Antimycobacterial activity of a novel Diarylquinoline (TBAJ-876) against diverse drug-sensitive (DS) and drug-resistant (DR) clinical isolates *of Mycobacterium tuberculosis* (Mtb)

T. Black,[1] A. Upton,[1] N. Fotouhi,[1] M. Beumont,[1] E. Sun,[1] E. Nuermberger,[2] P. Converse,[2] D. Almeida,[2] O. Komm,[2] S. Franzblau,[3] N. Kurepina,[4] B. Kreiswirth,[4]
[1]TB Alliance, Research & Development, New York, United States of America, [2]Johns Hopkins University School of Medicine, Center for TB Research, Baltimore, United States of America, [3]College of Pharmacy University of Illinois at Chicago, Institute for Tuberculosis Research, Chicago, United States of America, [4]Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, United States of America

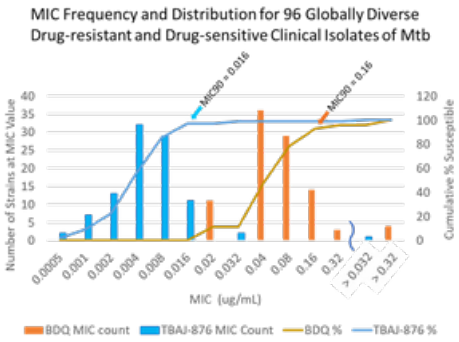
Type selection
Category: Scientific research
Prefered presentation type: Oral abstract presentation

Track selection
Track: A2: Drug and vaccine development, including for COVID-19
2nd Track: A3: TB diagnostics, including drug-resistance determination – Technical aspects and new developments

Title

Scientific Research Abstract Text

Background: Standardized in vitro MIC assays are used to compare relative potency of antimycobacterial drugs. For some classes of drugs, potency differences can be observed amongst different clades of Mtb. For second-generation drugs, the potential for cross-resistance or reduced potency may limit the effectiveness of new agents. Testing large panels of clinical isolates and strains having known resistance profiles is needed before advancing a novel Mtb drug into clinical development. Validating the in vitro activity in mouse infection models provides added confidence.
Design/Methods: The MICs of TBAJ-876 and BDQ were evaluated by an agar proportion method against a panel of 96 DS and DR clinical isolates representing broad phylogenetic and geographic diversity. MICs were also determined by MABA method for TBAJ-876, BDQ, and their mono-N-desmethyl metabolites (M3 and M2, respectively) against a panel of 5 DS clinical isolates representing 5 phylogenetic clades and against a panel of clinical and laboratory isolates with diverse Rv0678 mutations. The activity of TBAJ-876 and BDQ in combination with pretomanid and linezolid (PaL) was also assessed in BALB/c mice infected with an isogenic BDQ-R Rv0678 mutant selected in an H37Rv strain.
Results: Against 96 DS and DR clinical isolates, TBAJ-876 had an MIC90 of 0.016 mg/L vs. 0.16 mg/L for BDQ. TBAJ-876 and 876-M3 were at least 10x more potent than BDQ and BDQ-M2 against DS and Rv0678 mutant strains. TBAJ-876 also provided improved activity vs BDQ in mice infected with an Rv0678 mutant strain.



Conclusions: TBAJ-876 has consistent activity and ~10-fold better potency than BDQ against DS and DR Mtb including activity against some BDQ-R strains.

Summary

Summary: TBAJ-876 is a second-generation diarylquinoline with improved antimycobacterial activity. Comparative in vitro assays show ~ 10-fold lower minimum inhibitory concentration (MIC) for TBAJ-876 vs. bedaquiline (BDQ). Mouse infections with Rv0678 mutant strains, the most frequent cause of BDQ clinical resistance (BDQ-R), also establish the superior activity of TBAJ-876.

Other Fields
Did you benefit from the Abstract Mentor Programme (AMP)?: No
Do you have ethical clearance for this abstract?: Yes

Confirm submission
1. I confirm that I have previewed this abstract and that all information is correct.: Yes
2. I agree to the resubmission policy.: Yes
3. I have read the Stigmatising Language Policy, and confirm I have not used stigmatising language in the abstract.: Yes
4. The corresponding author is responsible for informing the other authors.: Yes
5. If accepted, I hereby agree to the attached information relating to the release, recording and publication of the presentations and session.: Yes
6. I understand that my abstract if accepted may be used by the Scientific Committee of The Union for the rapporteur session or shared with the media team. The media and communication teams may use the summary of the abstract for advertisement of the conference content.: Yes
Do you intend to apply for a scholarship? (After notifications are sent).: No