Antimicrobial Susceptibility Testing break-point for *M. tuberculosis* is 0.25 μg·mL^{-1}, thus 3/20 strains (15%) had a MIC equal to or lower than this break-point, and most strains (17/20, 85%) showed a MIC below or only slightly higher than that ($\leqslant 0.5$ μg·mL^{-1}).

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Cite this article as: Vesenbeckh S, Schönfeld N, Roth A, *et al.* Bedaquiline as a potential agent in the treatment of *Mycobacterium abscessus* infections. *Eur Respir J* 2017; 49: 1700083 [https://doi.org/10.1183/13993003.00083-2017].

TABLE 1 Minimal inhibitory concentrations (MIC) of bedaquiline for 20 *Mycobacterium abscessus* strains, according to subspecies (chi-squared test: p=0.135)

***M. abcessus* subspecies**	**Strains n**	**MIC µg·mL^{-1}**			
		0.12	**0.25**	**0.5**	**1.0**
M. abcessus* subsp. *bolletii	4	1/20 (5%)	1/20 (5%)	2/20 (10%)	0
M. abcessus* subsp. *abscessus	16	0	1/20 (5%)	12/20 (60%)	3/20 (15%)

Keeping in mind that only a few treatment options for *M. abscessus* infections are available [1, 2], bedaquiline could be an effective alternative in the multidrug second-line therapy of this mycobacterial disease. At standard oral doses, bedaquiline maintained a mean plasma concentration of 0.6 mg·L^{-1}, as shown in early pharmacokinetic studies [13], and it was extensively distributed to tissues, including the lungs [12]. Bedaquiline significantly reduced the bacterial burden in the lungs after 4 days of treatment at least in one *M. abscessus* -infected mouse model [11], but by contrast, Lerat *et al.* [14] reported in 2014 that bedaquiline showed almost no activity in his nude mice. Philley *et al.* [15] reported that when bedaquiline was used as salvage therapy in a human study of four patients with *M. abscessus* disease, there was clinical improvement in all cases at 3 months of treatment, a sustained reduction of bacterial load in sputum in half of all patients, and no severe side effects. However, after 6 months of observation, only one patient still showed improvement of clinical symptoms. In the study reported by Philley *et al.* [15], the same bedaquiline doses as those recommended for *M. tuberculosis* were used. Owing to the high intracellular accumulation rate of the lipophilic drug bedaquiline, it is likely that even with a slightly higher MIC compared with that for *M. tuberculosis*, the drug will be effective against *M. abscessus* strains without increasing drug doses. Early bactericidal activity trials might be helpful in selectively demonstrating the *in vivo* activity of bedaquiline without other background combination drugs.

Considering the rising incidence of *M. abscessus* infections worldwide as well as the frequent multidrug resistance with subsequent treatment failure, bedaquiline could be an alternative in multidrug treatment regimens for severe or relapsing disease, potentially including patients with underlying cystic fibrosis. In our study, only three patients with underlying cystic fibrosis were included, thus clinical trials involving patients with cystic fibrosis are necessary to confirm this potential use.

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Received: Jan 13 2017 | Accepted after revision: Feb 13 2017

Conflict of interest: None declared.

References

1 Robinson PD, Harris KA, Aurora P, *et al.* Paediatric lung transplant outcomes vary with *Mycobacterium abscessus* complex species. *Eur Respir J* 2013; 41: 1230–1232.
2 Schönfeld N, Haas W, Richter E, *et al.* Recommendations of the German Central Committee against Tuberculosis (DZK) and the German Respiratory Society (DGP) for the diagnosis and treatment of non-tuberculous mycobacterioses. *Pneumologie* 2016; 70: 250–276.
3 Olivier KN, Griffith DE, Eagle G, *et al.* Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease. *Am J Respir Crit Care Med* 2017; 195: 814–823.
4 Hards K, Robson JR, Berney M, *et al.* Bactericidal mode of action of bedaquiline. *J Antimicrob Chemother* 2015; 70: 2028–2037.
5 Diacon AH, Pym A, Grobusch MP, *et al.* Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; 371: 723–732.
6 Pontali E, Sotgiu G, D'Ambrosio L, *et al.* Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. *Eur Respir J* 2016; 47: 394–402.
7 Tadolini M, Garcia-Prats AJ, D'Ambrosio L, *et al.* Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. *Eur Respir J* 2016; 48: 938–943.
8 Lewis JM, Hine P, Walker J, *et al.* First experience of effectiveness and safety of bedaquiline for 18 months within an optimised regimen for XDR-TB. *Eur Respir J* 2016; 47: 1581–1584.

9 Schönfeld N, Bergmann T, Vesenbeckh S, *et al.* Minimal inhibitory concentrations of first-line drugs of multidrug-resistant tuberculosis isolates. *Lung India* 2012; 29: 309–312.
10 Keller PM, Homke R, Ritter C, *et al.* Determination of MIC distribution and epidemiological cutoff values for bedaquiline and delamanid in *Mycobacterium tuberculosis* using the MGIT 960 system equipped with TB eXiST. *Antimicrob Agents Chemother* 2015; 59: 4352–4355.
11 Obregón-Henao A, Arnett KA, Henao-Tamayo M, *et al.* Susceptibility of *Mycobacterium abscessus* to antimycobacterial drugs in preclinical models. *Antimicrob Agents Chemother* 2015; 59: 6904–6912.
12 Andries K, Verhasselt P, Guillemont J, *et al.* A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 2005; 307: 223–227.
13 Diacon AH, Pym A, Grobusch M, *et al.* The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; 360: 2397–2405.
14 Lerat I, Cambau E, Roth Dit Bettoni R, *et al.* In vivo evaluation of antibiotic activity against *Mycobacterium abscessus*. *J Infect Dis* 2014; 209: 905–912.
15 Philley JV, Wallace RJ Jr, Benwill JL, *et al.* Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. *Chest* 2015; 148: 499–506.