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 F1F0-ATP synthase, 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 $\leq 1 \mu g\cdot mL^{-1}$, and 17/20 (85%) had a MIC of $\leq 0.5 \mu g\cdot mL^{-1}$. Median MIC for all *M. abscessus* strains was 0.5 $\mu g\cdot mL^{-1}$, only slightly higher than that for *M. tuberculosis* (0.4 $\mu g\cdot mL^{-1}$) [10]. For each of the three *M. abscessus* strains isolated from patients with cystic fibrosis, the MIC was also 0.5 $\mu g\cdot mL^{-1}$. *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 $\mu g\cdot mL^{-1}$ and 0.25 $\mu g\cdot mL^{-1}$, respectively, both similar to ours.

The European Committee on Antimicrobial Susceptibility Testing break-point for *M. tuberculosis* is 0.25 $\mu g\cdot mL^{-1}$, 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 ($\leq 0.5 \mu g\cdot mL^{-1}$).

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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 pharmacokinetic studies [13], and it was extensively distributed to tissues, including the lungs [12]. 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.

### References


