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Drug-drug interaction management of bedaquiline and other medications associated with QT-interval prolongation

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Background

The M2 metabolite of bedaquiline may cause QT prolongation associated with a risk of torsades de pointes (TdP). Co-medications may also cause QT prolongation, and may further increase the risk of TdP. ECG monitoring is recommended before and during treatment with bedaquiline, esp. when patients have additional risk factors (e.g., co-medication, age >70 years, female gender, diabetes, cardiac disease, hypokalemia, etc). The frequency of ECG monitoring is dependent on local circumstances.

As part of the development of the on line DDI Manager® Tuberculosis tool (www.ddimanager.co/tuberculosis; under construction) we assessed the recommendations for drug-drug interaction (DDI) management of bedaquiline when combined with co-medications. The aim of the DDI Manager® Tuberculosis is to advise health care providers worldwide with recommendations for DDI management that can be easily applied when treating patients with tuberculosis.

Methods

The product labels of bedaquiline and 978 co-medications were searched for recommendations on ECG monitoring as part of DDI management. That information was compared to recommendations described on www.crediblemeds.org. We evaluated three types of DDIs leading to an increased risk on TdP: (1) inhibition of CYP3A-mediated metabolism of bedaquiline and M2 by co-medication; (2) additive effect of co-medication on QT prolongation; (3): 1&2 combined. Finally, we compared DDI management recommendations for a selected group of agents from our assessment with data from two Dutch (G-standaard & HealthBase) and two international (Lexicomp/Up-to-date® & Stockley) medication surveillance systems.

Results

We identified 143 (14.6%) co-medications in our database of 978 agents that - when combined with bedaquiline – potentially increase the risk of TdP (Figure 1). These 143 co-medications could be subdivided in 19 agents that were moderate/strong CYP3A inhibitors (not causing QT prolongation when given alone), 93 agents with a possible or known intrinsic risk of TdP (not being a moderate/strong CYP3A inhibitor), and 31 agents that have both an intrinsic risk of TdP and inhibit CYP3A. We labeled three agents “avoid use” because they have a known intrinsic risk of TdP AND are moderate/strong CYP3A inhibitors: erythromycin, clarithromycin, and dronedarone. In cases where bedaquiline is the preferred antituberculous agent, safer alternatives for these co-medications should be selected, if possible. In all other situations, DDI management recommendations were developed that if co-administration cannot be avoided, more frequent ECG monitoring than what is normally applied for bedaquiline alone is advised.

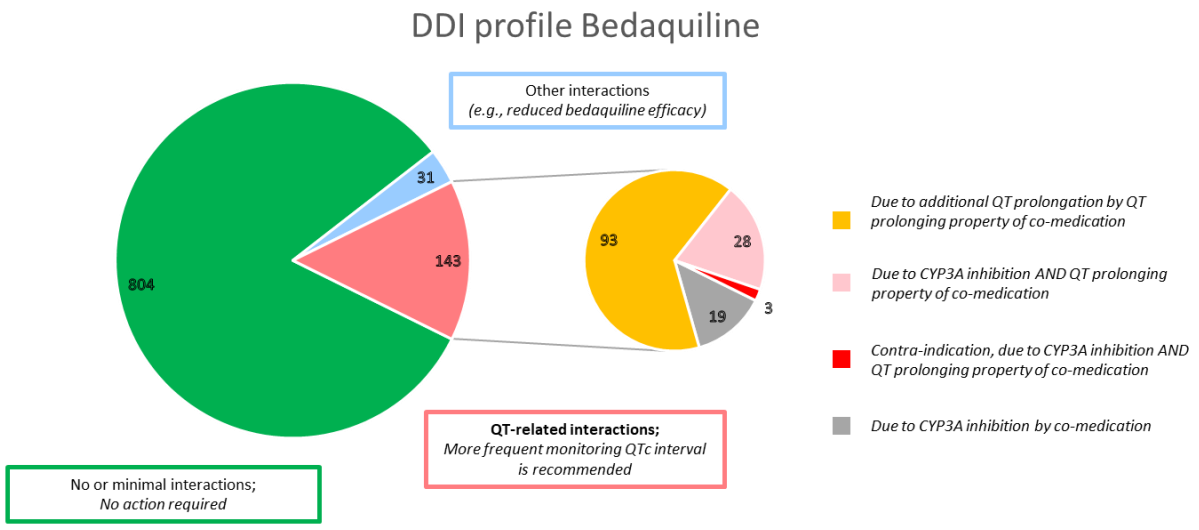

Figure 1. Drug-drug interaction (DDI) profile of bedaquiline analyzed with 978 co-medications, zoomed in on QT-related interactions with bedaquiline.

When we analyzed a random sample of 12 medications from our database, the consensus with the other databases was minimal: 2/12 (G-standaard); 2/12 (HealthBase), 2/12 (Stockley), and 5/12 (Lexicomp/Up-to-date®).

Conclusions

DDI management with bedaquiline to reduce the risk of TdP appeared to be needed in a small but significant subset of medications from our database (14.6%). In almost all cases, this included more intensive ECG monitoring than what is currently local practice. There was minimal consensus when comparing our results with a number of other DDI resources, illustrating the need for better guidance to clinicians on DDI management with bedaquiline.