Pharmacokinetics/pharmacodynamics of Epetraborole, a Novel Bacterial Leucyl-tRNA Synthetase Inhibitor, and High Intracellular Penetration in the Intracellular Hollow Fiber System Model of Mycobacterium avium Complex Lung Disease

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ABSTRACT

Epetraborole (EBO) is a boron-containing, oral inhibitor of bacterial leucyl-tRNA synthetase, an essential enzyme in protein synthesis; EBO demonstrates select activity against mycobacterial organisms. Drug-response studies in the intracellular hollow fiber system model of Mycobacterium avium complex (MAC) lung disease, of EBO, have suggested that EBO is highly efficacious in the in vivo setting in contrast to the in vitro setting. Understanding the integrated pharmacokinetics/pharmacodynamics (PK/PD) of EBO in the hollow fiber model is critical to the development of the drug in clinical studies.

METHODS

EBO penetration was approximately 500% into human alveolar macrophages. In pulmonary MAC in patients, immunohistochemistry has revealed intracellular MAC in both the extracellular and intracellular compartments. With SOC, 70% of patients develop treatment-related adverse events; 30% discontinue therapy. For drug concentrations, the central compartment of each HFS-MAC unit was sampled once a day for 15 days, and the HFS-MAC model was established. PK/PD parameter analysis was performed in Prism with each PK/PD parameter associated with the PK/PD parameter.

RESULTS

In the HFS-MAC dose fractionation study, the average AUC of EBO was approximately 500% above the MIC of MAC in healthy volunteers. Antimicrob Agents Chemother 2013;57;3334-3339.

CONCLUSIONS

- EBO achieved high concentrations inside MAC-infected monocytes, with an AUC penetration ratio of 11. Given the 50% ELF concentrations, EBO may be an efficacious drug in MAC disease.
- EBO microbial kill of intracellular MAC is strongly correlated with AUC.
- EBO resistance in HFS-MAC is driven by AUC early in infection.
- The PK/PD parameter linked to EBO resistance development was AUC, and in several strains matched the three-drug SOC (day 14; Poster No. 1697).
- The PK/PD parameter linked to EBO-resistant CFUs, based on AIC criteria, was AUC until day 7 when it appeared to change to %TMIC.

REFERENCES AND ACKNOWLEDGMENTS


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