Defining optimal fluoroquinolone exposure against Mycobacterium tuberculosis: contribution of murine studies

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We read with interest the research letter published by Forsman *et al*. in the *European Respiratory Journal* [1]. The authors determined the proportion of multidrug-resistant tuberculosis patients treated with moxifloxacin or levofloxacin who attained an optimal drug exposure for these drugs. The target exposure corresponded to the area under the curve ($AUC_{0\text{-}24h}$)/ minimal inhibitory concentration (MIC) ratio generating the optimal bactericidal activity. The authors based their calculations on the $AUC_{0\text{-}24h}$/MIC ratio measured in a preclinical model called Hollow Fiber System (HFS), an *in vitro* model used to assess anti-tuberculosis activity of candidate drugs. Based on this model, they reported that the target ratio was reached in only half of patients receiving moxifloxacin, and in none of those receiving levofloxacin.

Like other research groups, we have previously conducted studies in murine models that brought conclusions different from those of the HFS. No single preclinical model accurately reflects the very specific PK/PD conditions observed in human post-primary tuberculosis: in fact, each model has its own advantages and disadvantages. Compared to *in vitro* models, the main advantage for using an animal model is its ability to model both innate and adaptive immune response that participate *in vivo* to

the treatment efficacy, particularly against mycobacterial infections. Among animal models, the murine model has been used for more than sixty years and its capability to predict activity in human has been well established. When comparing results provided by murine studies to those provided by HFS, we have noted that the levofloxacin target $AUC_{0\text{-}24h}$/MIC ratio measured in mice was similar, around 150 [2, 3]. Nonetheless, the target $AUC_{0\text{-}24h}$/MIC ratio for moxifloxacin was measured in mice by two independent research teams at around 100 [2, 4] *i.e*. two times higher than the one measured in the HFS study cited by the authors [5]. If we take in consideration this higher ratio, the percentage of patients included in the study by Forsman *et al*. that reached the target exposure would be even lower, around 20-30%.

The authors suggest that, against strains harbouring the *gyrA* A90V mutation, generating a moxifloxacin MIC of 2 mg/L [2], high doses of moxifloxacin from 600 to 800 mg daily should be sufficient to reach the target exposure to kill *M. tuberculosis*. We agree with Forsman *et al*. that residual fluoroquinolone activity against the low-level resistant mutant A90V is a crucial issue, since this mutation represents the second most frequent DNA gyrase mutation, which is harboured by approximately 20% of fluoroquinolone-resistant strains [6]. However, it appears doubtful that doubling the dose of moxifloxacin can restore the activity against strains with 4- to 8-times higher MIC. Our group has measured the activity of moxifloxacin against A90V mutants in two different murine strains: these studies showed that high doses of moxifloxacin, equivalent to 800 mg/day in humans, generated bacteriostatic activity only [2, 7]. When combined with other second-line drugs, high doses of moxifloxacin increased the activity of the regimen but did not reach the level of the same regimen against a susceptible strain [8]. Thus, adding moxifloxacin 800 mg/day to a drug regimen against *M. tuberculosis* strains harbouring *gyrA* A90V mutation may likely only have limited effectiveness. This benefit has to be balanced with toxicity, in particular QT interval prolongation, which is also reported in association with the use of new drugs such as bedaquiline or delamanid. In addition to the clinical trial cited by the authors, observational evidence has also shown that, in bedaquiline-based regimens for multidrug-resistant tuberculosis, high-dose moxifloxacin is the main risk factor for QT prolongation [9].

In conclusion, we agree with the authors that moxifloxacin 400 mg/day and levofloxacin 500 mg/day are suboptimal doses with regard to anti-tuberculous activity. This finding is even more relevant in light of the possible inclusion of fluoroquinolones in shorter regimens for drug-susceptible tuberculosis, where fluoroquinolone exposure could be further reduced by the co-administration of rifamycins [10]. Possible approaches may include routine therapeutic drug monitoring and/or the use of higher fluoroquinolone doses. However, the benefit-risk of the latter strategy should be carefully evaluated.

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