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Mefloquine as a potential drug against multidrug-resistant tuberculosis

To the Editor:

In the article by ALSAAD *et al.* [1] in a recent issue of the *European Respiratory Journal* the authors reviewed six drugs with antimicrobial activity against *Mycobacterium tuberculosis* (phenothiazine, metronidazole,

doxycycline, disulfiram, tigecycline and co-trimoxazole) which are not listed in the World Health Organization guidelines on multidrug-resistant tuberculosis (MDR-TB) treatment, but could be potential candidates for this use. Despite of the release of new drugs (delamanid, bedaquiline), treatment alternatives are still warranted, last but not least because of treatment costs. We would like to extend this list by evaluating the anti-malaria drug mefloquine.

Mefloquine is a synthetic quinine analogue. The anti-malarial effects of mefloquine are thought to be due to its accumulation within the food vacuole of the parasite where it interacts with haem [2]. Beyond its indisputable ability in malaria treatment and prophylaxis, mefloquine is bactericidal against Gram-positive bacteria and also has a poor activity against Gram-negative bacteria [3]. The minimal inhibitory concentration (MIC) of mefloquine for strains of staphylococci and enterococci was found to be 16 μg·mL^{-1}, and the minimal bactericidal concentrations ranged from 16 to 32 μg·mL^{-1} [3].

GONÇALVES et al. [4] showed that mefloquine–oxazolidine derivates have in vitro activity against M. tuberculosis. In addition, mefloquine can inhibit the Mycobacteria species in a MIC range of 8–16 μg·mL^{-1}, as demonstrated by BERMUDEZ et al. [5] against Mycobacterium avium complex in vivo and in vitro.

We evaluated the in vitro activity of mefloquine against 21 MDR- and 92 non-MDR-TB strains detected in our centre between 2001 and 2013.

For this purpose we analysed the in vitro susceptibility test results of mefloquine assessed by MIC. Testing for MIC was performed on solid Middlebrook 7H10 agar plates as described elsewhere [6]. MICs were defined as the lowest drug concentration after twofold serially diluted concentration of mefloquine, that inhibits growth of >99% of a bacterial proportion of the tested tuberculosis strain on solid Middlebrook 7H10 agar plates within 14–21 days of incubation at 37°C.

Among the 113 M. tuberculosis strains, 21 showed a resistance in vitro against isoniazid and rifampicin, which defines MDR-TB and the other 92 strains were "fully sensitive" against all first-line antituberculosis drugs.

We found the MICs for mefloquine in 17 (81%) MDR-TB strains at 8 μg·mL^{-1} and in four (19%) MDR-TB strains at 4 μg·mL^{-1}. In 72 (78.2%) of the "fully sensitive" tuberculosis strains, we detected a MIC for mefloquine at 8 μg·mL^{-1}, in 10 (10.9%) fully sensitive tuberculosis strains at 4 μg·mL^{-1} and in other 10 (10.9%) tuberculosis strains at 16 μg·mL^{-1} (table 1).

Following oral administration of mefloquine, about 75–80% of the drug is absorbed, and time to peak concentration were found to be 7–24 h [7, 8]. There is little pre-systemic metabolism of the compound, which has a terminal elimination half-life of 14–41 days (medium 20 days) [7]. Mefloquine is quickly distributed throughout the body, and has a high affinity for lipids; in blood plasma it is essentially protein-bound. Mefloquine is metabolised mainly by the liver to produce carboxymefloquine, which has no anti-malarial activity and a toxicity and half-life similar to the parent molecule [9]. It is not known if the metabolite is active against M. tuberculosis, this needs to be explored in future studies.

It can be assumed that mefloquine is a drug with a very good tissue penetration. WERNSDORFER et al. [8] were able to show that 7 days after administration of 1250 mg mefloquine, which is a standard therapeutic dose, the intracellular concentration in leukocytes was >16 μg·mL^{-1}. Therefore, we can suspect that a regular weekly dose of mefloquine leads to intracellular concentrations >16 μg·mL^{-1} over 7 days. Besides favourable MICs, the administration of mefloquine once weekly could promote patients' compliance. Data about mefloquine concentrations in lung tissue are not available.

In conclusion, our data showed that mefloquine has good in vitro activity against M. tuberculosis and especially against MDR-TB strains.

But it must be mentioned that the incidence of side effects is high (47–90%) and that higher doses of mefloquine are associated with even higher frequencies of adverse events [8]. Vertigo, nausea and

TABLE 1 Minimal inhibitory concentrations (MIC) of mefloquine against multidrug-resistant tuberculosis (MDR-TB) and non-MDR-TB-strains

	Patients n	MIC μg·mL^{-1}		
		4	8	16
MDR-TB	21	4	17	
Non-MDR-TB	92	10	72	10

headache are the most frequently reported symptoms [10]. This may limit the potential drug's utility for some patients. For long-term treatment as it is desired for MDR-TB patients, the high intracellular concentration of mefloquine could allow the option to give the standard single dose of 1250 mg every two or three weeks after an initial reduction of bacterial burden [8]. Whether such a treatment regimen is effective and able to reduce toxicity so that it would enable to tolerate mefloquine for 6 months and more has to be investigated in prospective studies including clinical effectiveness and pharmacokinetics. In general, we believe that treatment periods limited to 6 months for a single drug even within a long-term combined treatment of MDR-TB should be handled with caution, because no long-term data on the development of secondary resistance exist for the two drugs proposed for 6 months treatment period (delamanid, bedaquiline) [11].

Other studies have also shown that synergy between drugs can be of additional value [3, 5, 12]. The possible *in vitro* synergy between mefloquine and other tuberculosis drugs could be investigated by using either solid agar plates and/or fluid cultures [12].

Despite the frequent side effects, we suggest that the well-known drug should be evaluated in clinical studies on MDR- and non-MDR-TB patients for short-term efficiency, dose finding, long-term safety and long-term tolerability.

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Mefloquine has *in vitro* activity against MDR- and non-MDR-TB and should be evaluated in clinical studies http://ow.ly/OYKEv

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