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Enhanced sterilizing potential of regimens containing a novel diarylquinoline (TBAJ-876) in a preclinical mouse model of tuberculosis.

T. Black,[1] N. Fotouhi,[1] M. Olugbosi,[2] M. Beumont,[1] E. Sun,[1] P. Converse,[3] R. Tasneen,[3] S. Tyagi,[3] D. Almeida,[3] O. Komm,[3] S.-Y. Li,[3] E. Nuermberger,[3]
[1]TB Alliance, Research & Development, New York, United States of America, [2]TB Alliance, Research & Development, Pretoria, South Africa, [3]Johns Hopkins University School of Medicine, Center for TB Research, Baltimore, 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

Title

Scientific Research Abstract Text

Background: The relapsing mouse model (RMM) effectively predicted the clinical mycobactericidal and sterilizing potential of the BPaL and BPaMZ regimens. The new diarylquinoline clinical candidate, TBAJ-876 combined with PaL, has been evaluated in RMMs to assess the exposure/response relationship and sterilizing potential relative to HRZE, BPaL, and BPaMZ. The model data will be used to evaluate the potential clinical activity of TBAJ-876 vs. Bedaquiline in PaL-containing regimens and will guide clinical dose selection and impact of using lower doses of L (linezolid).
Design/Methods: The BALB/c RMM with Mtb strain H37Rv was used. Dosing began 2 weeks post-infection (≥ 10^7 lung CFUs). Groups of mice (~5-10/arm/timepoint) were treated for various periods (0.5-6 months); 3 months after the end of each dosing period, lungs were harvested and assessed for bacterial burdens by plating. All marketed drugs were dosed orally 5 days per week to provide approximate human-equivalent dose (HED) exposures at approved doses. TBAJ-876 was dosed at 1.56, 3.125, 6.25, and 12.5 mg/Kg in the dose ranging study (~25, 50, 100, and 200 mg HED). Drug PK was assessed for some studies.
Results: Dose-dependent efficacy of TBAJ-876 was observed at doses up to 12.5 mg/Kg. The 3.125 mg/Kg dose of TBAJ-876 provided faster time to sterilization than 25 mg/Kg doses of bedaquiline when combined with PaL. The 6.25 mg/Kg of TBAJ-876 provided an approximately one month decrease in time-to-sterilization vs. bedaquiline when combined with PaL (with L dose lowered to achieve a 600 mg human equivalent dose) and provided a similar time-to-sterilization as the BPaMZ treated group.

Conclusions: These RMM studies show the potential for significant improvement in the sterilizing activity of regimens containing TBAJ-876 vs. bedaquiline at the likely achievable human exposures.

Summary

Summary: Bedaquiline (B)-containing regimens (BPaL, BPaLM, BHZEL and BPaMZ) provide excellent clinical efficacy with shortened treatment durations. Bedaquiline's full potential may be unrealized at recommended doses as tolerability concerns limit utilization of higher doses. TBAJ-876 is a new, more potent diarylquinoline with superior sterilizing activity at lower drug exposures in mouse models.

Other Fields
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