

Title: Cardiac safety of XDR-TB regimens including bedaquiline, delamanid, and clofazimine

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To the Editor,

I read with interest the recent report by Tadolini *et al* describing QT prolongation in a patient with XDR-TB being treated with both bedaquiline and delamanid [1]. QT prolongation is a recognized safety concern for both these drugs. In a placebo-controlled trial of delamanid in MDR-TB, QTcF intervals (using the Fridericia correction for heart rate [2]) increased 12.1 ms more from baseline in delamanid recipients over 6-10 weeks [3]. An increase of similar magnitude was observed in an open-label 24 week trial of bedaquiline, with most of the effect becoming apparent within the first 1-2 weeks [4]. The authors are correct that there is currently no clinical information regarding QT prolongation when these two drugs are co-administered.

However, readers may be less aware of QT prolongation due to clofazimine, which this patient also received as part of XDR-TB treatment. Clofazimine is a potent inhibitor of hERG (human ether-a-go-go-related gene) potassium channel signaling, with essentially complete inhibition occurring *in vitro* at sub-therapeutic concentrations [4, 5]. hERG mutations can result in QT prolongation and potentially fatal arrhythmias, including ventricular tachycardia and torsade de pointe [6, 7]. *In vitro* measurement of hERG signaling effects is an important preclinical drug development tool to identify potential arrhythmia-inducing compounds [8], although recent studies indicate the modulating effects of other channels [9]. Testing for hERG signaling effects was not available at the time clofazimine was developed, some 50 years ago.

Two studies and one case report confirm the QT prolonging effects of clofazimine. In one study, 105 patients with newly diagnosed drug-sensitive tuberculosis were treated for 2 weeks with one of seven drugs or regimens (N=15 per arm), of which 4 included clofazimine 100 mg daily [10]. By day 14, QT intervals in patients receiving clofazimine alone increased from baseline by a mean of 17 ms. Patients receiving regimens containing both clofazimine and bedaquiline had increases of 20 to 21 ms. Patients receiving neither drug had no change in QT (-3 to 2 ms). Given the unusual pharmacokinetics of clofazimine, it is unlikely that this short treatment interval (14 days) was sufficient to reach steady state effects.

In a second study, 233 patients with drug-resistant tuberculosis were treated for 24 weeks with bedaquiline in an open label single arm trial, in combination with an individualized background regimen [4]. Ten patients not receiving clofazimine at the time of enrollment were started on bedaquiline plus a background regimen including clofazimine. By week 24, their QTcF interval had increased 41.5 ± 8.4 ms (mean \pm SE) from baseline. In contrast, in patients whose background regimen did not include clofazimine, the QTcF interval increased by only 12.9 ± 4.1 ms ($P=.009$).

Lastly, one case report describes ventricular tachycardia and torsade de pointe occurring in a 66 year old man who had been treated for recurrent erythema nodosum leprosum with 300 mg of clofazimine per day for 11 months [11].

These findings indicate that clofazimine may indeed have been an important contributor to the QT prolongation in the patient reported by Tadolini *et al*. Studies are needed to determine if clofazimine potentiates the combined QT prolonging effects of bedaquiline plus delamanid as it does with bedaquiline alone. The safety of regimens containing bedaquiline plus delamanid may be substantially improved if clofazimine can be omitted.

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