Clinical Pharmacology Considerations for Antifungal Drug Development

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This talk addresses key steps and ideas to ensure patients receive the right regimen of a novel agent the first time

Two key areas for discussion

- Identification of the initial regimen (selection of the candidate dose and schedule)
  - This is largely obtained from preclinical models and PK-PD bridging techniques
- Ensuring the candidate regimen remains fit for purpose
  - As the compound transitions from healthy volunteers to patients or special populations
  - (or as it makes its way into real-world settings)

Historical context

- For lethal diseases it is not reasonable to design a clinical study that delineates the entire dose-exposure-response (DER) relationship
  - Nonclinical PK-PD fulfils this purpose
- It is also worth remembering many IFDs are rare and difficult to prospectively identify
  - Clinical trials are simply infeasible
- Older antifungal agents were developed using what might now be considered relatively crude approaches
  - Plasma concentrations that exceed the MIC_{90} for the proposed dosing interval
  - Voriconazole and caspofungin were developed this way

What are the key ideas and challenges for identifying a candidate regimen for patients?

Of a new antifungal drug, or a new indication for a licensed compound

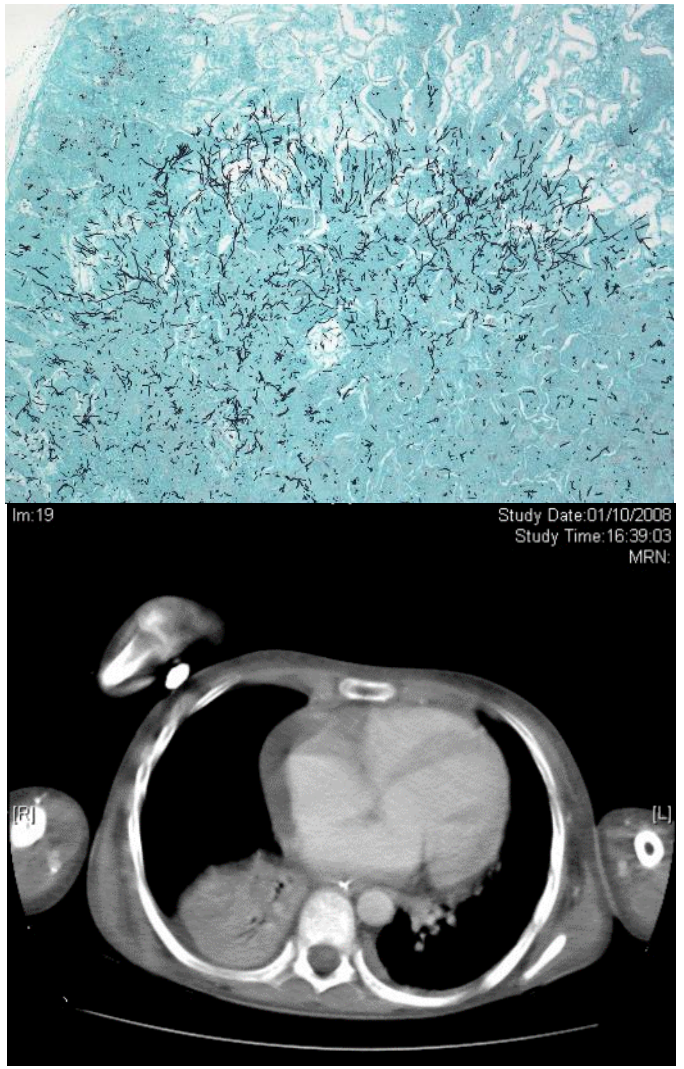
#1 Robust pharmacodynamic models are available to delineate initial PK-PD relationships

- These provide information to plan the dose and schedule
- *Candida* models are relatively straightforward
  - Mostly *Candida albicans*
  - *Candida glabrata* and *Candida parapsilosis*
- *Aspergillus* models progressively developed through 2000s
  - Endpoints include PCR, galactomannan and survival
- Cryptococcus models
  - Meningoencephalitis
- Generally, these models enable a clear indication of the relevant pharmacodynamics and therapeutic potential of a new agent

Hope at al J Antimicrob Chemother. 2016 Nov;71(11):3008-3019

#2 Models can also serve as adjunctive evidence of clinical efficacy)

- See very interesting debate at FDA meeting 5 Mar ‘20 on Animal Models to Support Antibacterial Development
- Idea of separating
  - “relatively well-controlled and early” models designed to establish PK-PD
  - vs. more faithful mimics of human disease
- John Rex’s notes, https://amr.solutions (8 Mar ‘20)
- Rabbit models of *Aspergillus* spp., *Candida* spp. and *Cryptococcus* species all fulfil this role
  - Clinically relevant background immunosuppression
  - Comparable pathogenesis
  - Clinically relevant readouts (e.g. $\log_{10}$CFU/mL in CSF, GM)
  - “Severe” in that they are universally lethal
- Micafungin for neonatal hematogenous *Candida* meningoencephalitis is a good example[1]



[1]Hope et al J Infect Dis. 2008 Jan 1;197(1):163-71

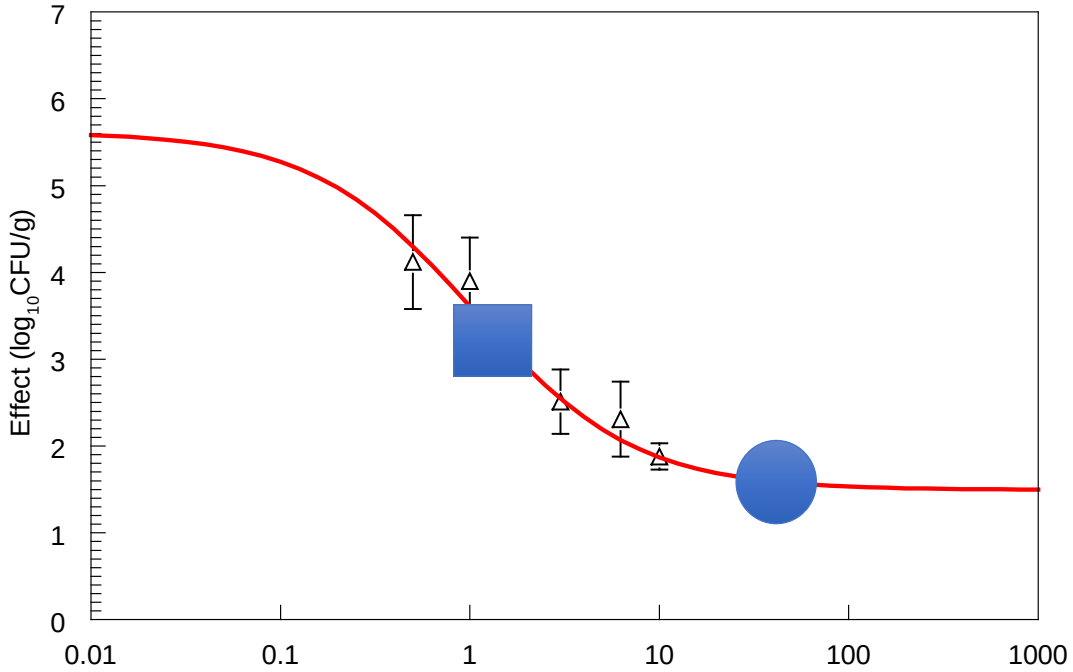
#3 If nonclinical data is being used as adjunctive evidence of clinical efficacy…

- Some thought probably needs to be given about the QA issues
- Secure data repositories may need be considered
- GLP generally not used by academic laboratories
- Standardization of models may need further consideration

#4 There is a problem with defining study endpoints: this needs more debate

- By this I mean what is the fungal equivalent of stasis, 1- to 2-log drop used in development of antibacterial agents?
- This is really where the clinical regimen is defined

Benchmarked endpoint = the effect induced with a clinically relevant exposure from a licenced agent



Requiring near maximal efficacy will generally take the drug beyond its safety margin

Transition to the Clinic

The first steps in the bridge are relatively straightforward

- First-in-human PK data (drug exposures) provide an insight as to whether exposures required for efficacy are achievable
- Best addressed with a population model and Monte Carlo simulation
- Failure to achieve desired drug exposure targets may trigger the requirement for more PK studies
  - Micafungin for neonates a good example
  - 4 mg/kg escalated to 15 mg/kg to get the necessary exposures predicted from rabbit model[1,2]

[1]Smith et al Pediatr Infect Dis J. 2009 May;28(5):412-5
[2]Benjamin et al Clin Pharmacol Ther. 2010 Jan;87(1):93-9.

#5 Getting good estimates of variability is key

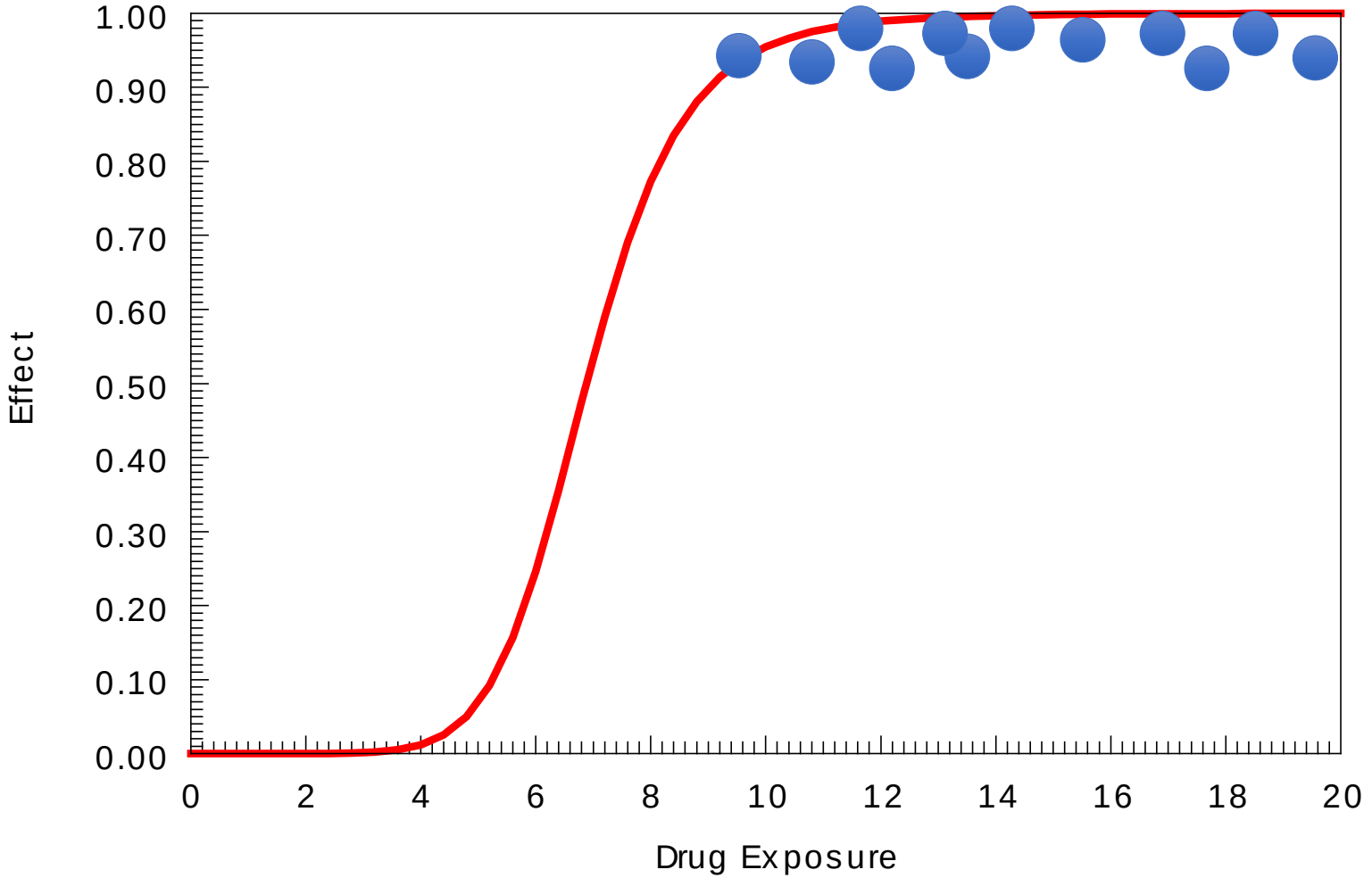
- PK variability is generally higher in patients (e.g. CV% for clearance may double)
- It is possible to artificially inflate variance in simulators
  - Taking volunteer data
  - This is “stressing” the performance of the planned dose
- Progressive understanding of PK enables refinement of adequacy of dosing
  - Effect of food, renal impairment, hepatic impairment etc.
- Planning PK sub-studies in an early cohort of patients (c.f. volunteers) and refitting population PK models is also helpful

#6 Planning for PK-PD sub-studies in Phase II/III

- PK-PD sub-study in patients completes the bench-to-bedside loop
- However, there are some issues
  - The PK is generally poor quality and requires co-modelling with richer data
  - Uninformative PK results in imprecise estimates of drug exposure (or bias)
  - The pharmacodynamic endpoint may be problematic
    - GM has been used in IA [requires rich serial data]1
    - Rate of decline in $\log_{10}$CFU/mL in cryptococcal meningitis [serial LPs increasingly accepted]2
    - ACM and clinical response are relatively crude “noisy” endpoints3

[1]Kovanda et al Clin Infect Dis. 2017 Jun 1;64(11):1557-1563.
[2]Jarvis et al Clin Infect Dis. 2019 Jan 18;68(3):393-401.
[3]Desai et al Antimicrob Agents Chemother. 2017 Nov 22;61(12):e01034-17.

#7 A PK-PD sub-study ensures patients are "on top of the dose-response relationship



If a dose-exposure response ***is*** seen something has gone wrong or the drug is very variable

#8 All information related to dose-response can be used for TDM and control

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CLINICAL THERAPEUTICS

Software for Dosage Individualization of Voriconazole: a Prospective Clinical Study

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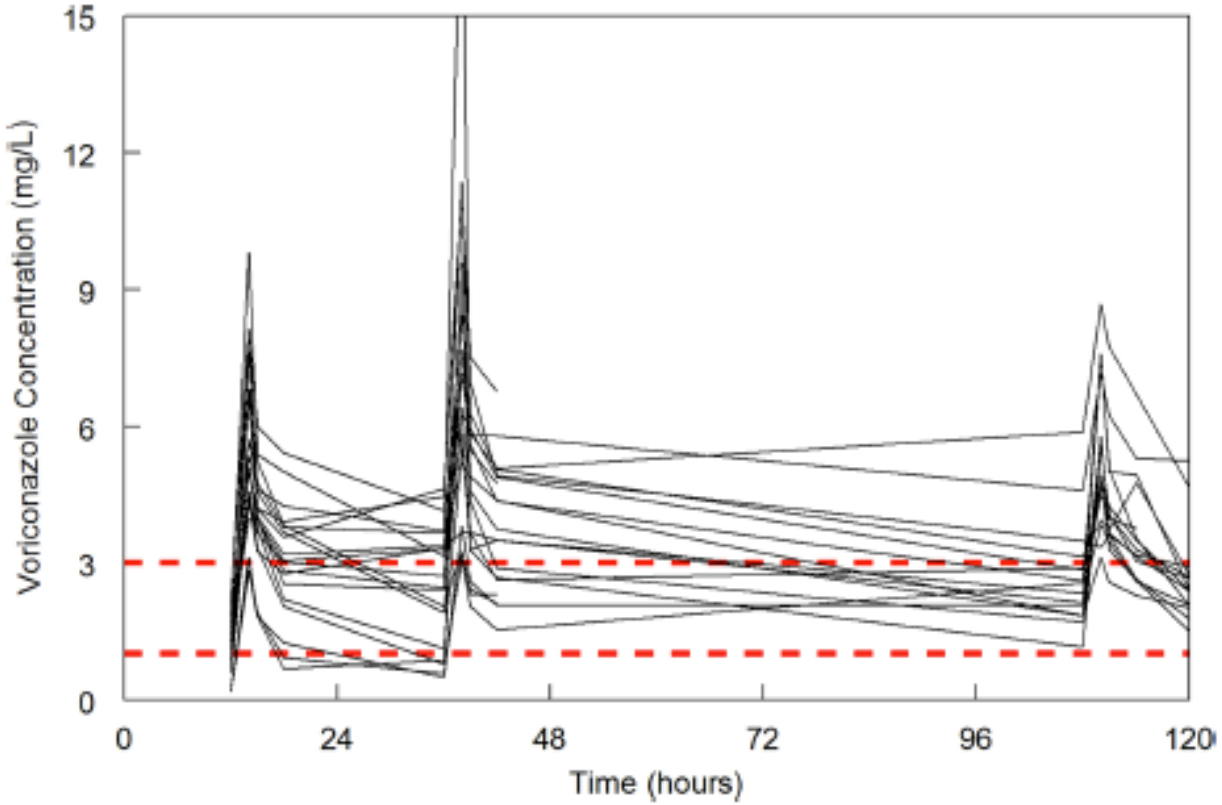
Hope at al Antimicrob Agents Chemother. 2019 Mar 27;63(4):e02353-18.



This all works extraordinarily well; however,

- Regulatory position unclear
- Infrastructure not in place
- Pharmacoeconomic benefit unclear
- Demonstrating patient benefit remains challenging

Conclusions

- The models, approaches and pathways for antifungal agents are progressively more mature
- I have noticed differences between FDA and EMA in terms of the way in which data from different models/ endpoints are weighted. Some consistency would be helpful
- While it is not the primary responsibility of FDA (or EMA) it is a significant concern that there does not appear to be a new generation of investigators interested in antifungal therapeutics