Regulatory Perspective on Clinical Pharmacology Considerations for Antifungal Drug Development

Jason Moore, PharmD
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
US Food and Drug Administration
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Disclaimer

The opinions contained in this presentation are my own and do not necessarily represent the views of the FDA.
Objectives

• To establish framework for further discussion
• To discuss high-level clinical pharmacology considerations relevant for antifungals
  – Animal Models
  – Formulation Development
  – Exposure-Response Analyses
  – Drug-Drug Interactions
Animal Model Utility

• Animal models are potentially useful to demonstrate proof of concept
• Challenges remain in use of animal models to establish clinical effectiveness
  – Selection of appropriate animal model
Example: Micafungin

- Difficulty in establishing effectiveness of micafungin in pediatric patients <4 months
  - Dissimilar disease presentation from adults and older pediatric patients
- Rabbit model of hematogenous Candida meningoencephalitis supported dosing for clinical trial and labeling information
- Section 8.4 Use in Special Populations – Pediatric Use
  “[A] dose regimen of approximately 10 to 25 mg/kg once daily may be necessary to lower fungal burden in the CNS in pediatric patients younger than 4 months of age.”

Formulation Development

• Beneficial to have both IV and PO formulations available
  – Wide range of fungal infection severity
  – Step-down therapy (IV->PO) with same antifungal agent

• Concerns with antifungal formulations
  – Echinocandins are only available IV
  – Issues with PO formulation for azole antifungals
Exposure-Response (E-R) Analyses

• Important to evaluate E-R relationships to support efficacy and safety in clinical trials
  – Inform dose regimen selection
  – May indicate need for therapeutic drug monitoring (TDM)

• Some antifungal drugs include E-R data in labeling
  – E.g., posaconazole, micafungin, voriconazole

• Although not included in labeling, TDM is often used clinically for azole antifungals
  – 2016 IDSA guidelines recommend TDM with use of azoles (posaconazole, voriconazole, itraconazole) for treatment or prophylaxis of invasive aspergillosis

Drug-Drug Interactions (DDI)

• Some antifungals have significant DDI liability
  – Azole antifungals are CYP substrates and inhibitors
  – Voriconazole and itraconazole have 30+ listed DDIs in labeling

• Patients with invasive fungal infections often have severe comorbidities

• Many concomitant medications in target patient population
  – Transplant recipients: Sirolimus, Everolimus, Tacrolimus, Cyclosporine
  – Patients with HIV: Protease Inhibitors

• DDI potential must be evaluated in vitro and in vivo, as applicable
Example: Posaconazole

• Formulation Development
  – Delayed-Release Tablet (2013)
  – IV Solution (2014)

• DDIs
  – CYP 3A4 substrates/modulators
  – Drugs affecting GI motility or pH

• E-R Relationship
  – Assessed for oral suspension
  – Increase in efficacy with increase in $C_{avg}$
  – Opportunity to optimize prophylaxis despite variable absorption using TDM
  – TDM used clinically

Other Important Clinical Pharmacology Studies

• In Vitro CYP Metabolism/Transporter
• Single- and Multiple-Ascending Dose PK
• Food-Effect
• Bioequivalence/Bioavailability
• Mass Balance/ADME
• Hepatic/Renal Impairment
• Thorough QT
Summary

• Clinical pharmacology drug development for antifungals is similar to other disease states

• Several areas that may require special consideration relative to other therapeutic areas
  – Animal Model Utility
  – Formulation Development
  – E-R Analysis/TDM
  – DDI Characterization
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