FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Regulatory Perspective on Clinical Pharmacology Considerations for Antifungal Drug Development

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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.”

Hope WW, Mickiene D, Petraitis V, et al. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous Candida meningoencephalitis: implications for echinocandin therapy in neonates. J Infect Dis. 2008;197(1):163-71.
Petraitiene R, Petraitis V, Hope WW, et al. Cerebrospinal fluid and plasma (1-->3)-beta-D-glucan as surrogate markers for detection and monitoring of therapeutic response in experimental hematogenous Candida meningoencephalitis. Antimicrob Agents Chemother. 2008;52(11):4121-9.

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

Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1-e60.

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
  - Oral Suspension (2006)
  - 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

Jang SH, Colangelo PM, Gobburu JV. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther. 2010;88(1):115-9.

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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